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Sporadic Cerebral Small Vessel Disease and Cognitive Abilities

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Dedicated to Russ Hamilton

Thesis Abstract

Cerebral small vessel disease (SVD) is a leading cause of vascular cognitive impairment, contributing to multiple neurological disorders ranging from stroke, to mild cognitive impairment and dementia. However, despite a huge number of studies on the subject, we have a limited understanding of how SVD affects cognitive ability. This thesis aims to address this knowledge gap, by examining domain-specific cognitive abilities in a range of clinical and non-clinical presentations of SVD.

In the introductory chapters of this thesis I will discuss what is meant by the term cerebral small vessel disease (SVD), describing key radiological features of SVD and its varied clinical and non-clinical presentations. However, before considering the current consensus on how SVD impacts different domains of cognitive ability, I will first consider what happens to these abilities in the context healthy cognitive ageing. Finally, I will consider the current consensus on the pattern of cognitive changes that occur in SVD and will examine the vast and often conflicting evidence that underpins this.

To gain a comprehensive overview of the published literature examining cognitive abilities in SVD, Chapter 4 presents a systematic review and meta-analysis of 69 studies presenting cognitive data for at least one cohort with SVD (n=3679) and one comparison control group without SVD (n=3229). Results indicated that relative to controls, cohorts with SVD performed more poorly on cognitive tests in all of the cognitive domains examined. Meta-regression analyses suggested that fewer years of education in the SVD vs. control groups accounted for a proportion of the differences in their test scores in some cognitive domains. Further meta-regression analyses suggested that cohorts with SVD-related cognitive impairment or dementia performed more poorly on tests in certain cognitive domains than cohorts with stroke or non-clinical presentations of SVD. Overall, however, SVD cohorts performed more poorly than controls on cognitive tests in all domains, regardless of their SVD presentation.

Chapters 5 and 6 focus more closely on the key radiological markers of SVD and their associations with cognitive test scores using data from the Lothian Birth Cohort 1936 (LBC1936): a cohort of relatively healthy, community-dwelling, older individuals. To increase

the fidelity with which SVD is typically measured, I combined computational volumes and visually-rated MRI markers of SVD to construct a variable representing the total MRI-visible burden of SVD. The study in Chapter 5 presents the results of cross-sectional associations between this latent SVD variable and latent variables of processing speed, verbal memory and visuospatial ability, within a structural equation modelling framework (SEM; n=540; mean age 72.6±0.7 years). Age, sex, vascular risk, depression status, and age-11 IQ were included as covariates. The latent SVD variable was negatively associated with all cognitive factors, in line with the results of the systematic review and meta-analysis. However, after accounting for the shared variance between the different cognitive domains (a construct described as general cognitive ability, which previous studies have not accounted for), only the association between the latent SVD variable and processing speed remained significant. This suggests that SVD's association with slowed processing speed is not driven by, but is independent of its association with poorer general cognitive ability.

In Chapter 6 this work is developed further by exploring associations between the latent SVD variable and decline in the same latent cognitive factors over a period of 9 years, from the age of around 73 to 82, again in the LBC1936. This was carried out using latent growth curve modelling within a SEM framework. Age, sex, vascular risk, and age-11 IQ were included as covariates. Results indicated that the latent SVD variable was associated with greater decline in general cognitive ability and processing speed. However, after accounting for the covariance between tests of processing speed and general cognitive ability, only the association between greater SVD burden and decline in general cognitive ability remained significant. Whereas the results of Chapter 5 suggested that SVD burden at age 73 may have specific and independent effects on processing speed measured at the same age, the results of our longitudinal analyses suggest that SVD burden at age 73 associates with declining processing speed due to SVD's overarching association with general cognitive decline.

In the final chapter of this thesis, I summarise the findings of these three studies, discuss their limitations, and make recommendations for future research.

Lay Summary

Blood circulates throughout the brain via a complex network of vessels. As people grow older, some of the small vessels that carry blood into the deepest parts of the brain become damaged - this is known as cerebral small vessel disease, or SVD for short. Some of the damage caused by SVD is visible on brain scans. These visible markers of SVD accumulate with age and are commonly seen on the brain scans of people over the age of 60, although for the majority of people, SVD doesn't cause any obvious problems. For other people, however, SVD can lead to stroke or dementia, two conditions that have a negative impact on our cognitive functions. Because of this, SVD is known to be one of the leading causes of cognitive impairment in old age.

Currently, it is unclear which aspects of our cognitive functions are affected by SVD. Some researchers and clinicians believe that SVD mainly affects the speed of thinking and the ability to carry out complex tasks, whereas other functions, such as memory and language, remain relatively unaffected. However, previous research on this topic has produced mixed results, suggesting that this might not actually be the case. It is important to understand precisely which types of cognitive functions are affected by SVD, so that symptoms of SVD can be accurately measured and monitored. This is particularly important in clinical trials, which test whether treatments for SVD are effective in preventing cognitive impairment and dementia. The work in this thesis will examine the cognitive functions of people with SVD, in order to gain a better understanding about how they are affected by the disease.

The first study in this thesis is a review of the published research literature examining the cognitive test scores of people with signs of SVD on brain scans, or who had stroke or dementia due to SVD. I gathered together and re-analysed data from 69 studies and found that compared with healthy individuals, people with SVD were impaired in most major cognitive functions, including those that are typically thought to be unaffected. The pattern of cognitive impairments was similar whether study participants had stroke, dementia, or had no obvious signs or symptoms of SVD. Additional analyses suggested that people with SVD might have lower cognitive test scores than healthy people, because they have fewer years of education.

The second and third studies in this thesis examine the relationship between markers of SVD on brain scans and cognitive test scores, using data from a research study called the Lothian Birth Cohort 1936. All participants in this study were born in 1936 and took a cognitive test in 1947, at the age of 11, as part of a nation-wide survey of Scotland's school children. Over 60 years later, at the age of 70, some of these people were invited to join the Lothian Birth Cohort 1936 and have provided a wealth of data, including cognitive test scores and brain scans at the ages of 70, 73, 76, 79, and 82. In the second study of this thesis I used data from age 73 only. Using mathematical modelling, I combined information about the four markers of SVD visible on participants' brain scans into a single measure of total SVD burden. Results of this study indicated that having a greater burden of SVD was related to having slower thinking skills at the age of 73. This result remained the same after accounting for participants' age, sex, vascular health (e.g. whether participants had high blood pressure or diabetes etc.), depression status, and differences in childhood cognitive test scores. These results suggested that, as commonly thought, SVD might specifically affect speed of thinking.

The third and final study of this thesis extended this work further by examining the relationship between total SVD burden at the age of 73 and the *change* in cognitive functions over a 9-year period, between the ages of 73 and 82. Results of this study indicated that the previously observed relationship between greater SVD burden and slowed thinking skills is likely due to SVD's relationship with declining cognitive function more generally (i.e. the decline of multiple cognitive functions simultaneously). Once again, these results remained the same after accounting for participants' age, sex, vascular health, and differences in childhood cognitive test scores. Overall, the studies in this thesis do not support the popular belief that SVD selectively affects certain types of cognitive functions, but suggest that most major cognitive functions are impaired.

In the final chapter of this thesis, I summarise the findings of these three studies, discuss their limitations, and make recommendations for future research.

Declaration

I declare that I have written and constructed this thesis and that the work has not been submitted for any other degree or professional qualification. The work is my own, except where the work forms part of a published article that is authored by multiple individuals. For jointly authored work, I outline my contribution and the contributions of my co-authors below. I confirm that in this thesis the appropriate credit has been given where I refer to the work of others.

The analyses presented in Chapter 4 have been published as a Theoretical Article in *Alzheimer's and Dementia* (available at https://doi.org/10.1002/alz.12221). An earlier version of this work was uploaded to the *medRxiv* preprint server (available at https://doi.org/10.1101/2020.02.10.20020628). Co-authors of this work were Ellen Backhouse, Esther Janssen, Angela Jochems, Caragh Maher, Tuula Ritakari, Anna Stevenson, Lihua Xia, Ian Deary, and Joanna Wardlaw. The systematic review and meta-analysis were conceptualised and designed by OH and supervised by JW and ID. OH conducted the initial literature search and OH, EB, TR, AS, and CM screened papers for inclusion in the review. OH, EB, XL and EJ extracted data from eligible papers. OH and AJ categorised cognitive test data into domains. OH analysed and interpreted the data with contributions from JW and ID. OH wrote the first draft of the manuscript – all authors contributed to later versions.

The work presented in Chapter 5 is undergoing the second round of review at *Neurobiology of Aging*. The version presented here has been uploaded to the *medRxiv* preprint server (available at https://doi.org/10.1101/2021.02.02.21250986). Co-authors of this work were Simon Cox, Lucia Ballerini, Mark Bastin, Janie Corley, Alan Gow, Susana Muñoz Maniega, Paul Redmond, Maria Valdés-Hernández, Joanna Wardlaw, and Ian Deary. OH designed the study and analysed and interpreted the data, supervised by JM and ID. SRC advised on data analysis and data interpretation. LB developed the automated PVS quantification pipeline and conducted image processing. MEB, SMM and MVH carried out image processing. JC and AJG carried out data collection. PR carried out data management and quality checking. JMW and IJD advised on study design, statistical analysis and data interpretation. OH wrote the initial draft of the manuscript and all authors contributed to later versions.

The work presented in Chapter 6 is currently under review at *Molecular Psychiatry.* The version presented here has been uploaded to the *medRxiv* preprint server (available at https://doi.org/10.1101/2021.03.28.21254499). Co-authors and co-author contributions are the same as for Chapter 5, with the addition of Adele Taylor, Danielle Page, Judy Okely and Federica Conte. AT and DP carried out data collection. JO and FC advised on writing code for the statistical analyses.

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I extend my thanks to the participants of the Lothian Birth Cohort 1936, whose time and effort over many years have contributed to the generation of an invaluable dataset. Thank you also to the core members of the Lothian Birth Cohort team, particularly Paul Redmond, Janie Corley, Adele Taylor and Danielle Page, whose hard work maintains the Lothian Birth Cohort 1936 dataset. I would like to thank the Wellcome Trust, who support the Translational Neuroscience PhD programme, the College of Medicine and Veterinary Medicine at the University of Edinburgh, who funded my PhD studentship, and Jane Haley for her all-round support and for her work in coordinating the PhD programme.

As almost the entirety of this thesis has been written under a period of national lockdown (exactly one year to the day today), my friends have played a huge role in keeping me motivated. Cesca, Gail, Chloe and Al Morgan – thank you for the lunchtime walks, cake drop-offs, and for your words of encouragement. I am also grateful to my mum ("you're *still* screening papers?!?") and my brother for always being interested in my work, for encouraging me, and for celebrating my PhD milestones with me over the last four years. I am also grateful to two of my biggest cheerleaders, my dad and my uncle Duncs, who are no longer here to see me over the finish line, but who have motivated me all the way through.

Although I'm sure he would have called me a smart arse, my dad would have been proud of me for getting to this point – this thesis is dedicated to him.

Finally, my heartfelt thanks go to my partner, Tom, whose championing and encouragement have kept me buoyant, especially during this last year of lockdown. Thank you for the endless cups of tea, (and breakfasts and lunches and dinners) – I'm excited to close my laptop and venture beyond the Leith boundaries with you.

Table of Abbreviations

Aβ	Amyloid beta
AD	Alzheimer's disease
APOE e4	E4 variant of apolipoprotein E gene
BBB	Blood brain barrier
BMI	Body mass index
CADASIL	Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy
CFA	Confirmatory factor analysis
CSF	Cerebrospinal fluid
CT	Computed tomography
dMRI	Diffusion magnetic resonance imaging
FA	Fractional anisotropy
FLAIR	Fluid attenuated inversion recovery
g	General cognitive ability
GRE	Gradient-recalled echo
LBC1936	Lothian Birth Cohort 1936
MD	Mean diffusivity
MMSE	Mini Mental State Examination
MoCA	Montreal Cognitive Assessment
MRI	Magnetic resonance imaging
NAWM	Normal appearing white matter
PCA	Principal components analysis
PVS	Visible perivascular space
RCT	Randomised controlled trial
RSSI	Recent small subcortical infarct
SEM	Structural equation modelling
SVD	Cerebral small vessel disease
TIA	Transient ischaemic attack
VaD	Vascular Dementia
VCI	Vascular cognitive impairment
VRF	Vascular risk factor
WAIS	Wechsler Adult Intelligence Scale
WMH	White matter hyperintensity
WMS	Wechsler Memory Scale

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General introduction

In the 21st century, global life expectancies are continuing to rise. Whereas increased longevity in the 20th century was primarily due to reductions in child and infant mortality, the current increase in global life expectancy is largely due to reduced mortality in the older age groups living in high income countries (Mathers, Stevens, Boerma, White, & Tobias, 2015). As the prevalence of cognitive impairment and dementia increase exponentially with age, the number of people with dementia in the UK alone is predicted to reach two million by 2050 (an increase of 146% since 2014; Prince et al., 2014). Perhaps the greatest impact of cognitive impairment is the personal burden it places on the individuals who experience it and on those who care for them, both of whom are at greater risk of anxiety, depression, and poorer quality of life (Hussenoeder et al., 2020; Nys et al., 2006). Cognitive impairment also incurs a substantial financial burden, both for individuals and for society as a whole. Individuals with cognitive impairment typically use more health care services and require greater support with activities of daily living, either from unpaid family carers, or from paid care services (Reppermund et al., 2013; Rockwood, Brown, Merry, Sketris, & Fisk, 2002). In 2014 the overall economic cost of dementia in the UK was estimated at £23.6 billion and is predicted to increase to £59.4 billion by 2050 (Lewis, Schaffer, Sussex, O'Neill, & Cockcroft, 2014).

Causing approximately 20% of strokes and 40% of dementias worldwide, cerebral small vessel disease (SVD) is the primary cause of vascular cognitive impairment (VCI). The meaning of the term VCI has been refocused several times in recent years (Hachinski et al., 2006; O'Brien et al., 2003; Sachdev et al., 2014; Skrobot et al., 2018), but broadly refers to cognitive impairments due to underlying vascular contributions, which can range in severity from subtle subclinical cognitive decline, to mild cognitive impairment (MCI) and dementia (Gorelick et al., 2011; van der Flier et al., 2018). As a common pathway between stroke and dementia, SVD represents a prime target for reducing the prevalence of VCI and the personal and economic burdens it places upon our societies. However, despite a huge number of studies on the subject, the nature of the cognitive impairments associated with SVD remains poorly understood. This PhD aims to fill that knowledge gap by gaining a more accurate understanding of SVD-related cognitive impairments. It is important to clarify that the work in this thesis is not an attempt to characterise a cognitive 'profile' associated with

SVD. As SVD pathology contributes to both stroke and dementia, SVD manifests in a broad range of clinical (and non-clinical) presentations, to which a singular pattern of cognitive impairments is unlikely to be applicable.

In Chapter 1, I will discuss what is meant by the term *cerebral small vessel disease*. I will also describe its key radiological features and its varied clinical presentations. However, before considering how cognitive abilities are affected in SVD, I will first consider what happens to cognitive abilities in the context of healthy cognitive aging. This will be the focus of Chapter 2; I will briefly describe the measurement and structure of cognitive abilities, and what happens to these abilities as we age. In Chapter 3, I will describe recent consensus on the pattern of cognitive impairments associated with SVD, and will review studies that report associations between radiological features of SVD and cognitive test scores. Throughout this thesis, I use the term 'impairment' to denote any reduction in cognitive ability relative to an individual's typical ability (i.e. a decrement), as opposed to a normative standard, or a diagnostic construct, unless otherwise stated.

Chapter 1 Introducing sporadic cerebral small vessel disease

The term SVD refers to a collection of clinical, cognitive, neuroimaging and neuropathological abnormalities caused by dysfunction of the arterioles, capillaries and venules that perforate brain's white and deep grey matter. The causes of SVD are not yet fully understood, but involve numerous complex and inter-related mechanisms that are thought to centre on endothelial dysfunction and disruption of the blood brain barrier (BBB) - a highly specialised interaction of membranes and cell types that regulate the movement of molecules, ions, and cells between the blood and the central nervous system (Quick, Moss, Rajani, & Williams, 2020; Wardlaw et al., 2017). Other potential mechanisms underlying SVD include reduced vessel pulsatility, reduced ability of the cerebral blood vessels to dilate in response to increased brain demand for oxygen and nutrients, and impaired interstitial fluid drainage (Wardlaw, Smith, & Dichgans, 2019). Whereas current neuroimaging methods lack the spatial resolution required to visualise cerebral microvessels directly, the downstream impact of their dysfunction is visible on neuroimaging as a collection of larger-scale radiological features. The following are considered to be the key radiological features of SVD, each of which have been standardised according to the STRIVE criteria shown in Figure 1 (Standards for Reporting and Imaging of Small Vessel Disease; Wardlaw, Smith, Biessels, et al., 2013).

1.1 Key radiological features of SVD

1.1.1 White matter hyperintensities of presumed vascular origin (WMH)

One of the earliest formal descriptions of WMH (and their potential associations with cognitive impairments) was made by Hachinski and colleagues in 1987, who observed patchy areas of low signal-intensity on computed tomography (CT), coining the term "leukoaraiosis" to describe them. Just over 25 years later, in 2013, a systematic review identified over 50 different terms used to describe WMH, which has led to great variation in understandings of their pathophysiology and clinical significance. The STRIVE criteria define WMH as areas of increased signal intensity on T2-weighted magnetic resonance imaging (MRI), or decreased signal intensity on T1-weighted sequences (Wardlaw et al., 2013). Typically appearing bilaterally and often symmetrical in appearance, WMH are frequently observed in the subcortical white matter and deep grey matter structures of older individuals. Following

STRIVE recommendations, the broader term “subcortical hyperintensities” can be used to refer to hyperintense lesions appearing in the deep grey matter as well as in the white matter. WMH are often classified as either periventricular or deep, with periventricular WMH appearing as caps around the frontal horns and as narrow strips along the outer edges of the lateral ventricles, and deep WMH appearing as punctate foci in the subcortical white matter (Schmidt et al., 2011). However, periventricular WMH typically conflate with deep WMH as disease severity progresses and both are likely to be part of a continuous pathology (Valdés Hernández et al., 2014).

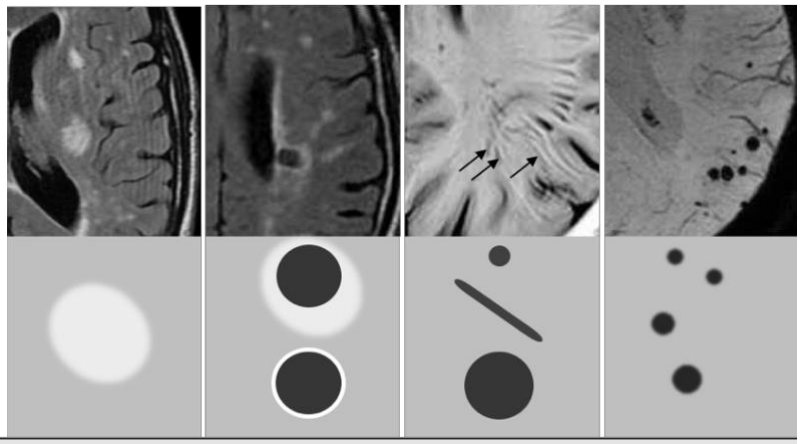
Whereas the standardised term “white matter hyperintensities of presumed vascular origin” refers to a limited pattern of signal alterations on neuroimaging, the underlying pathological changes that they represent vary considerably (Fazekas et al., 1993; Gouw et al., 2011; Wardlaw, Valdés Hernández, & Muñoz Maniega, 2015). Pathological reports of WMH have described a proinflammatory environment, as indicated by microglial and endothelial activation (Fernando et al., 2004), albumin extravasation suggesting breakdown of the BBB (Simpson et al., 2010), as well as axonal degeneration, and loosening and loss of white matter fibres, often attributed to cerebral ischaemia (Gouw et al., 2011).

Complementing pathological observations, advanced neuroimaging methods enable in-vivo examination of structural tissue changes underlying WMH morphology. Diffusion imaging (dMRI) quantifies the diffusion of water molecules, thus providing a measurement of the microstructural organisation of the brain’s white matter (Le Bihan, 2014; Le Bihan et al., 2001). The most commonly used dMRI metrics are mean diffusivity (MD) and fractional anisotropy (FA), indicating the magnitude and directional coherence of water molecule diffusion, respectively. dMRI examinations of WMH typically indicate significantly increased MD and significantly decreased FA, relative to normal appearing white matter (NAWM) (Bastin et al., 2009), suggesting that WMH represent areas of increased water content and water mobility. One potential mechanism underlying these altered diffusion metrics is the development of interstitial oedema, secondary to endothelial failure, or decreased vasoreactivity (Wardlaw et al., 2015). However, these microstructural changes aren’t limited to the visible WMH; individuals with a greater burden of WMH demonstrate a similar pattern of altered water molecule diffusion (increased MD and decreased FA) throughout the NAWM more generally (Muñoz Maniega et al., 2015; see also Lee et al., 2009). These

microstructural alterations demonstrate a spatial gradient; NAWM closest to the visible WMH exhibits the greatest degree of microstructural alteration and is known as the "WMH penumbra" (Maillard et al., 2011; Muñoz Maniega et al., 2019). Together, these observations suggest that WMH are part of a continuum of white matter damage that extends beyond the visible lesion and is diffuse throughout the brain (Wardlaw et al., 2015).

WMH can be quantified using a wide range of visual rating scales. Mäntylä and colleagues (1997) identified 13 MRI-based WMH visual rating scales published between 1986 and 1994 and more have been published subsequently (Prins et al., 2004; Wahlund et al., 2001). Whereas visual ratings of WMH are relatively quick to carry out, both inter and intra-rater reliability have been found to vary (Mäntylä et al., 1997; Wardlaw, Ferguson, & Graham, 2004) and discrepancies in scoring between different scales make cross-comparison of samples difficult. Computational methods for WMH quantification are now available and are widely used, although differences in scanning parameters can also impact reliability of measurement between centres (Heinen et al., 2019).

Age is the strongest predictor of WMH burden, although estimates of the age-related prevalence of WMH vary. Among the lower estimates, the Helsinki Aging Brain Study observed WMH in 11-21% in individuals with a mean age of 64 years, and in 38-65% of those with a mean age of 83 years (Ylikoski et al., 1995). Other population-based studies such as the Cardiovascular Health Study and Rotterdam Scan Study report higher estimates, observing WMH in approximately 95% of individuals over the age of 60 (de Leeuw et al., 2001; Longstreth et al., 1996). Previously considered to be 'clinically silent', WMH are now recognised as risk factors themselves. A recent comprehensive meta-analysis by Debette and colleagues found that the presence of WMH increased the risk of incident stroke, all-cause dementia (including Alzheimer's disease (AD)) and death (Debette, Schilling, Duperron, Larsson, & Markus, 2019). WMH are also associated with cognitive decline (Kloppenborg, Nederkoorn, Geerlings, & van den Berg, 2014), depression (Direk et al., 2016), subtle neuropsychiatric symptoms (Clancy et al., 2021), impaired gait and balance (Pinter et al., 2017), and poor urinary continence (Poggesi et al., 2008; Sakakibara et al., 2012).



	White matter hyperintensity	Lacune	Perivascular space	Cerebral microbleeds
Usual diameter	variable	3 -15 mm	≤ 2mm	≤ 10 mm
Comment	located in white matter	usually have hyperintense rim	usually linear without hyperintense rim	detected on GRE seq., round or ovoid, blooming
DWI	↔	↔/(↓)	↔	↔
FLAIR	↑	↓	↓	↓
T2	↑	↑	↑	↓
T1	↔/(↓)	↓	↓	↔
T2* / GRE	↑	↔ (↓ if hemorrhage)	↔	↓↓

Figure 1: Definitions of key radiological features of SVD according to STRIVE criteria (Wardlaw et al. 2013). DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery; SWI, susceptibility-weighted imaging; GRE, gradient-recalled echo. Adapted from Wardlaw et al., Lancet Neurology, 2013; 12: 822-38, with permission from Elsevier (licence number 5010341055200, dated 15th February 2021).

1.1.2 Lacunes of presumed vascular origin

Lacunes are subcortical cavities filled with cerebrospinal fluid (CSF), round or ovoid in shape and between 3 and 15mm in diameter. Lacune-like lesions <3mm in diameter are likely to be visible perivascular spaces (PVS; see section 1.1.3), however, both lacunes and PVS can be found in areas of extensive WMH, which along with their similar appearance can lead to difficulty distinguishing between the two (Potter, Doubal, et al., 2015). Lacunes usually occur in the territory of a perforating arteriole, consistent with a previous acute small lacunar infarct (the lesion that causes most lacunar strokes), or haemorrhage that has cavitated to form a lacune (Wardlaw et al., 2013). Despite this, not all lacunes are associated with traditionally stroke-like symptoms, but can appear to be 'clinically silent' and are often found incidentally. Typically few in number, lacunes are often quantified using visual rating scales

(Benisty et al., 2009), however, computational methods have also been used to quantify their number and volume (Benjamin et al., 2014). A 2007 systematic review of cognitively healthy older-age cohorts estimated the prevalence of silent lacunes at between 8 and 28% (Vermeer, Longstreth, & Koudstaal, 2007).

1.1.3 Visible perivascular spaces (PVS)

PVS (also known as Virchow-Robin spaces) are fluid-filled spaces that surround the arteries, arterioles, and venules of the brain, following the course of the vessel from the subarachnoid space through the brain parenchyma (Wardlaw, Smith, Biessels, et al., 2013). When enlarged, PVS are visible on MRI and appear as hyperintense (on T2-weighted MRI) or hypointense (on T1-weighted MRI) lines or dots (diameter <3mm), depending on their orientation to the imaging plane. Limited spatial overlap between venules and MRI-visible PVS suggests that the majority of visible PVS could be periarteriolar (Bouvy et al., 2014; Jochems et al., 2020). Visible PVS are observed primarily in the basal ganglia or centrum semiovale and ratings of PVS in these two regions correlate positively with one another (Ballerini et al., 2020; Doubal, MacLullich, Ferguson, Dennis, & Wardlaw, 2010).

There is no clear consensus on the anatomy or physiology of perivascular spaces, however, both human and animal studies have implicated PVS in the movement and drainage of fluid, and in the clearance of waste products from the brain (Brown et al., 2018; Wardlaw et al., 2020). Safe experimental manipulation of the delicate systems responsible for fluid and metabolite transportation might not be possible in humans, therefore, much of the in-vivo experimental data exploring the pathophysiology of visible PVS in SVD comes from the study of rodents. Using particle tracking in live mice, one recent study observed that reduced vessel pulsatility (induced by increasing arterial blood pressure (BP)) reduced net CSF flow in the PVS (Mestre et al., 2018). Enlarged PVS in SVD, therefore, could partly be due to impaired drainage of interstitial fluid, secondary to reduced vessel pulsatility. Visible PVS are also associated with markers of endothelial dysfunction in humans with SVD, suggesting a key role for BBB dysfunction in their pathogenesis (Wang et al., 2016). Rodent models suggest that this association might be driven by a loss of pericytes, opening up the BBB and triggering inflammation in the PVS (Brown et al., 2018; Montagne et al., 2018).

To date, the majority of studies have quantified PVS using visual rating scales (Heier et al., 1987; Hiroki & Miyashita, 2001; Laveskog, Wang, Bronge, Wahlund, & Qiu, 2018; Patankar et al., 2005; Potter, Chappell, Morris, & Wardlaw, 2015; Rouhl, van Oostenbrugge, Knottnerus, Staals, & Lodder, 2008). More recently, however, advances in MRI acquisition and image analysis have enabled computational quantification of PVS, including their volume, length and width (Ballerini et al., 2018; González-Castro et al., 2017; Ramirez et al., 2015). Whereas small numbers of PVS might be visible in the brains of healthy younger adults, greater numbers of PVS become visible with advancing age (Francis, Ballerini, & Wardlaw, 2019). Visible PVS in the basal ganglia have been associated with increased risk of stroke, both intracerebral haemorrhage (Duperron et al., 2019) and lacunar stroke subtype (Potter, Doubal, et al., 2015), increased risk of incident dementia (Zhu et al., 2010), and increased risk of vascular death (Gutierrez et al., 2017).

1.1.4 Cerebral microbleeds

Cerebral microbleeds appear on T2*-weighted gradient-recalled echo (GRE) or susceptibility-weighted MRI sequences as round or oval hypointensities, typically, but not exclusively, 2-5mm in diameter (Wardlaw, Smith, Biessels, et al., 2013). They are usually observed in cortico-subcortical regions and in the deep grey and white matter of the cerebral hemispheres, brainstem and cerebellum. A distinction is often made between deep cerebral microbleeds (presumed mostly hypertensive) and lobar microbleeds (presumed mostly due to cerebral amyloid angiopathy), although many individuals have a mixture of both (Puy et al., 2021; Viswanathan & Greenberg, 2011). Pathologically, microbleeds most often represent hemosiderin-laden macrophages, consistent with previous micro haemorrhages (Shoamanesh, Kwok, & Benavente, 2011). Cerebral microbleeds are most commonly measured using visual rating scales (Cordonnier et al., 2009; Gregoire et al., 2009), although computational methods for their detection have been developed (Seghier et al., 2011).

Numbers of cerebral microbleeds increase with age; their prevalence is estimated to range from 5% in relatively healthy community-dwelling individuals aged 45-50 years, to 36% in those aged 80 years or older (Cordonnier, Al-Shahi Salman, & Wardlaw, 2007; Poels et al., 2010; Sveinbjornsdottir et al., 2008). As with other radiological markers of SVD, small numbers of cerebral microbleeds can be observed in healthy older adults, without apparent symptomatology. However, microbleeds also confer a two-fold increased risk of ischaemic

stroke and a three to four-fold increased risk of intracerebral haemorrhage, and all-cause mortality (Debette et al., 2019; Greenberg et al., 2009). The anatomic distribution of cerebral microbleeds appears to play a role in clinical presentations, with deep microbleeds more closely related to arteriolosclerosis and lobar microbleeds more commonly associated with cerebral amyloid angiopathy (CAA; Pasi & Cordonnier, 2020). It follows that individuals with dementia often have greater numbers of microbleeds in lobar regions, although microbleeds alone don't appear to increase the risk of incident dementia on the basis of currently available evidence (Debette et al., 2019).

1.2 The radiological burden of SVD

The abovementioned radiological markers appear to be indicative of multiple complex pathophysiological mechanisms at play, however, in the context of advancing age and increased vascular risk, they are all understood to represent vulnerability and dysfunction of the cerebral microvasculature caused by SVD. Many studies have demonstrated that WMH, PVS, lacunes and microbleeds are closely associated with one another (Ghaznawi et al., 2019; Gouw et al., 2008; Rouhl et al., 2008; Zhu et al., 2010). WMH, for example, associate positively with the burden of lacunes (Benjamin et al., 2014; Vermeer et al., 2003), visible PVS (Doubal et al., 2010) and cerebral microbleeds (Cordonnier et al., 2007). In the longitudinal Age Gene/Environment Susceptibility-Reykjavik Study (AGES-Reykjavik) participants with large PVS (>3mm) at baseline had an increased risk of incident lacunes, microbleeds, and WMH progression over a 5.2 year follow-up period (Ding, Sigurðsson, et al., 2017). Further support for the close association between MRI markers of SVD comes from a recent meta-analysis, which found that increased numbers of visible PVS were associated with the presence of lacunes and microbleeds, although they found no significant association between PVS and WMH burden (Francis et al., 2019) However, the authors of this study noted that the latter finding might not reflect the true picture, as several studies demonstrating significant positive associations between visible PVS and WMH were excluded from the meta-analysis. Lending further support to the consideration of WMH, PVS, lacunes and microbleeds as indices of a shared underlying construct, the burden of visible PVS and WMH were found to be greater in individuals with lacunar stroke (i.e. SVD-related stroke) than in individuals with cortical stroke (i.e. large artery stroke; Doubal et al., 2010; Potter, Doubal, et al., 2015). Similarly, in a large cohort of participants with a history of vascular disease (n=999; mean years of age 59±10), participants with lacunes had greater risk of deep

and confluent WMH (indicating more severe SVD pathology) than participants without lacunes (Ghaznawi et al., 2019).

Spatial relationships between radiological markers of SVD also indicate the likelihood of common, or related underlying mechanisms. WMH, for example, have been found to preferentially form around visible PVS (Wardlaw et al., 2020) and lacunes typically form at the edge of pre-existing WMH (Duering et al., 2013). The latter phenomenon was examined in a longitudinal study of 276 individuals with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), a form of SVD caused by mutations in the *NOTCH3* gene. Over a 4.5-year period, the vast majority of incident lacunes (91.3%) were found to develop at the edge of pre-existing WMH, whilst 5.8% of incident lacunes developed fully inside a WMH, and the remaining 2.9% of lacunes developed in tissue that appeared normal at baseline, but was hyperintense at follow-up (Duering et al., 2013).

It has also been demonstrated that the four MRI markers of SVD described in this chapter can, statistically at least, be combined to form a unitary construct. Owing to correlations among visual ratings of deep and periventricular WMH, visible PVS, lacunes and microbleeds, Staals and colleagues (2015) constructed a single latent variable that captures their shared variance (see Figure 2). The authors suggested that the statistical feasibility of constructing a latent variable representing total SVD burden indicates that its constituent features are jointly indicative of an underlying SVD state. The authors of this study also demonstrated clinical relevance of the SVD variable in its associations with poor general cognitive ability. The development of a latent variable representing the 'total' SVD burden by Staals and colleagues informs the empirical work presented in Chapters 5 and 6 of this thesis, where it will be discussed in greater detail.

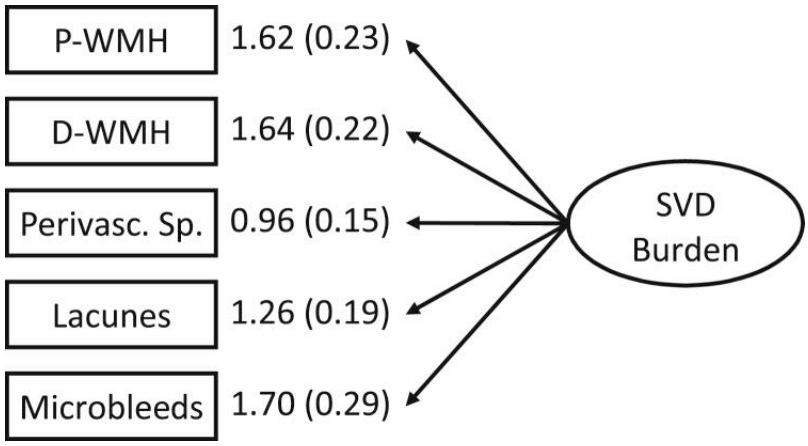


Figure 2: Illustration of the latent SVD variable constructed by Staals and colleagues (2015) using confirmatory factor analyses (CFA). Following standard structural equation modelling (SEM) conventions, variables in an ellipse are latent, therefore unobserved, and variables in boxes are observed, measured variables. Single headed arrows represent a relationship between the variables, which in this example are either linear or logistic regressions. Numbers represent unstandardised factor loadings, e.g. every 1-unit increase in the latent variable leads to an increase of approximately 1.7 microbleeds. Abbreviations: D-WMH: deep white matter hyperintensities; Perivasc. Sp: visible perivascular spaces; P-WMH: Periventricular white matter hyperintensities; SVD: cerebral small vessel disease. Reproduced from Staals et al., Neurobiology of Aging, 2015; 36(10): 2806–11, with permission from Elsevier.

1.3 Clinical consequences of SVD

In the vast majority of cases, these radiological features of SVD accumulate over time without overt clinical symptoms. A recent meta-analysis suggested that MRI-markers of SVD associate with subtle neuropsychiatric symptoms, such as increased apathy (Clancy et al., 2021), however, these symptoms are rarely noticed, thus individuals can amass a substantial radiological burden of SVD before it is detected incidentally on neuroimaging. Because of this, WMH, lacunes, visible PVS and microbleeds were once thought to be "clinically silent" (and are occasionally still described as such in the research literature). However, it is now known that SVD contributes to, and in some cases is the primary cause of, a spectrum of disorders ranging from stroke, to MCI, and multiple major dementias. SVD causes approximately 20% of all strokes, increases the risk of recurrent ischemic stroke, and associates with poorer functional outcomes post-stroke (Georgakis, Duering, Wardlaw, & Dichgans, 2019; Pasi & Cordonnier, 2020). SVD also contributes to approximately 40% of all dementias and increases the odds of developing incident dementia (van Uden et al., 2015; Zeestraten et al., 2017). Whereas stroke and dementia are often considered separately, they convey mutual risk to one another. For example, stroke doubles the chance of developing

dementia and poor cognitive performance increases the risk of stroke (Kuźma et al., 2018). Additionally, increasing evidence supports the hypothesis that stroke and dementia share underlying mechanisms (Kapasi, DeCarli, & Schneider, 2017; Sweeney et al., 2019). For example, BBB dysfunction has been identified as one of the earliest detectable mechanistic changes in the preclinical stages of dementia, occurring prior to the development and accumulation of typical AD biomarkers such as amyloid beta (Aβ) and phosphorylated tau (Montagne et al., 2015). Arterial stiffness, another pathological hallmark of SVD, has also been associated with the deposition of Aβ and its accumulation over time (Hughes et al., 2014). Vascular pathologies are now considered to contribute substantially to the cognitive deficits observed in most major forms of dementia, including AD. In 2017 the World Health Organization highlighted the prevention of stroke via the management of traditional vascular risk factors, as a means of preventing dementia (Hachinski et al., 2019). In a recent study examining carriers of the e4 variant of apolipoprotein E (*APOE e4*), the primary susceptibility gene for AD, BBB breakdown in the hippocampus and parahippocampal gyrus was associated with poorer cognitive ability independently of Aβ or tau accumulation (Montagne et al., 2020). Whereas these findings have yet to be replicated, they suggest that this gene variant might contribute to AD and its resultant cognitive decline through BBB dysfunction, rather than solely through more traditional AD biomarkers.

1.4 Key risk factors for SVD

1.4.1 Socio-demographic and lifestyle factors

Age is the primary risk factor for the development and progression of SVD. As described above, the prevalence of WMH, visible PVS, lacunes and cerebral microbleeds increase with age and are found in the majority of individuals over the age of 60. In contrast, it is unclear whether biological sex may act as a risk factor for SVD. There is some evidence that men may be at slightly greater risk of SVD than women (Gannon, Robison, Custozzo, & Zuloaga, 2019; Staals, Makin, Doubal, Dennis, & Wardlaw, 2014); however, the under-recruitment of women in stroke research may limit knowledge on this topic and the lack of sex-disaggregated reporting limits the scope of meta-analyses (Carcel et al., 2019; Jiménez-Sánchez et al., 2021). Lifestyle factors such as smoking (Hara et al., 2019; Karama et al., 2015; Power et al., 2015; Staals et al., 2014), poor diet (Gardener et al., 2012; Hankey, 2017), and high salt intake (Makin et al., 2017; Marketou et al., 2019) have been associated with MRI markers of SVD or increased SVD risk, but trials of risk-lowering interventions have

produced mixed results (Wardlaw et al., 2019). Additionally, a recent meta-analysis of early life risk factors for SVD found lower childhood socioeconomic status, lower childhood IQ, and fewer years of education to be associated with increased radiological burden of SVD (Backhouse, McHutchison, Cvoro, Shenkin, & Wardlaw, 2017), although these risk factors are related to one another and may convey interdependent effects.

1.4.2 Vascular risk factors

Common vascular risk factors (VRF) such as hypertension, hypercholesterolemia and diabetes mellitus are associated with increased brain burden of SVD and, owing to their potential for modification, have received a great deal of attention. After age, hypertension is the second most important risk factor for SVD – it has multiple profound effects on the brain's arterioles, capillaries and venules, which are thought to contribute, either directly or indirectly, to the development of the disease (Iadecola et al., 2016). In the presence of chronic hypertension, cerebral arteries undergo adaptive changes, including thickening of the vessel media and narrowing of the lumen, in order to limit stress on the arteriolar walls and smaller branches of the cerebrovascular tree (Laurent & Boutouyrie, 2015). Despite this, loss of smooth muscle cells and luminal narrowing are still detected in smaller penetrating arterioles that supply subcortical areas of the brain. Hypertension also promotes the deposition of collagen and fibrin, stiffening the cerebral vessels and reducing their pulsatile movement, and has been associated with disruption of the BBB in both humans and in animal models (Katsi et al., 2020). Although many individuals with SVD are not hypertensive (Lammie, Brannan, Slattery, & Warlow, 1997), individuals with hypertension typically demonstrate a greater burden of WMH (de Leeuw et al., 2002; Dufouil et al., 2001; van Dijk et al., 2004). High BP has also been associated with a higher 0-4 total SVD burden score, which allocates 1 point for the presence of WMH, visible PVS, lacunes, and cerebral microbleeds (Klarenbeek, van Oostenbrugge, Rouhl, Knottnerus, & Staals, 2013; Staals et al., 2014). A recent meta-analysis also found that greater variability in systolic BP was associated with increased burden of WMH across 6 studies, but not with increased burden of lacunes or microbleeds, although the amount of data contributing to the latter analyses was limited (Ma et al., 2020).

Evidence from randomised controlled trials (RCT) of BP-lowering treatments to slow the progression of SVD have produced mixed results (Wardlaw, Smith, & Dichgans, 2013).

Whereas some RCTs of BP lowering treatments have shown no significant effect on slowing the progression of WMH (Firbank et al., 2007; The SPS3 Study Group, 2013; Weber et al., 2012) or white matter damage on dMRI (Croall et al., 2017), others have demonstrated significant effects (Dufouil et al., 2005; The SPRINT-MIND Investigators for the SPRINT Research Group, 2019a; White et al., 2019, see also Wardlaw et al., 2021). In an MRI sub-study of the PROGRESS (Perindopril Protection Against Recurrent Stroke) trial, participants with cerebrovascular disease, treated with either single or dual antihypertensive treatments, demonstrated a 43% reduction in the risk of developing new WMH compared with the placebo group after a mean follow-up period of 36 months (Dufouil et al., 2005). The mean total volume of new WMH was also lower in the active treatment group, with the greatest effect observed in participants with larger WMH volumes at study entry. More recently, investigators of the SPRINT-MIND trial, a sub-study of the SPRINT (Systolic Blood Pressure Intervention) trial, found that participants with hypertension who were subject to intensive (<120mmHg) versus standard (<140mmHg) BP lowering had smaller increases in WMH volume over a median period of 3.4 years (The SPRINT-MIND Investigators for the SPRINT Research Group, 2019a). Encouraging results have also been observed in the INFINITY trial, in which patients aged 75 and over with systolic hypertension and MRI evidence of WMH were randomised to receive intensive BP treatment (24-hour mean systolic BP of ≤130mmHg), or standard treatment (≤140mmHg) with antihypertensive therapies (White et al., 2019). Results of the trial indicated that over a 3-year period, participants randomised to intensive BP treatment had smaller increases in WMH volume than those in the standard treatment group.

A recent meta-analysis of five RCTs testing the effects of BP lowering on WMH progression in cohorts with covert (i.e. non-clinical) SVD (including the SPRINT-MIND and INFINITY trials) found that overall, participant groups receiving intensive BP management demonstrated slower progression of WMH compared with controls – an effect that appears to be driven by studies comparing intensive versus standard BP lowering, as opposed to those comparing active antihypertensive treatment to placebo (Wardlaw et al., 2021). These results are similar to those of two earlier meta-analyses, which also included participants with clinical presentations of SVD (Lai et al., 2018; van Middelaar et al., 2018). Overall, therefore, there is evidence to suggest that BP lowering slows progression of SVD (indexed by radiological markers of the disease; Wardlaw et al., 2021), although it is important to recognise that

these RCTs demonstrate only modest effects in terms of slowing WMH progression, despite fairly intensive interventions and achieving substantial differences between the mean BP levels of the treatment groups.

Observational studies have also identified hyperlipidemia as a risk factor for SVD, although the relationship between higher lipids and SVD is unclear. Whereas several studies have found associations between higher lipid levels and a greater burden of SVD (Dearborn et al., 2015; Dickie et al., 2016; Gyanwali et al., 2019), others have found the opposite (Jimenez-Conde et al., 2010; Longstreth et al., 2004; Romero et al., 2014). Schilling and colleagues (2014) examined associations between lipid fractions and WMH volume and lacunes in two independent population-based cohorts, the 3C-Dijon Study (n=1,842; mean years of age 72.8±4.1) and the Epidemiology of Vascular Aging Study (EVA; n=766; mean years of age 68.9±3.0). In both cohorts, higher triglyceride levels were associated with greater WMH volume and increased frequency of extensive WMH, and with higher frequency of lacunes in the 3C-Dijon cohort only. Unexpectedly, however, greater levels of low-density lipoprotein (LDL) cholesterol were associated with lower severity and frequency of WMH in a meta-analysis of both cohorts, although these associations became non-significant after correcting for other VRFs, *APOE* genotype and inflammatory markers (Schilling, 2014). Unexpected results were also found in two independent hospital-based cohorts of patients with acute ischaemic stroke (n=631, mean years of age 64.8±15.6; and n=504, mean years of age 69.1±12.8). In both cohorts, patients with a history of hyperlipidaemia had less severe WMH at the time of stroke (Jimenez-Conde et al., 2010). However, this study did not present information on stroke subtype for either cohort and excluded participants with more severe strokes who might have had more severe WMH.

Unfortunately, evidence from RCTs on the benefits of statins for reducing the radiological burden of SVD is also mixed. In the PROSPER (Prospective Study of Pravastatin in Elderly at Risk) study, pravastatin showed no significant impact on the progression of WMH in 535 participants (mean years of age 75.0±3.0) with increased vascular risk over a mean follow-up period of 33 months (ten Dam et al., 2005). Similar results were later found in the ROCAS (Regression of Cerebral Artery Stenosis) study, which found no effect of simvastatin on WMH progression in 106 patients (mean years of age 60.1±9.5) with asymptomatic middle cerebral artery stenosis over a treatment period of two years (Mok et al., 2009). More recently

however, in the VITATOPS (VITAmins To Prevent Stroke) MRI sub-study, stroke patients with confluent WMH who took statins pre-stroke (n=51, mean years of age 73.59±7.8) had lower WMH volumes at 2 year follow-up compared with non-statin users (n=30, mean years of age 76.9±7.9), although no effect of statin use on lacunes or microbleeds was found (Xiong et al., 2014).

Although there have been some encouraging results from trials of BP and lipid lowering treatments on the reduction of SVD burden, they are countered by trials demonstrating null effects, underscoring the complex nature of the relationships between vascular risk and SVD pathology. Whereas the management of traditional VRFs is important and is generally supported by trial data, alone it appears to be insufficient to slow the progression of MRI markers of SVD. This may be unsurprising given that a latent variable of vascular risk (comprising systolic and diastolic BP, smoking status, blood HbA1C and cholesterol levels) was previously estimated to account for only 1.4 to 2% of the variance in WMH burden in a cohort of 540 relatively healthy older adults (Wardlaw et al., 2014). Although further trials are needed to explore the impact of VRF management on SVD burden, alternative drug targets such as BBB integrity, endothelial dysfunction, perivascular inflammation, are being explored, with trials ongoing (Bath & Wardlaw, 2015; Clancy et al., 2021; Wardlaw et al., 2019).

1.5 Summary

In this chapter I have described what is meant by the term cerebral small vessel disease, and have described four key radiological markers of the disease (WMH, visible PVS, lacunes, and microbleeds), both in terms of what they look like on neuroimaging and in terms of the underlying tissue changes that they are thought to represent. I also highlighted the varied (inter-related) presentations of SVD, which range from subtle changes in physical, behavioural and cognitive traits, to stroke, cognitive impairment, and dementia. In this thesis I will explore the cognitive changes associated with SVD. However, before considering the potential cognitive impact of SVD, it is important to consider how cognitive abilities are affected in the context of healthy ageing. In Chapter 2, I will discuss what cognitive abilities are (is there one cognitive ability, or are there many?), how they are assessed, and what happens to our cognitive abilities as we grow older.

Chapter 2 Cognitive ability and cognitive ageing

The overall aim of this thesis is to advance current understanding of the cognitive changes associated with sporadic SVD. However, before examining SVD-related cognitive changes, it is important to consider how cognitive abilities change in the context of 'typical' or 'healthy' cognitive ageing. In this chapter, I will briefly describe what cognitive ability is and how it is measured and structured. Finally, I will discuss what happens to our cognitive abilities as we grow older.

2.1 What is cognitive ability?

Cognitive ability is a broad term that refers to the many different mental skills used to "understand complex ideas, to adapt effectively to the environment, to learn from experience, to engage in various forms of reasoning, [and] to overcome obstacles by taking thought" (Neisser et al., 1996, p. 77). These are the kinds of mental skills that we recruit to carry out almost any task in our day-to-day lives. Multiple different terms are used to refer to cognitive ability, including cognitive function, cognition, and intelligence. Whereas these terms may convey subtle differences in meaning, they are often used interchangeably and each refer generally to the skills involved in "the selection, storage manipulation and organisation of information" (Deary & Batty, 2007, p. 378). There has been much debate over whether human cognitive ability should be considered as a singular construct, or as multiple cognitive abilities (Deary, 2001). However, it is now considered acceptable to acknowledge both a singular, overarching construct of general cognitive ability and multiple narrower abilities, which cluster into groups known as cognitive domains, as explained below.

There is no formal consensus on naming conventions, descriptions, or indeed the number of different cognitive domains that exist; a systematic review of cohort studies assessing cognitive outcomes in older adults noted 115 different cognitive domain names used in 62 cohort studies (Lara et al., 2015; Mathers et al., 2015). The following are brief descriptions of some of the most commonly-assessed cognitive domains in studies of ageing (further detail is available in Lara et al., 2015 and Mathers et al., 2015):

2.1.1 Executive function

Executive function, often called executive control or cognitive control, refers to a family of mental processes that give rise to goal-directed behaviour. Many different mental processes can be included under the umbrella of executive function, but the core features generally include inhibitory control (i.e. the ability to withhold or suppress thoughts, behaviours, or attention), working memory (i.e. the ability to hold information in mind and manipulate it), and cognitive flexibility (i.e. the ability to see things from a different perspective, either spatially or interpersonally, or to change the way one thinks about something, for example, by adapting a strategy; Diamond, 2012).

2.1.2 Processing speed

This refers to the speed at which an individual can process information. Processing speed is often measured by tasks that involve either rapid response to, or rapid exposure to intellectually simple content that places little demand upon other cognitive skills, as opposed to tasks that require careful thought or reasoning.

2.1.3 Episodic memory

Episodic memory, also referred to as declarative memory, is a broad term that refers to the ability to learn and later recall information. Episodic memory is typically described as the ability to recollect events that have previously been experienced (i.e. memories that have a specific spatial and temporal context) and is usually contrasted with semantic memory, which refers to the ability to recollect more general information about the world. Common tests of episodic memory involve learning information, such as a list of words or a story, and recalling it after a period of delay.

2.1.4 Working memory

Working memory refers to the ability to temporarily hold information in mind and manipulate it. Tests of working memory typically require the test-taker to remember a list of items before repeating it back to the examiner, often with some modification such as repeating the items in the reverse order.

2.1.5 Reasoning

Reasoning refers to the ability to think logically, to see patterns and solve problems, and is often further divided into verbal and non-verbal reasoning. Tests of reasoning might require the test taker to complete a sequence by identifying its governing rule.

2.1.6 Visuospatial ability

This is the ability to interpret and manipulate visual and spatial information. Visuospatial ability is often tested by asking the test-taker to construct or manipulate figures or patterns in two or three dimensions.

2.2 How is cognitive ability measured?

There are thousands of different cognitive tests and they take many different forms. Some cognitive tests present the test-taker with either written verbal or pictorial information, whereas others involve stimuli being read aloud to the test-taker, or might require the test-taker to interact with physical objects. Tests are available for the measurement of both general and domain-specific cognitive abilities. However, cognitive domains do not represent discrete categories of mental skill, thus a single cognitive test will likely recruit abilities from more than one cognitive domain. Therefore, to adequately assess domain-specific ability, multiple different tests of that domain should be administered (Lara et al., 2015; J. Mathers et al., 2015).

It is not possible to describe a large number of cognitive tests here, however, Table 1 presents brief descriptions of some of the cognitive tests that were administered as part of the Lothian Birth Cohort 1936 (LBC1936), a study of cognitive ageing in community-dwelling older adults, data from which are used in the analyses presented in Chapters 5 and 6 of this thesis (Deary et al., 2007). Several of the tests are sub-tests of the Wechsler Adult Intelligence Scale III (WAIS-III^{UK}; Wechsler, 1998a) or Wechsler Memory Scale-III (WMS-III^{UK}; Wechsler, 1998b), two of the most widely used test batteries in cognitive research.

	Test name	Test description	Domain assessed
WAIS -III^{UK}	Block Design	The test-taker is shown two-dimensional patterns made up of squares and triangles. They are then required to reproduce these patterns using cubes within a two-minute time limit for each design.	Constructional ability/visuospatial ability
	Matrix Reasoning	The test-taker is presented with a series of patterns, which build up in a logical manner. The test-taker is required to work out the rule governing the series in order to select one final missing pattern.	Non-verbal reasoning
	Letter-Number Sequencing	The examiner reads aloud a series of alternate letters and numbers. The test-taker is required to repeat the numbers in numerical order, followed by the letters in alphabetical order.	Working memory
	Digit Symbol Coding	Write down the number that corresponds to a given symbol and do as many as possible within two minutes.	Processing speed
	Symbol Search	The test-taker examines a row of abstract symbols to see if it contains a pair of target symbols. They indicate yes or no as quickly as possible and repeat this as many times as possible in the allocated time.	Processing speed
WMS -III^{UK}	Logical Memory I Logical Memory II	The test taker listens to a story read aloud by the examiner and is required to immediately recall as many elements as possible from the story. This happens for two stories and the second story is read twice. The test-taker is then informed that they will be asked about the stories again later. After a delay, the test-taker is asked to recall as many elements as possible from the two stories that were read to them during Logical Memory I.	Verbal declarative memory (immediate and delayed)
	Backwards Digit Span	The test-taker listens to strings of numbers read aloud by the examiner and is required to repeat the numbers in the reverse order. The number strings increase in length as the test goes on.	Working memory
	Verbal Paired Associates	The test-taker listens to a list of word pairs read aloud by the examiner. They are then given the first word of a word pair and are asked to recall its partner word. There are eight pairs of words and the list is repeated four times in different orders. There is also a delay condition in which the test-taker is again required to recall partner words after a time delay.	Verbal learning and memory (immediate and delayed)
	Spatial Span	The test-taker watches as the examiner touches a series of blocks in a spatial array. The test-taker is then required to touch the blocks in the same order as the examiner. The task becomes more difficult as more blocks are touched. The test is then repeated, with the test-taker being required to touch the blocks in the reverse order.	Non-verbal spatial learning and memory
	Inspection Time (Deary et al., 2004)	The test-taker is presented with two parallel vertical lines on a computer screen and is asked to indicate, without time pressure, which of the two was longer in length. The stimuli are presented at different durations lasting between 6 and 200 milliseconds.	Processing speed
	Simple and Four Choice Reaction Time (Deary, Der, & Ford, 2001)	The test-taker observes a screen upon which a number between 0 and 4 will appear. When the number appears, the they must press a button on an electronic console that corresponds to the same number. In the simple reaction time test, there are eight practice and 20 test trials. In the Four Choice Reaction Time test, the test taker is presented with a number from 1-4 and must press the button corresponding to the same number as quickly as possible.	Processing speed

Table 1: Names and descriptions of a selection of the cognitive tests that were administered as part of the LBC1936 (Deary et al., 2007).

2.2.1 Cognitive screening tools

Cognitive screening tools offer a brief assessment of cognitive ability and are frequently used in clinical and research settings where rapid cognitive assessment is required, or where it might be inappropriate or challenging for the test-taker to complete a lengthier cognitive test battery (e.g. due to ill health, fatigue etc.). In comparison with the more in-depth neuropsychological tests described above, cognitive screening tools provide relatively crude measures of global cognitive ability. Screening tests are commonly used to detect non-specific cognitive impairment (indicated by scores below a certain cut-off), but can be liable to ceiling effects in cognitively unimpaired samples, thus are not sensitive to variation within the typical range of cognitive performance. Popular cognitive screening tests such as the Montreal Cognitive Screening Assessment (MoCA; Nasreddine et al., 2005) or the Mini Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975) have been validated in multiple languages, facilitating cross-comparison of scores between studies and clinical centres.

2.3 The structure of cognitive ability

In neuropsychology, cognitive tests are often grouped into domains on the basis of the functions they attempt to measure, or perhaps the neuroanatomical locus of those functions, thus it is common to describe cognitive domains as If they were discrete faculties of mental ability. For example, as will be discussed in Chapter 3, SVD is often thought to selectively affect performance in the domains of executive function and processing speed, with other domains of cognitive ability remaining relatively unaffected (Peng et al., 2019; Rosenberg et al., 2016). However, in the sub-field of differential psychology, cognitive tests are typically organised on the basis of the statistical relationships between test scores, thus both the cognitive test scores and the cognitive domains into which they are grouped are considered to be inter-related. Several different theories have been proposed to explain the structure of these relationships and are briefly described below.

2.3.1 General cognitive ability

It has been described as one of the most reproduced findings in Psychology, that scores on almost all cognitive tests correlate positively with one another (Carroll, 1993; Spearman, 1904). In other words, an individual who performs well on one cognitive test is likely to also perform well on other cognitive tests. Conversely, an individual who performs poorly on one

cognitive test is likely to perform poorly across the board. This phenomenon was first noted over 100 years ago by Spearman (1904), who suggested that this "positive manifold" was due an overarching *general* factor of cognitive ability, a construct that he called "*g*". On a typical battery of cognitive tests, general cognitive ability is found to account for approximately 40% of the variability in individual cognitive test scores and approximately 60% of the variability in broader domains of ability (Carroll, 1993). General cognitive ability is also a robust construct; different measures of *g* derived from diverse cognitive test batteries have been found to correlate highly—that is, they rank individuals similarly—with correlation coefficients ranging from 0.77 to 1.0 (Johnson, Bouchard, Krueger, McGue, & Gottesman, 2004; Johnson, Nijenhuis, & Bouchard, 2008).

Measures of general cognitive ability are commonly constructed using data reduction techniques, which when applied to a set of cognitive test scores, can discover and provide individual estimates for a single variable representing *g.* One popular method of doing this is to run a principal components analysis (PCA). Using a linear combination of cognitive test scores, a PCA creates several index variables, or components, one of which (typically the first unrotated component) can be extracted and used as a measure of *g.* Of course, this would only be done if the correlation matrix and PCA's diagnostic statistics indicated the presence of a general component, as invariably occurs with cognitive test scores (Carroll, 1993). Factor analysis is another technique commonly used to estimate *g.* This can be used in an exploratory or confirmatory way (typically within a structural equation modelling (SEM) framework). Factor analysis tests whether the correlation or covariance among observed variables is due to a common, underlying latent factor or factors. As latent variables cannot be directly observed, the value of a factor is estimated based on the covariance structure of the observed data. Factor analysis, specifically confirmatory factor analysis (CFA), can also be used to test whether the existence of a hypothesised construct (in this case, general cognitive ability) is supported by the data (in this case, the covariance between cognitive test scores).

2.3.2 Carroll's Three Stratum theory of cognitive ability

Whereas all cognitive test scores tend to correlate positively with one another, certain clusters of scores correlate more strongly with one another than they do with other test scores. This observation forms the basis of Carroll's theory that narrow cognitive abilities can

be grouped into several broad cognitive domains, and that these domains can be grouped together beneath the umbrella of an overarching general factor of cognitive ability (Carroll, 1993). Carroll structured these different cognitive groupings, from the narrowest to the most general, in a three-levelled hierarchy as seen in Figure 3. At the apex of the hierarchy is *g*, representing the common variance among the broad categories or domains of cognitive ability in stratum II below. Repeating the same pattern, the broad abilities in stratum II represent the shared variance in the cognitive abilities in stratum I. The abilities in stratum I are the most narrowly defined cognitive abilities in the hierarchy, which in a factor analysis, would be represented by individual cognitive test scores.

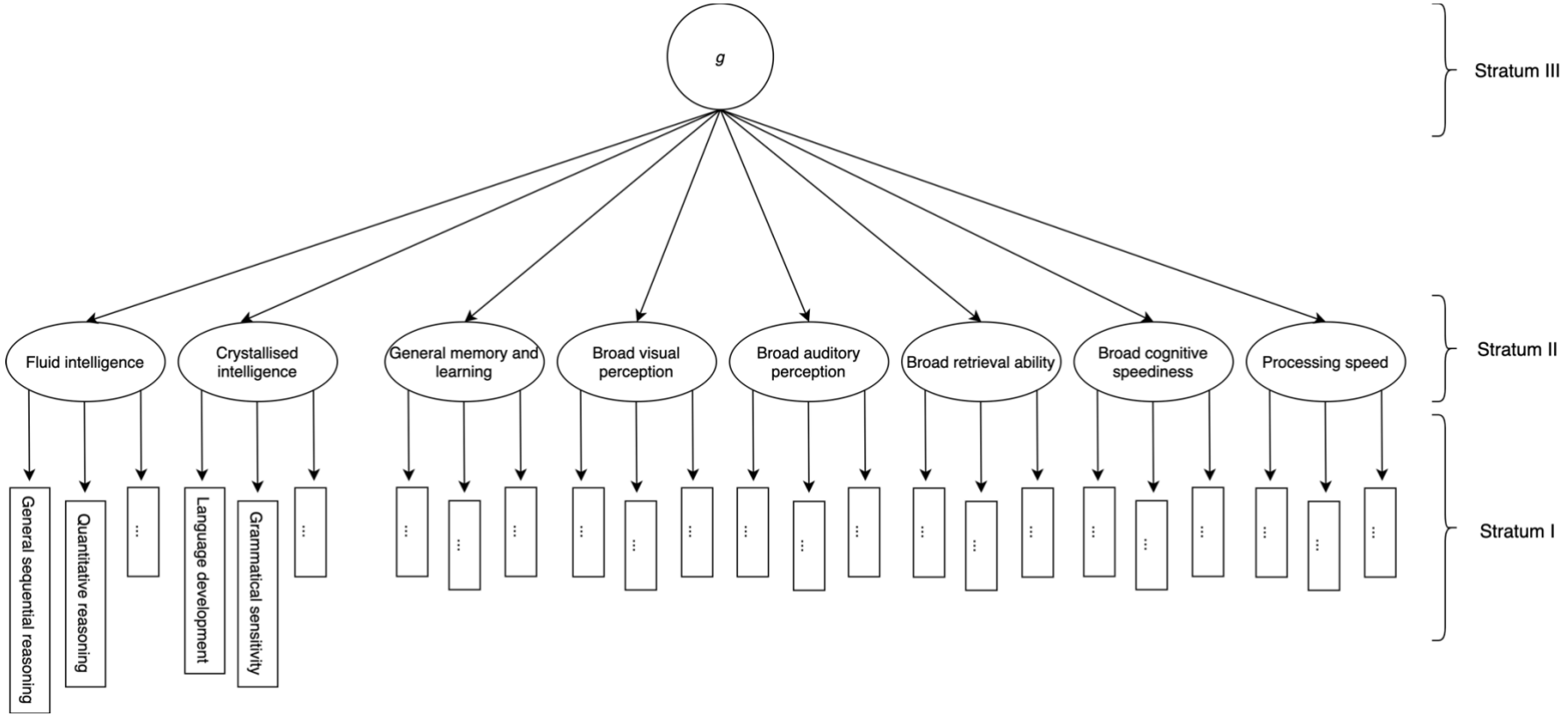


Figure 3: An illustration based on Carroll's (1993) hierarchical model of cognitive ability. At the top of the hierarchy (stratum III) is general cognitive ability, representing the shared variance among the eight broad cognitive abilities in stratum II. The broad abilities of stratum II, in turn, represent the shared variance among the narrow mental skills at the bottom of the hierarchy, some examples of which are given for fluid and crystallised intelligence.

2.3.3 Crystallised and Fluid cognitive abilities

Prior to Carroll's hierarchical model, Horn and Cattell proposed a model that distinguished between two broad categories of general cognitive ability: crystallised and fluid abilities. This model is often referred to as the G_f- G_c model. According to Horn and Cattell, fluid abilities refer to fundamental cognitive processes that involve the "ability to maintain span of immediate awareness, […] concept formation and attainment, reasoning and abstracting", thus are part of the inherent human cognitive skillset (Horn & Cattell, 1967, p. 109). On the other hand, crystallised intelligence, refers to learned knowledge that accumulates over time – it demonstrates "the extent to which one has appropriated the collective intelligence of his [sic] culture for his own use" (Horn & Cattell, 1967, p. 111). The distinction between these two constructs was driven largely by their diverging trajectories during early to mid-adulthood (Horn & Cattell, 1967), which is now known to extend into older age (this will be discussed further in section 2.4). Fluid and crystallised intelligence appear in stratum II of Carroll's cognitive hierarchy (see Figure 3), but are represented as cognitive domains as opposed to the broad, inclusive categories of cognitive ability described by Horn and Cattell.

2.3.4 The Cattell-Horn-Carroll (C-H-C) hierarchy of cognitive abilities

Today, a hybrid of these three approaches to understanding, categorising and structuring cognitive ability predominates (Spearman's theory of general intelligence, Carroll's three strata theory, and Horn and Cattell's G_f - G_c model). The model approximates Carroll's three strata model of cognitive ability, but with some modification to the number and interpretation of some strata II abilities, although the model is to some extent *dynamic* as it continues to be modified with new research (McGrew, 2005). One major difference between Carroll's original hierarchical model and the C-H-C model is that there is less emphasis on *g* in the C-H-C; whilst *g* is included in the model, its role is ambiguous and it can be omitted by the model user if desired (Benson, Beaujean, McGill, & Dombrowski, 2018).

Whereas the C-H-C structure of cognitive abilities is widely accepted, it is important to mention that there are several critics of *g* who suggest that the different domains of cognitive ability are, in fact, independent of one another (for a brief review, see Box 2 in Deary, Penke, & Johnson, 2010). However, it is difficult, if not impossible, to ignore the wealth of statistical evidence for shared variance across diverse batteries of cognitive test

scores (Carroll, 1993) and for the robust nature of different measures of *g*, thus these opposing theories have not been widely taken up (see Deary, 2012, p. 457).

2.4 Cognitive ageing

Cognitive ability is a dynamic construct. Much like MR images of SVD's key radiological markers, cognitive test scores provide a static snapshot of an ongoing process. For individuals in their mid-twenties and older, this process is one of cognitive ageing (Salthouse, 2010a). Examining age-related changes in domain-specific cognitive test scores reveals two broadly distinct trajectories. The first trajectory belongs to a group of abilities that typically peak in the early twenties or thirties and decline into later life. These are more fluid-type abilities, which Horn and Cattell regarded as part of our inherent cognitive skillset. Fluid abilities include those that often involve effortful processing at the time of assessment, such as processing speed, reasoning, visuospatial ability and episodic memory. In contrast, the trajectory of more crystallised abilities increases gradually until the mid-sixties and demonstrates a shallower slope of decline much later on. In contrast to fluid abilities, crystallised abilities rely on learned knowledge and experience, such as mathematical and vocabulary knowledge. These diverging trajectories are illustrated in Figure 4, which shows cross-sectional data from groups of people at different ages on measures of domain-specific cognitive abilities. It should be noted, however, that most cognitive tests are probably a mix of fluid and crystallised skills with the balance of these being more or less biased to one or the other (Craik & Bialystok, 2006).

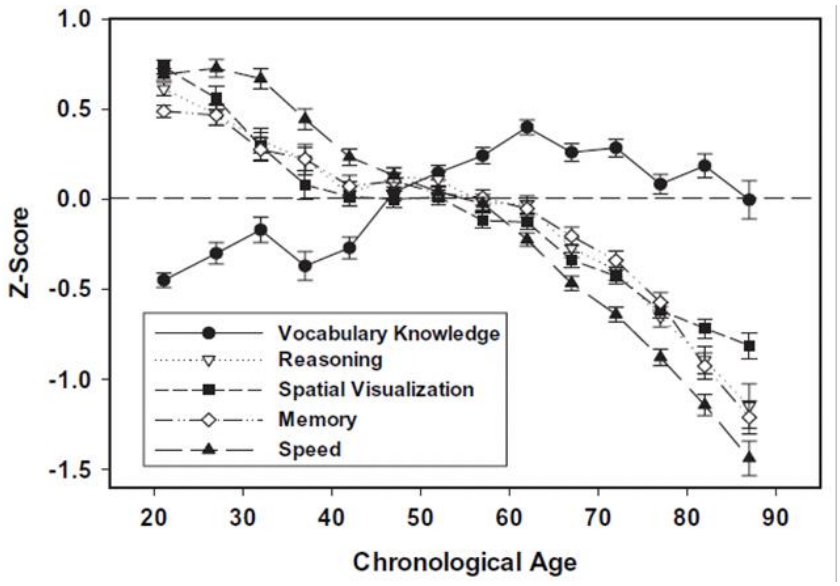


Figure 4: Mean age-related trends in domain specific cognitive abilities. Data are from multiple studies by Salthouse and colleagues (2009) using the WAIS-IV (Wechsler, 2009a) and the WMS-IV (Wechsler, 2009b). Sample sizes range from 2369 to 4149; whiskers show standard errors. Reproduced from Salthouse, Journal of the International Neuropsychological Society, 2010; 16(5): 754–60, with permission from Cambridge University Press.

In Figure 4, vocabulary knowledge (a measure of mostly crystallised ability) has a clear upward trajectory. It peaks around the age of 60 before exhibiting a fairly shallow decline over the following years. The other abilities (more fluid abilities) peak much earlier in the mid-twenties or so, and show a marked decline from the thirties onwards. Longitudinal studies of cognitive ageing that test the same groups of individuals repeatedly over time, show similar results after accounting for practice effects, cohort attrition, and cohort effects (Rönnlund & Nilsson, 2006; Salthouse, 2010b).

There is some variation in the rate of decline in fluid cognitive abilities; for example, in Figure 4 processing speed appears to have a steeper rate of decline compared with visuospatial ability (or "spatial visualisation" as it is described in the figure). However, just as a positive manifold has been observed in the correlational structure of cross-sectional cognitive test scores, a positive manifold exists among rates of age-related change in cognitive test scores (Tucker-Drob, Brandmaier, & Lindenberger, 2019). In other words, an individual who shows a steep decline over time in their performance on a given cognitive test is likely to show steep declines in their performance on other cognitive tests too. It is important to appreciate that this was determined on longitudinal data whereas Figure 4 is based on cross-sectional data.

In a recent meta-analysis of 22 longitudinal datasets comprising of over 30,000 individuals, it was estimated that an average of 60% of the variation in cognitive decline was shared across cognitive abilities, thus was attributable to an overall change in general cognitive ability (Tucker-Drob et al., 2019). Results of the meta-analysis also showed that the influence of general cognitive ability was stronger in older ages, accounting for approximately 45% of the variance in domain-specific cognitive changes at the age of 45, and approximately 70% of variance at the age of 85. It appears, therefore, that advancing age (in adulthood) has a relatively small effect on individual domains of cognitive ability and instead mainly affects general cognitive ability (Salthouse, 2016).

2.5 The stability of individual differences in cognitive ageing

In cognitive ageing, one can examine two types of stability: one type is the stability of mean levels of cognitive abilities over time (as discussed above), but a second type is the stability of individual differences. Whereas all individuals will experience some cognitive decline over the course of their lives, people vary in the amount of decline they experience. This means that if individuals were to be ranked in order of their cognitive performance in early life, the rank order for each individual would change somewhat if their cognitive performance were to be measured and ranked again in later life. In order to investigate stability in individual differences in cognitive ageing, one requires cognitive test scores from the same individuals in childhood and old age, preferably from the same cognitive test at both timepoints. There are several research cohorts in Scotland with such datasets, owing to the fact that on two occasions, in 1932 and 1947, the Scottish Council for Research in Education carried out nation-wide cognitive testing of schoolchildren aged 11 years old (Scottish Council for Research in Education, 1933, 1949). The Lothian Birth Cohort studies of 1921 (LBC1921; Deary, Whiteman, Starr, Whalley, & Fox, 2004) and 1936 (Taylor, Pattie, & Deary, 2018) were established as follow-up studies to the Scottish Mental Surveys of 1932 and 1947, respectively. Over 60 years after the original surveys, individuals who had taken part were invited to join the Lothian Birth Cohorts and recruited participants were tested on the same cognitive test that they had undertaken in childhood, thus providing a rare comparison of cognitive ability in childhood and later life. Figure 5 depicts the lifetime stability in individual differences in cognitive ageing, using data from the LBC1921. Along the x-axis are participants' scores on the Moray House Test number 12 (MHT), a test of general cognitive ability, measured the age of 11 and along the y-axis are scores from the same test measured

at the age of 80. If individual differences in MHT scores were 100% stable (i.e. the same in childhood as in older age), the data points in Figure 5 would fall along the red line, which has been added to the figure post-hoc for illustrative purposes. However, this is not the case; the data points in Figure 5 are distributed about the red line, indicating some degree of instability in intelligence differences across the life course. Indeed, analyses from the LBC1921 and from other longitudinal studies with available childhood cognitive data, have estimated that levels of childhood cognitive ability account for approximately 50% of the individual differences in the level of cognitive ability at the age of 70 (Deary, 2014). Whereas some of the remaining variance in cognitive change will be due to measurement error, the remaining 50% (or so) of peoples' differences in cognitive ability in older age is presumably due to factors that influence the rate of age-related cognitive decline. These outstanding factors are likely to be exposures that are either protective of, or detrimental to, cognitive ability in later life, and identifying them is the focus of many longitudinal studies of cognitive ageing.

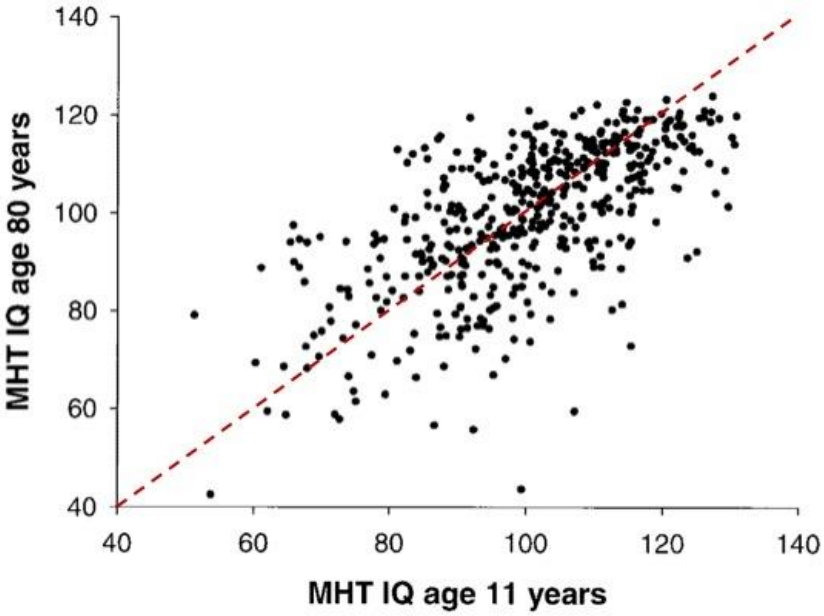


Figure 5: Scatterplot comparing LBC1921 participants' age-corrected Moray House Test scores (converted to IQ units) at age 11 and age 80. Adapted from Deary et al. *Journal of Personality and Social Psychology,* 2004; 86(1): 130-47, with permission from the American Psychological Association (licence number 5027180296823, dated 13th March 2021).

So far, a multitude of risk and protective factors for cognitive ageing have been proposed, ranging from genetic contributions to lifestyle and socio-demographic factors (Salthouse, 2014). A comprehensive meta-analysis of 127 observational studies, 22 randomised controlled trials, and 16 systematic reviews, found current tobacco use, diabetes mellitus, and possession of the *APOE* e4 allele to be associated with greater rates of cognitive decline, and identified physical exercise as a potentially protective factor (Plassman, Williams, Burke, Holsinger, & Benjamin, 2010). After adjusting for the confounds of childhood cognitive ability, analyses of LBC1936 data have produced similar findings, highlighting the protective effects of physical fitness and exercise on rates of cognitive decline (Gow, Pattie, & Deary, 2017; Ritchie et al., 2016), and the detrimental effects of smoking (Janie Corley, Gow, Starr, & Deary, 2012) and possession of *APOE e4* (Ritchie et al., 2016). Overall, few clear determinants of cognitive change have been identified, however, it is likely that rates of cognitive decline depend on many different factors that each account for only a small proportion of the variance in cognitive changes (Corley, Cox, & Deary, 2018).

2.6 Summary

In this chapter, I have described what is meant by the term cognitive ability, how cognitive ability is measured and how cognitive test scores can be grouped into different cognitive domains. I described how general cognitive ability, or *g*, accounts for a large proportion of variance in cognitive test scores and how this observation has informed theories on the structure of cognitive ability. I also described the importance of general cognitive ability in the process of healthy cognitive ageing, as it accounts for the majority of variance in the decline of domain-specific abilities. Finally, I highlighted the importance in identifying the predictors of individual differences in cognitive ageing and the importance of accounting for childhood cognitive ability in analyses aiming to do so.

Although there is currently no accepted definition of what constitutes 'normal' versus 'pathological' cognitive aging, the data discussed in this chapter are mainly from healthy, community-dwelling populations, thus the process of cognitive ageing described reflects that which is typically experienced in the absence of overt neurological disease. However, longitudinal population-based or community-based studies typically include some individuals who experience more notable cognitive decline owing to underlying pathologies such as mild stroke or early-stage dementia, which may steepen the average cognitive trajectory of the

whole study group. It is difficult, therefore, to draw comparisons between estimated rates of typical age-related cognitive decline and those of groups with neurological conditions or neurodegenerative disease. As SVD pathology is present across a broad spectrum of clinical and non-clinical presentations, estimating how SVD might 'alter' the typical trajectory of age-related cognitive decline is particularly challenging. One way to approach this is to examine associations between biomarkers of SVD and cognitive changes – this will be the focus of Chapter 3. I will explore the research literature examining associations between MRI markers of SVD, which were introduced in Chapter 1, and both cross-sectional levels of cognitive abilities and decline in cognitive abilities over time. Understanding the structure of cognitive ability, the process of healthy cognitive ageing, and the potential confounds surrounding the prediction of later-life cognitive ability, will be important for the interpretation of this research and will inform the analyses that follow in Chapters 4, 5, and 6.

Chapter 3 Cognitive ability and SVD

In this final introductory chapter, I will consider the current consensus on the pattern of cognitive impairments associated with sporadic SVD, and will review some of the literature underpinning this consensus. To date, the majority of the literature examining cognitive impairments in SVD has focused on associations between individual radiological markers of the disease and cognitive performance. In this chapter, I will examine this literature, in addition to some more recent studies which test associations between a 'total SVD burden' score and cognitive outcomes. The majority of studies discussed herein use data from population-based or community-based cohorts, therefore individuals with non-clinical presentations of SVD are somewhat over represented. In contrast, the systematic review and meta-analysis presented in the Chapter 4 does not pre-select literature based on a certain lesion type, so provides a more in-depth examination of cognitive impairment in different clinical and non-clinical presentations of SVD.

3.1 The current consensus on SVD-related cognitive impairments

Recent consensus statements on the identification and management of SVD in clinical practice, suggest that SVD primarily associates with poorer performance on cognitive tests in the domains of processing speed and executive function, but that memory and language abilities remain relatively well preserved (Peng et al., 2019; Rosenberg et al., 2016). As a brief reminder, processing speed refers to the speed at which a person can understand and respond to information (often tested using the speed of responses to simple decisions), and executive function encompasses skills such as planning, organization, and switching attention, which enable goal-directed behaviours (Lara et al., 2015; Mathers et al., 2015). This profile of SVD-related cognitive impairments is frequently reported in the research literature, but the studies underpinning this suggestion are conflicting and require careful consideration. First, many of the studies examining SVD-related cognitive impairments have small participant samples, so could be insufficiently powered to detect cognitive deficits. Second, many of these studies focus on narrowly defined subtypes of SVD (i.e. genetic SVDs such as CADASIL), or on individuals with a high disease burden who may not represent the full spectrum of sporadic SVD. It could also be the case that some studies may be influenced by expectations of the cognitive impairments they will observe. Based on the 'understanding' that SVD causes deficits in executive function and processing speed,

researchers might neglect to test for impairments in other domains of ability such as memory or language, which are more typically associated with dementia. Thus, no evidence of SVD's association with these cognitive domains could arise because the association has largely not been tested.

3.2 Associations between individual radiological markers of SVD and cognitive abilities

3.2.1 White matter hyperintensities and cognitive abilities

WMH are the most commonly investigated radiological marker of SVD. There have been several large-scale meta-analyses examining the associations between WMH burden and impairment or decline in different domains of cognitive ability, and between WMH and risk of adverse clinical outcomes including incident stroke, dementias, and death (Debette et al., 2019; Hu et al., 2021; Kloppenborg et al., 2014). Evidence supporting associations between greater WMH burden and poorer cognitive abilities has been comprehensively summarised in a meta-analysis by Kloppenborg and colleagues (2014). In 23 cross-sectional studies of healthy older individuals without cognitive impairment or dementia (n=8685), greater prevalence and severity of WMH was associated with poorer performance on tests of memory, processing speed, executive function (including attention), visuospatial ability, and language (Kloppenborg et al., 2014). Pooled estimated effect sizes for the cognitive domain scores ranged from *r*=-0.08 to *r*=-0.15, with the overall effect for the association between WMH and cognitive ability across all domains estimated at *r*=-0.10; (95%CI -0.08 to -0.13). In a more limited dataset of only six longitudinal studies, Kloppenborg and colleagues found that WMH prevalence or severity was also associated with greater *decline* in all cognitive domains over time periods that varied between 1 and 10 years, with the exception of visuospatial ability and language, which were not included in the meta-analysis owing to a lack of available data. Effect sizes for the associations between WMH burden and decline in individual cognitive domains ranged between -0.04 and -0.32 and the overall pooled estimated effect size was *r*= -0.10 (95%CI -0.05 to -0.13; 6 studies, n=3834; Kloppenborg et al., 2014). The results of Kloppenborg's meta-analyses suggest that increasing incidence and severity of WMH are associated with poorer cognitive abilities, both cross-sectionally and longitudinally. Overall, effect sizes were small (Funder & Ozer, 2019), but this is perhaps unsurprising considering the study included only relatively-healthy older adults without

cognitive impairment or dementia, rather than clinical samples with more established cognitive symptoms.

Interestingly, Kloppenborg and colleagues noted a dearth of literature examining associations between WMH and performance on tests of visuospatial ability (assessed in only 16% of included studies) or language (5% of studies) and were unable to conduct meta-analyses of test scores in these domains. In contrast, 73% of included studies carried out tests that are thought to assess executive function. It could be the case that there are additional studies that have found mostly null associations between WMH and visuospatial and language abilities, but that due to publication bias these results remain unpublished. However, it could also be the case that these domains are not tested in SVD samples owing to their perceived lack of importance in relation to cerebrovascular disease, or because common practice is less likely to include such tests in cognitive test batteries.

Kloppenborg's meta-analyses (2014) tested the associations between WMH burden and cognitive abilities in the absence of clinically identified cognitive impairment or dementia, thus their results likely reflect the insidious, sub-clinical cognitive changes associated with mild SVD. However, it is possible that the trajectories of these SVD-related cognitive changes will result in overt cognitive impairment for some of the individuals in these initially-healthy samples. In a recent meta-analysis of a minimum of 9,338 participants from 12 studies, WMH were associated with an increased risk of incident stroke (hazard ratios (HR) ranged from 2.5 (95%CI 1.7-3.5) to 3.2 (95% CI 1.5-6.5)), dementia (HR 1.8; 95%CI 1.4-2.4), AD (HR 1.5; 1.2-1.8), and death (HR 2.0; 95%CI 1.7-2.4; Debette et al., 2019). These associations were mostly found in the general population as well as in populations at higher risk of vascular disease and dementia. Additionally, in a recent meta-analysis of 104 studies of individuals who had already experienced ischaemic stroke, moderate to severe WMH at baseline was associated with a substantially increased risk of cognitive impairment (relative risk 2.29, 95%CI 1.5-3.5) and dementia (RR 2.17; 1.7-2.7; Georgakis et al., 2019). Overall, there is general consensus that WMH associate with impairments across a range of cognitive domains in non-clinical presentations of SVD (although evidence supporting WMH-related deficits in visuospatial and language abilities is limited), but that WMH also confer greater risk of clinical SVD presentations such as stroke and dementia.

3.2.2 Lacunes and cognitive abilities

The literature examining cross-sectional associations between lacunes and cognitive abilities in SVD is fairly extensive, focusing additionally on the potential role of lacune location in determining cognitive outcomes. Unless specifically referring to a study including individuals with lacunar stroke (e.g. St. George's (SCANS) study), the studies discussed in this section examine associations between primarily asymptomatic or 'silent' lacunes observed incidentally on neuroimaging (as opposed to symptomatic lacunar infarcts) and cognitive abilities. As lacunes are less prevalent than WMH or PVS, where possible, I will detail the proportion of participants in each study who had lacunes on neuroimaging.

Several large population-based studies have examined cross-sectional associations between lacunes and performance on cognitive tests. In the Rotterdam Scan study (n=1015, mean age: 72.1±7; 21% with lacunes), the Cardiovascular Health study (n=3660; minimum age 65; 23% with lacunes), and the Memory and Morbidity in Augsburg study (MEMO; n=268; age range 65-83; 16% with lacunes), participants with lacunes on neuroimaging demonstrated poorer performance on tests of general cognitive ability (Rotterdam Scan and CHS), processing speed (CHS and MEMO), and memory (MEMO only) than participants with no evidence of lacunes (Baune, Roesler, Knecht, & Berger, 2009; Longstreth et al., 1998; Vermeer et al., 2003). Negative associations have also been found between the number and/or volume of lacunes and performance on tests of executive function in healthy community-dwelling older individuals (standardised ß range: -0.22 to -0.26; Carey et al., 2008; Koga et al., 2009) and in individuals with lacunar stroke and confluent WMH (Benjamin et al., 2014). Countering these findings, however, are several studies that find no associations between lacunes and cognitive test performance (Nitkunan, Barrick, Charlton, Clark, & Markus, 2008), or in which associations between lacunes and cognitive measures attenuated to non-significance after accounting for age (prior to adjustment, unstandardised ß -3.5; SE 1.4; van de Pol et al., 2007), or WMH volume (prior to adjustment standardised ß ranged from -0.16 to -0.26; Mungas et al., 2001). Despite the latter result reported by Mungas et al. (2001), lacunes have been found to associate with impaired cognitive performance independently of WMH (standardised ß ranged from -0.22 to -0.25; Benisty et al., 2009; Carey et al., 2008). Two separate studies using data from the Leukoaraiosis and Disability Study (LADIS; n=387, mean age 73.1±5; 48% with lacunes; Jokinen et al., 2011) and the MEMO study (n=268; age range 65-83; 16% with lacunes;

Baune et al., 2009) found that measures of lacunes and WMH were negatively associated with cognitive outcomes in the same statistical model (standardised ß: lacunes -0.08, WMH -0.09; Jokinen et al., 2011). Upon entering an interaction term into the model (lacunes x WMH), there was no significant interaction between the two markers, suggesting that any effects of lacunes and WMH on cognitive performance are additive rather than synergistic (Baune et al., 2009; Jokinen et al., 2011).

The anatomical location of lacunes has been highlighted as an important factor in determining domain-specific cognitive impairments in SVD. In LADIS participants (n=387, mean age 73.1±5; 47.8% with lacunes), and in individuals with symptomatic lacunar stroke from the SCANS study (n=120; mean age 70±10), lacunes in the deep grey matter only (basal ganglia and thalamus) were associated with slowed processing speed and executive function (standardised ß ranged from -0.19 to -0.25; Benisty et al., 2009; Benjamin et al., 2014). Additionally, in individuals with subcortical vascular cognitive impairment and dementia (n=136; mean age 73.8±7; 90% with lacunes), a greater number of lacunes in the frontal regions of the brain was associated with poorer performance on tests of memory and executive function (unstandardised ß (SE) ranged from -0.033 (0.01) to -0.008 (0.002); Park et al., 2014). Taken together, results from these studies support the notion that lacunes are more commonly associated with deficits in executive function due to their disruption of the cortical-subcortical white matter tracts that subserve these cognitive abilities (O'Sullivan et al., 2004). It has also been suggested that, in contrast, WMH are associated with a broader range of cognitive impairments owing to their diffuse distribution throughout many regions of the brain (Koga et al., 2009). There is appeal in the idea that visually discrete lacunes and diffuse WMH might exert differential effects on cognitive abilities - it fits with much of the available evidence (Biesbroek, Weaver & Biessels, 2017). However, little is known about whether or not lacunes associate with deficits in cognitive domains other than processing speed and executive function as these associations have rarely been tested; only one of the cross-sectional studies reported here included tests of language (Mungas et al., 2001) and none examined visuospatial ability, reasoning, or any major domains of cognitive ability other than executive function, processing speed and memory.

Whereas cross-sectional studies have emphasised the potential role of lesion location in the association with cognitive outcomes, results of longitudinal studies have emphasised the

importance of lesion burden and increasing lesion burden over time. A greater number of lacunes at baseline was associated with greater decline in general cognitive ability and executive function over five years in individuals with symptomatic lacunar stroke (Benjamin et al., 2018), and with greater decline in general cognitive ability, processing speed and memory over an average of four years in participants from the Rotterdam Scan study (n=739; age range 60-90 years; Vermeer et al., 2003), both independently of WMH volume (standardised estimates ranged from -0.01 to -0.19). When participants in the latter study were divided into groups according to the presence or absence of lacunes on baseline and follow-up MRI, significant cognitive decline was observed only in participants who developed incident lacunes during the study period, regardless whether then had lacunes at baseline (Vermeer et al., 2003). In other words, new lacunes appeared to be an important driver in the progression of cognitive decline in the Rotterdam Scan cohort. Likewise, in LADIS participants the development of new lacunes paralleled a steeper rate of decline in executive function and processing speed, independently of WMH volume increases (standardised ß -0.08; Jokinen et al., 2011). Finally, in a mixed cohort of healthy older individuals and individuals with MCI, or dementia (n=103; age range 56-87 years), greater baseline lacunar volume as well as greater increase in lacunar volume over the study period were associated with greater decline in executive function over three years, independently of cortical grey matter and hippocampal volume (unstandardised ß (SE) -2.66 (0.83) and -2.97 (1.08); Mungas et al., 2005). The effect size of this association increased after the exclusion of participants with dementia, suggesting that these associations were not confounded by the progression of dementia pathology.

Overall, findings from both cross-sectional and longitudinal studies appear to support associations between greater lacune burden and poorer performance on tests of executive function and processing speed. Negative associations between lacune burden and poorer memory abilities have been less consistent. Alongside the baseline burden of lacunes, increasing lacune burden appears to predict the severity of cognitive decline independently of WMH volume and increasing dementia pathologies. In a recent meta-analysis by Debette and colleagues (2019), asymptomatic lacunes were only associated with increased risk of incident dementia prior to correction for multiple testing, although the authors noted that this could be due to relatively low numbers of lacunes in the included samples.

3.2.3 Visible perivascular spaces and cognitive abilities

The relatively small amount of literature reporting cross-sectional associations between visible PVS and cognitive abilities has been summarised by two recent meta-analyses (Francis et al., 2019; Hilal et al., 2018). First, in five population-based studies of older adults without dementia (total n=3575; mean ages ranged between 63.4 and 73.2 years), no significant associations were observed between total visible PVS count or the burden of PVS in specific brain regions, and measures of general cognitive ability (Hilal et al., 2018). Similarly, in the second meta-analysis on this topic, which included only three studies (Francis et al., 2019), no significant associations were observed between visually-rated PVS in the basal ganglia and cognitive test scores in hypertensive individuals (two studies; n=109, mean age: 56.1±12; and n=659, mean age: 62.8±5.3), or in adults with ischaemic stroke or transient ischaemic attack (TIA; one study, n=430, mean age: 64.7±13). However, two small cross-sectional studies which were not included in either of these meta-analyses have reported opposing results. In a mixed cohort of cognitively healthy individuals and individuals with MCI or AD (n=50, n=70 and n=31 respectively; overall mean age: 74.9±7), visually-rated PVS score was negatively associated with scores on the MMSE (*r*=-0.21; Chen, Song, & Zhang, 2011). In a study of 97 healthy male volunteers (mean age: 67.8, range 65-70), higher visually-rated PVS scores in both the centrum semiovale and basal ganglia were associated with poorer performance on tests of visuospatial ability and non-verbal reasoning (r_s= -0.22 and -0.21; MacLullich et al., 2004). In both of these studies, measures of PVS were associated with WMH ratings (correlations between 0.48 and 0.55), but neither study accounted for WMH burden in associations between PVS and cognitive outcomes, thus their findings could be due to confounding by WMH-cognitive associations.

Four longitudinal studies have tested associations between visible PVS and cognitive *decline,* again producing mixed results. In 120 individuals with ischaemic stroke and confluent WMH from the SCANS study (mean age 70.0±10), neither visually-rated PVS scores nor PVS volume were related to changes in cognitive measures over a five-year period (Benjamin et al., 2018). Similarly, analyses of the population-based Three-City Dijon study (n=1778; mean age: 72.4±4) found no associations between visible PVS and cognitive outcomes in the full study sample, however, when examining only participants with severe visible PVS in the basal ganglia, PVS burden was associated with greater decline in processing speed, after accounting for WMH and lacunes (standardised ß -0.15; Zhu et al., 2010). In contrast, in the

population-based AGES-Reykjavik Study (n=2612, mean age: 74.6±5) greater numbers of large visible PVS (>3mm) in the basal ganglia and centrum semiovale were associated with a greater decline in processing speed between baseline and five-year follow-up, independently of vascular risk, symptomatic stroke, and *APOE* e4 allele carriership (unstandardised ß -0.02, 95% CI -0.01 to 0.00), although no such associations were found for change in executive function or memory abilities (Ding et al., 2017). Finally, in the population-based Sydney Memory and Ageing Study (n=414; age range 79.8±5), participants with severe PVS pathology in the centrum semiovale and basal ganglia had greater decline than participants with less severe PVS burden in general cognitive ability, but not in any cognitive domain scores over four years (Paradise et al., 2021). This association in the severe PVS group remained significant after correction for demographic differences, *APOE* e4 carrier status, vascular risk, WMH volume and the presence of lacunes and microbleeds (standardised ß -0.18).

Although the precise temporal development SVD pathology is unknown, it has been suggested that visible PVS could occur relatively early on in the disease process (Deramecourt et al., 2012). If this is the case, then any contribution of visible PVS to cognitive impairment or cognitive decline might be more easily detected in healthier populations who have yet to develop extensive SVD pathology. As SVD progresses, any associations between visible PVS and cognitive abilities could become masked by other radiological markers of SVD. If this were true it could explain why significant PVS-cognitive associations have mostly been observed in cohorts of relatively healthy older individuals (Ding et al., 2017; MacLullich et al., 2004; Paradise et al., 2021).

Overall, the literature examining associations between visible PVS and cognitive abilities has produced mixed results; it is unclear whether or not the burden of visible PVS is associated with poorer cognitive test scores cross-sectionally, or with declining cognitive abilities over time. Mixed results have also been found regarding the relationship between PVS and poorer clinical outcomes, with some but not all studies finding associations between greater PVS burden and increased risk of stroke, dementia and vascular death (Debette et al., 2019; Paradise et al., 2021). The conflicting findings discussed here might be attributable to the different visual rating scales used to quantify PVS, or due to difficulties in identifying PVS, which can be obscured by extensive WMH, or can have a similar appearance to lacunes

(Potter, Doubal, et al., 2015). As computational methods for quantifying PVS become more widely used, a clearer consensus may emerge on whether PVS are negatively associated with cognitive test scores, and if so, whether PVS are a proxy of SVD damage more generally, or confer risk in and of themselves.

3.2.4 Cerebral microbleeds and cognitive abilities

There have been several meta-analyses examining associations between cerebral microbleeds and cognitive abilities in recent years (Lei et al., 2013; Li et al., 2017; Wu et al., 2014). The results of these three meta-analyses concur that individuals with cerebral microbleeds typically score more poorly on tests of cognitive ability relative to controls. However, due to inconsistencies in the methods used to quantify microbleeds (i.e. raw microbleed count vs. categories of microbleed burden; microbleeds counted in the whole brain vs. specific brain regions), many studies were excluded from the meta-analyses, therefore, they summarise only a small amount of the available literature. Additionally, as the majority of studies included in these meta-analyses measure cognitive ability using cognitive screening tests (e.g. MMSE, MoCA), they offer little insight into associations between microbleeds and domain-specific cognitive impairments.

Multiple studies have examined cross-sectional associations between cerebral microbleeds and performance on in-depth cognitive tests, in cohorts with varying presentations of SVD. In two separate studies of individuals with suspected stroke or TIA (n=55, mean age: ~67, 45% with microbleeds; Werring et al., 2004; and n=329, mean age: ~65, 23% with microbleeds; Gregoire et al., 2013), executive dysfunction was more prevalent in patients with microbleeds, than it was in patients without microbleeds (60% vs. 30%; and 38% vs. 25%). In the former study, greater executive impairment was found in patients with microbleeds in the basal ganglia (Werring et al., 2004), whereas the main effect in the latter study was mostly driven by lobar microbleeds (Gregoire et al., 2013). As was found in studies examining region specific lacune burden, these results suggest that microbleeds associate with executive dysfunction potentially via disruption of frontal-subcortical circuits (Martinez-Ramirez, Greenberg, & Viswanathan, 2014). However, associations between microbleeds and a wider range of cognitive domains have been observed in data from healthy older individuals and those with increased vascular risk (Chung et al., 2016; van Es et al., 2011; Zhang et al., 2018). In the PROSPER study (n=439, mean age 77.0±3, 24% with microbleeds)

individuals with infratentorial microbleeds, and in the l-Lan longitudinal ageing study (n=959, mean age 62.5±9, 14% with microbleeds) individuals with lobar microbleeds demonstrated poorer performance on tests of memory and visuospatial ability than participants with no microbleeds at all, or without microbleeds in lobar regions, independently of WMH volume (Chung et al., 2018; van Es et al., 2011). Multi-domain cognitive impairments have also been found in relation to microbleeds in cohorts with dementia (Goos et al., 2009; Seo et al., 2007). In the first of these studies, in participants with subcortical VaD (n=86), a greater number of microbleeds was associated with poorer performance on tests of attention, verbal memory, visual memory, language, visuospatial ability and executive function, after correction for age, education, ischaemic severity and number of lacunes (Seo et al., 2007). Similar results were found in a subsequent study examining participants with AD and microbleeds (n=21) versus those without microbleeds (n=42) (Goos et al., 2009).

Several large population-based studies have examined associations between cerebral microbleeds and decline in cognitive abilities over time (Akoudad et al., 2016; Ding et al., 2017; Li et al., 2020; Meier et al., 2014). In the AGES-Reykjavik study, both the presence and severity of microbleeds were associated with greater decline in composite scores of general cognitive ability, processing speed, executive function, and verbal memory over five years (standardised ß ranged from -0.31 to -0.34; Ding et al., 2017). In the population-based Rotterdam Scan Study (n=3257, mean age 59.6±8, 15% with microbleeds), participants with >4 microbleeds performed worse than those without microbleeds on tests across multiple cognitive domains (mean difference in z-scores ranged from -0.6 to -0.1; Akoudad et al., 2016). In 197 dementia-free participants of the community-based Northern Manhattan study (mean age: 84.2±5, 27% with microbleeds), participants with >2 lobar microbleeds (n=11) had significantly greater decline in executive function (standardised ß –0.072), although this study measured declining cognitive ability *prior to* any MRI scan (Meier et al., 2014). Finally, in 792 participants of the Alzheimer's Disease Neuroimaging Initiative (ADNI; mean age: 72.7±7), a prospective longitudinal study of healthy older individuals, and individuals with MCI or dementia, a greater number of microbleeds was associated with greater declines in composite scores of general cognitive ability, executive function, and memory over an average of four years (standardised ß ranged from-0.01 to -0.03; Li et al., 2020). These associations were adjusted for age, sex, education, *APOE* e4 status, and

baseline diagnosis, however, after additionally controlling for WMH volume, all associations in this study became non-significant.

Overall, results from longitudinal studies suggest that individuals with microbleeds experience greater declines across multiple domains of cognitive ability than those without. In some studies, it appears that the topographical distribution of microbleeds may play a role in determining the presence or absence of cognitive impairments. As described in Chapter 1, although individuals often have microbleeds in both deep and lobar regions, microbleeds in deep regions are presumed to be mostly hypertensive, whereas microbleeds in lobar regions are mostly associated with cerebral amyloid angiopathy (CAA; Puy et al., 2021; Viswanathan & Greenberg, 2011). Due to its co-occurrence with AD pathology, individuals with CAA may be more likely to develop cognitive decline, which may underlie some of the observed associations between lobar microbleeds and poorer cognitive abilities (Chung et al., 2016; Gregoire et al., 2013; Meier et al., 2014). However, when grouping participants according to the location of microbleeds, sample sizes tend to become very small (the study by Meier and colleagues (2014) included only 11 participants with >2 lobar microbleeds), so these results should be interpreted with caution. It is also important to note that the detection of microbleeds is highly influenced by MRI parameters, such as field strength and sequences used (Puy et al., 2021; Wardlaw et al., 2013). Studies comparing microbleeds detected on neuroimaging and at post-mortem examination have estimates of false-negative rates of pre-mortem imaging as high 48% (Haller et al., 2018). Therefore, further caution is warranted in interpreting the findings of studies that categorise participants on the basis of small differences in numbers of observed microbleeds.

Countering the notion that the topographical distribution may influence the presence or extent of cognitive impartments in SVD, a large multicentre trial by Zhang and colleagues (2018) found that the presence of microbleeds was associated with MCI status regardless of whether they were located anywhere in the brain (n=215), in strictly lobar regions (n=67), or in deep or infratentorial regions (n=148). Results from several studies have also suggested that cognitive impairments are associated with greater numbers of microbleeds, as opposed to their presence or absence (Akoudad et al., 2016; Ding, Sigurosson, et al., 2017; Goos et al., 2009; Gregoire et al., 2013; Li et al., 2020; Meier et al., 2014; Zhang et al., 2018),

suggesting that a greater burden of microbleeds may cause more widespread disruption of white matter tract networks, resulting in greater cognitive deficits.

3.3 Associations between measures of total SVD burden and cognitive abilities

The last four sections have provided an overview of associations between individual radiological markers of SVD and cognitive abilities. However, as discussed in Chapter 1 (section 1.2), the key radiological markers of SVD are closely inter-related; as well as being aetiologically related, positive correlations among measures of WMH, visible PVS, lacunes and microbleeds are widely reported, and some of these markers demonstrate spatial relationships with one another. There is justification, therefore, in asking whether the key radiological features of SVD might be combined into a single variable representing 'total' SVD burden. Only a handful of studies have investigated associations between measures of total SVD burden and cognitive abilities, the main findings of which are summarised in Table 2 (cross-sectional studies) and Table 3 (longitudinal studies) – note that Table 3 also contains results of cross-sectional associations that arose from studies with longitudinal designs.

Cohort	n=	Mean years of age	Detail of total SVD burden score	Key results (fully-adjusted models):	Analyses corrected for
Lothian Birth Cohort 1936: Community-dwelling older adults (Staals et al., 2015)	680	72.7±1	1) 0-4 sum score: 1 point for the presence of WMH, PVS, lacunes, and microbleeds 2) Latent variable constructed using: Fazekas scores of pWMH and dWMH, # lacunes, # microbleeds	*Greater SVD sum score associated with:* - Poorer general cognitive ability; unstandardised ß (SE): -0.082 (0.03) - Poorer memory (although not after correction for multiple testing); -0.084 (0.04) - No significant association with processing speed *Greater latent SVD score associated with:* - Poorer general cognitive ability (unadjusted model only); -0.165 (0.05) - Poorer processing speed (unadjusted model only); -0.117 (0.04) - No significant association with memory	Age, sex, age-11 IQ, vascular health status, cerebral atrophy
Individuals at risk of SVD (59% hypertensive; 41% lacunar stroke) (Huijts et al., 2013)	189	HTN: 65.0±12 Lacunar stroke: 56.5±12	0-4 sum score: 1 point for presence of WMH, lacune, visible PVS, microbleed	*Greater SVD burden score associated with:* - Poorer general cognitive ability; *r* = -0.18 - Poorer processing speed *r* = -0.18 - Poorer executive function (unadjusted model only); *r* = -0.31 - Poorer memory (unadjusted model only); *r* = -0.33	Age, sex
Atahualpa Project: community-dwelling older adults (Del Brutto et al., 2018)	331	70.1±8	0-4 sum score: 1 point for moderate-severe WMH, ≥10 visible PVS, lacune in deep grey matter, and microbleed in deep grey matter	*Greater SVD score was associated with:* - Poorer performance on the Spanish MoCA; unstandardized ß (95% CI): 5.85 (1.16–10.54)	Age, sex, vascular risk
Individuals with amnestic MCI, AD, subcortical vascular MCI, or subcortical VaD (Banerjee et al., 2018)	243	72.2±8	0-4 sum score: 1 point for presence of Fazekas pWMH ≥2 or dWMH ≥3, ≥10 visible PVS in basal ganglia, lacune, and microbleed	*Greater SVD score associated with:* - Poorer executive function; unstandardized ß: -4.31 (2.09) - Poorer visuospatial ability -0.95 (0.44) - No significant association with language - No significant association with memory	Age, sex, education

Table 2: A summary of the main findings from cross-sectional studies examining associations between total SVD burden and measures of cognitive ability

Cohort	n=	Mean years of age	Detail of SVD burden score	Follow-up period	Key results (fully-adjusted models)	Analyses corrected for
LADIS: initially non-disabled older adults with mild to severe WMH (Jokinen et al., 2020)	560	73.5±5	Average of the z-scores of WMH vol., lacune vol., grey matter, vol. and hippocampal vol.	3 years	*Greater SVD score associated with poorer baseline levels and steeper decline in:* - General cognitive ability; linear mixed models, F for main effect 101.2; interaction with time F 5.1 - Processing speed F 120.6; F 37.3 - Executive function F 148.3; F 21.5 - Memory F 54.4; F 7.4	Age, sex, years of education, study centre
Hypertensive individuals, 30% with lacunar stroke (Uiterwijk et al., 2016)	130	58.7±12	0-4 sum score: 1 point for presence of WMH, lacune, visible PVS, microbleed	4 years	*Greater SVD burden score associated with steeper decline in:* - General cognitive ability; unstandardized ß (95%CI): 0.09 (0.02–0.16) - Executive function 0.13 (0.05–0.22) - Processing speed (unadjusted model only) 0.11 (0.07–0.22) - No significant association with memory	Age, sex, education, anxiety & depression, vascular risk, patient group, baseline cognitive score
2 independent subgroups of ASPS Study: community based older-age cohort (Al Olama et al., 2020)	541	65.7±9	0-3 sum score: 1 point for presence of WMH, lacune, or microbleed	cohort 1: median 3 years cohort 2: median 2 years	*Greater SVD score associated with poorer baseline levels of:* - General cognitive ability (effect sizes not provided) - Processing speed *Greater SVD score associated with steeper decline in:* - General cognitive ability - Executive function	Age, sex, years of education
St. George's SCANS Study: Lacunar stroke + confluent WMH (Al Olama et al., 2020)	121	70.0±10	As above	3 years	*Greater SVD score associated with poorer baseline levels of:* - General cognitive ability (effect sizes not provided) - Processing speed - Executive function *Greater SVD score associated with steeper decline in:* - General cognitive ability - Executive function	Age, sex, years of education
RUN-DMC Study: symptomatic cardiovascular disease, no dementia (Al Olama et al., 2020)	503	65.6±8	As above	5 years	*Higher SVD score associated with poorer baseline levels of:* - General cognitive ability (effect sizes not provided) - Processing speed *Higher SVD score associated with steeper decline in:* - General cognitive ability (effect sizes not provided) - Processing speed - Executive function	Age, sex, years of education

Table 3: A summary of main findings from longitudinal studies examining associations between total SVD burden and measures of cognitive decline

The majority of the studies listed in Tables 2 and 3 have estimated SVD burden using a 0-3 or 0-4 SVD sum score, which allocates 1 point for the presence of key MRI markers of SVD. In relatively healthy community dwelling individuals from the LBC1936 (Staals et al., 2015), the Atahualpa Project (Del Brutto et al., 2018), and the Austrian Stroke Prevention Study (ASPS; Al Olama et al., 2020), greater SVD sum score was associated with poorer general cognitive ability, and additionally associated with slowed processing speed in ASPS participants. Similar results were found in individuals with symptomatic SVD from the RUN-DMC study; greater SVD sum score was associated with poorer performance on tests of general cognitive ability and processing speed (Al Olama et al., 2020). Both the ASPS and the RUN-DMC study also examined measures of executive function, but found no significant associations between these measures and the SVD sum score. This runs contrary to the literature reviewed in section 3.2, in which executive function was associated fairly consistently with individual SVD markers. It could be the case, however, that executive function was relatively intact in the ASPS and RUN-DMC cohorts, which both included relatively healthy older adults. As the umbrella of executive function includes several different cognitive abilities such as attention and working memory, it tends to be tested in disparate ways, so these differences could also be due to differences in the tests used to measure executive function. Indeed, in two cohorts with overt clinical presentations of SVD (lacunar stroke, and SVD-related MCI or dementia), greater SVD sum score was found to be associated with poorer executive function (SCANS study: Al Olama et al., 2020; Banerjee et al., 2018), although not in a third study in which approximately 40% of the sample had lacunar stroke (Huijts et al., 2013).

In almost all analyses measuring SVD burden with the simple SVD sum score, SVD score demonstrated a negative association with processing speed (Al Olama et al., 2020; Huijts et al., 2013). The exception to this was the study by Staals et al (2015). This, however, is likely due to the fact that Staals and colleagues accounted for the covariance between the processing speed score and a measure general cognitive ability in their analyses. As discussed in Chapter 2, the shared variance among cognitive test scores (thus, across different cognitive domains) can be attributed to the overarching construct *general cognitive ability.* By removing the variance associated with general cognitive ability from their processing speed variable, Staals and colleagues have tested the association between the SVD sum score and the variance in cognitive test scores that is unique to their measure of processing speed. In the context of the wider literature, their null result suggests that SVD's

association with processing speed may be due to its overarching association with general cognitive ability, underscoring the importance of accounting for the confounding covariance between all cognitive test scores. However, this result is yet to be replicated.

Longitudinal studies (summarised in Table 3) have observed associations between greater SVD sum score and greater decline in general cognitive ability, and executive function in relatively healthy aging cohorts, in individuals with symptomatic SVD and, in those with hypertension or lacunar stroke (Al Olama et al., 2020; Uiterwijk et al., 2016). Only in the RUN-DMC study did greater SVD sum score associate with steeper decline in processing speed (Al Olama et al., 2020).

3.3.1 Associations between continuous measures of total SVD burden and cognitive abilities

Whereas the SVD sum score captures information from a range of inter-related SVD markers, the conversion of continuous or ordinal MRI data into binary variables likely results in a loss of information and statistical power (Streiner, 2002). This conversion is particularly costly for WMH volumes, which typically have a high degree of variability, and could be the reason for the surprising lack of observed associations between SVD sum scores and declining processing speed. A reduction of continuous counts of lacunes and microbleeds to ordinal or binary scores also likely results in a loss of important information; as discussed in the previous section, there is some evidence to suggest that the number of these lesions may be more closely associated with cognitive outcomes than their mere presence or absence.

To increase the fidelity of SVD burden quantification, two recent studies developed a continuous total SVD score (Jokinen et al., 2020; Staals et al., 2015). In the first of these studies, Staals and colleagues (2015) used CFA (see Chapter 1, Figure 2) to combine visual ratings of WMH, visible PVS, lacunes and microbleeds using data from the LBC1936. The latent SVD variable was associated with poorer general cognitive ability and poorer processing speed, however these associations became non-significant after the addition of covariates, which included age, sex, childhood IQ, vascular health status, and cerebral atrophy. There was no association between total SVD burden and memory test scores. Although Staals' latent SVD variable was continuous, its constituent variables were ordinal measures from visual ratings of WMH, visible PVS, lacunes and microbleeds. More recently,

in the LADIS cohort, Jokinen and colleagues (2020) constructed a continuous measure of SVD burden by averaging z-scores of WMH volume, lacune volume, cerebral grey matter volume and hippocampal volume. In this study a greater SVD score was associated with lower concomitant levels and greater decline in tests of general cognitive ability, processing speed, executive function, and memory, after accounting for age, sex and education.

Upon assessing associations between the 0-4 SVD sum score and MoCA score in the Atahualpa cohort (Del Brutto et al., 2018), the SVD sum score accounted for similar proportion of variance in MoCA scores (R^2 = 0.33), as each individual radiological marker of SVD did (R^2 values ranged between 0.31 and 0.32). This suggested that the 0-4 SVD sum score afforded little additional predictive power over the individual contributions of WMH, visible PVS, lacunes and microbleeds. However, this was not the case for the continuous measures of SVD burden constructed by Staals et al. (2015) and Jokinen et al. (2020). In both of these studies the magnitudes of the associations between SVD burden and cognitive outcomes surpassed those of models using a simple 0-4 SVD burden score (Staals et al., 2015) or individual MRI markers of SVD (Jokinen et al., 2020) as predictors of cognitive performance. It could be the case that continuous measures of SVD burden better capture the variability in global effects of SVD on the brain, in turn, potentially affording more accurate estimations of SVD's impact on cognitive performance.

3.4 Summary

I began this chapter by describing the current consensus on the cognitive impairments associated with SVD: slowed processing speed and poorer executive function alongside relative preservation of memory and language skills. The vast majority of the literature supporting these claims comes from studies testing associations between individual radiological markers of SVD and cognitive test scores, however, this literature is often conflicting and is incomplete in places. Multiple meta-analyses have suggested that WMH associate with poorer cognitive performance across several major domains of cognitive ability, although the majority of studies focus on deficits in processing speed and executive function. There is disagreement as to whether visible PVS associate with cognitive changes in SVD, which may be due to challenges with their identification on neuroimaging. Many studies suggested that lacunes and microbleeds associate with poorer scores on tests of executive function and processing speed, and a small number of studies suggested

additional associations with poorer memory abilities. These findings could be due to the location of these lesions in frontal and subcortical regions, although studies examining lesion location tend to rely on small sample sizes and may not account for overall lesion burden. Overall, very few of the studies reviewed in this chapter examined cognitive abilities in domains other than processing speed, executive function, and memory. Therefore, little is known about whether SVD-related brain changes associate with deficits in the domains of visuospatial ability, reasoning and language. It remains to be determined precisely which domains of cognitive impairment are impaired in sporadic SVD. In addition, it is not yet understood whether any associations between SVD burden and impairments in specific domains of cognitive ability will remain after accounting for covariance between domain-specific cognitive test scores (as discussed in Chapter 2).

In recent years, a handful of studies have examined association between variables incorporating multiple radiological markers of SVD burden. These variables may be more effective in capturing the global effects of SVD on the brain, with continuous measures of SVD burden offering even greater sensitivity to this. However, it is yet to be determined whether continuous measures of total SVD burden increase the fidelity with which SVD is currently measured, or whether they improve the prediction of cognitive outcomes over and above measures of SVD burden derived from visual rating scales only.

Although the majority of the studies discussed in this chapter have focused on relatively healthy community-based or population-based samples, cognitive impairment is also common in clinical presentations of SVD. For example, studies recruiting individuals with lacunar stroke have estimated the prevalence of post-stroke MCI to be between 34% and 47%, and post-stroke dementia to be between 10% and 16% (Jacova et al., 2012; Makin, Turpin, Dennis, & Wardlaw, 2013; Mchutchison et al., 2019). Although the studies reviewed in this chapter suggest that SVD-related cognitive changes occur across the full spectrum of SVD presentations, from relatively healthy older individuals, to those with stroke and dementia, it is still unclear whether the cognitive impact of SVD might vary between different clinical and non-clinical presentations of the disease. This knowledge gap, in addition to those described above, will be addressed by the studies presented in chapters 4, 5, and 6 of this thesis.

3.5 Aims of the thesis

The overall aim of this thesis is to advance current understanding of the cognitive changes associated with sporadic SVD. More specifically, the aims of this thesis are:

- *Primary aim:*
    - To assess which domains of cognitive ability are impaired in individuals with sporadic SVD
- *Secondary aims:*
    - To assess whether the pattern of SVD-related cognitive impairments varies between different presentations of the disease
    - To assess whether any SVD-related impairments in specific cognitive domains remain after accounting for their association with general cognitive ability.

Chapter 4 presents the results of a systematic review and meta-analysis of the literature reporting cognitive test results for healthy ageing cohorts with radiological evidence of SVD, cohorts with SVD-related stroke, and cohorts with SVD-related MCI or dementia. This study aims to assess which cognitive domains are impaired in sporadic SVD and additionally, whether the pattern of SVD-related cognitive impairments differs according to the clinical or non-clinical presentation of the disease.

Chapter 5 presents the first of two empirical studies examining associations between radiological markers of SVD and cognitive abilities in the LBC1936. The first study examines whether a modified version of the continuous total SVD burden variable constructed by Staals and colleagues (2015) associates cross-sectionally with performance on tests of general cognitive ability, processing speed, verbal memory, and visuospatial ability at the age of 73. Importantly, in these analyses, I account for the shared covariance between cognitive domain scores and general cognitive ability. In doing so, I attempt to answer the question of whether SVD burden associates with domain-specific cognitive test scores *independently* of SVD's association with general cognitive ability. I also aim to determine whether there is any benefit in measuring the total burden of SVD (vs. individual radiological markers) in the prediction of cognitive test scores.

The study presented in Chapter 6 is a further development of this work, examining associations between the modified continuous SVD burden score and *decline* in cognitive abilities between the ages of 73 and 82. By accounting for the covariance between domain-specific measures of cognitive ability and general cognitive ability, I aim to determine whether SVD burden has independent associations with declines in specific domains of cognitive ability, or whether these associations could be due to SVD's overarching association with declining general cognitive ability.

Finally, Chapter 7 presents a summary and discussion of the findings from Chapters 4, 5, and 6, a discussion of study limitations, and avenues for future research.

Chapter 4 Examining available evidence on the pattern of cognitive impairments associated with sporadic SVD

4.1 Introduction

The literature reviewed in Chapter 3 largely examined associations between key radiological markers of SVD and cognitive abilities. Whereas the examined literature provides a good indication of the direct associations between the radiological burden of SVD and cognitive outcomes, as discussed, factors such as the method of lesion quantification, or the location of lesions in the brain adds further complexity to the interpretation of these associations. Additionally, the cognitive outcomes associated with SVD cannot be fully accounted for by the visible radiological burden of SVD alone, as demonstrated by individuals who have a high burden of SVD on neuroimaging, but experience few overt clinical symptoms.

Taking an alternative approach to examining the cognitive impairments associated with SVD, this chapter presents the results of a systematic review and meta-analysis of cognitive test scores for cohorts with either radiological *or* clinical evidence of SVD. As a common pathway between stroke and dementia, the clinical presentations of SVD vary considerably. However, stroke and dementia presentations are often considered separately, thus little is known about how SVD-related cognitive impairments might differ across different SVD presentations. By including a broader range of cohorts with varying clinical and non-clinical presentations of SVD without pre-selecting for particular lesion types, this review aims to gain a clearer understanding of the cognitive impairments associated with SVD in a sample that more accurately reflects the heterogenous nature of sporadic SVD.

This study has been published as a theoretical article in *Alzheimer's and Dementia* - a PDF copy of the publication is included in Appendix A and supplementary files for the published article are available online (https://doi.org/10.1002/alz.12221). An earlier version of this work was uploaded to the *medRxiv* preprint server (available at https://doi.org/10.1101/2020.02.10.20020628).

In this chapter, the study is presented in the format in which it was originally submitted for publication, before being adapted into a theoretical piece. Supplementary files for this work are presented in Appendix B.

Cognitive impairment in sporadic cerebral small vessel disease: a systematic review and meta-analysis

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Abstract

Background: The full range of cognitive impairments in cerebral small vessel disease (SVD) is unknown.

Methods: We searched MEDLINE, Embase, and PsycINFO for studies reporting cognitive data for SVD cohorts, and controls. We used random-effects meta-analyses to test differences in cognitive abilities; and meta-regressions to investigate effect modifiers, and cognitive differences between clinical presentations of SVD.

Results: Pooling data from 69 studies, controls (n=3679) outperformed SVD cohorts (n=3229) on tests of executive function, processing speed, memory, visuospatial ability, language, attention, and reasoning (pooled standardised mean difference range: -0.936 to -0.622; $p \leq 0.001$). Differences in education between SVD and control groups contributed to some cognitive effect sizes. SVD cohorts with cognitive impairments demonstrated poorer performance in some domains than cerebrovascular, or non-clinical SVD cohorts.

Discussion: Regardless of clinical presentation, SVD cohorts showed impairments relative to controls, in all cognitive domains examined. Lower levels of education in SVD participants may contribute to these effects.

Keywords: Cerebral small vessel disease; vascular cognitive impairment; cognitive ability; lacunar stroke; vascular dementia; systematic review; meta-analysis.

Introduction

Cerebral small vessel disease (SVD) refers to a collection of neuroimaging and neuropathological abnormalities found in the brain's white and deep grey matter. White matter hyperintensities (WMH) and lacunes of presumed vascular origin, cerebral microbleeds and enlarged perivascular spaces likely reflect multiple pathological changes affecting the brain's small vessels, such as endothelial dysfunction, impaired cerebral blood flow, and reduced vessel pulsatility. The relationships between these mechanisms are complex and not yet fully understood [1,2]. Whereas the radiological markers of SVD have previously been considered clinically 'silent', their presence has been associated with cognitive impairment, depression, impaired gait and balance, and urinary incontinence [3,4].

SVD has varied clinical manifestations - it causes approximately 25% of acute ischaemic stroke, increases the risk of recurrent ischaemic stroke, and associates with poorer functional outcomes post-stroke [5,6]. SVD is also a major cause of vascular dementia (VaD), and increases the risk of incident dementia [6]. In most cases, SVD manifests sub-clinically, with few overt symptoms. For example, cohort studies of healthy older individuals often include subpopulations who show features of SVD on neuroimaging, but have no history of stroke, dementia, and no subjective cognitive concerns. The term vascular cognitive impairment (VCI) encompasses these various presentations of SVD, referring to any severity of cognitive impairment (from subclinical deficits to dementia) with underlying vascular contributions [7,8].

The cognitive manifestation of VCI is often characterised as deficits in executive function and speed of information processing, with little attention paid to other domains of cognitive ability [9,10]. Studies supporting this suggestion are often small and focus on a narrowly-defined subtype of SVD, or on those with a high disease burden, who may not represent the full spectrum of sporadic SVDs. Despite increasing recognition of cerebrovascular contributions to non-vascular and mixed dementias [11], individuals with cerebrovascular presentations of SVD are rarely considered in the same study as those with predominantly cognitive presentations, so little is known about how cognitive impairments may differ between SVD subtypes. In part, this is due to differing routes into clinical care and so, into clinical research. In addition to this, variation in naming conventions for SVD lesions [12] impairs between-study comparisons.

To examine the nature of SVD-related cognitive impairment across multiple cognitive domains and to account for its varied clinical and non-clinical presentations, we conducted a systematic review and meta-analysis of domain-specific cognitive abilities in individuals with clinical or radiological signs of SVD. We aimed to clarify the nature of SVD-related cognitive impairment, to assess contributions of underlying factors such as age, level of education or burden of vascular risk, and to assess whether SVD-related cognitive impairments vary according to clinical, or non-clinical presentations of the disease.

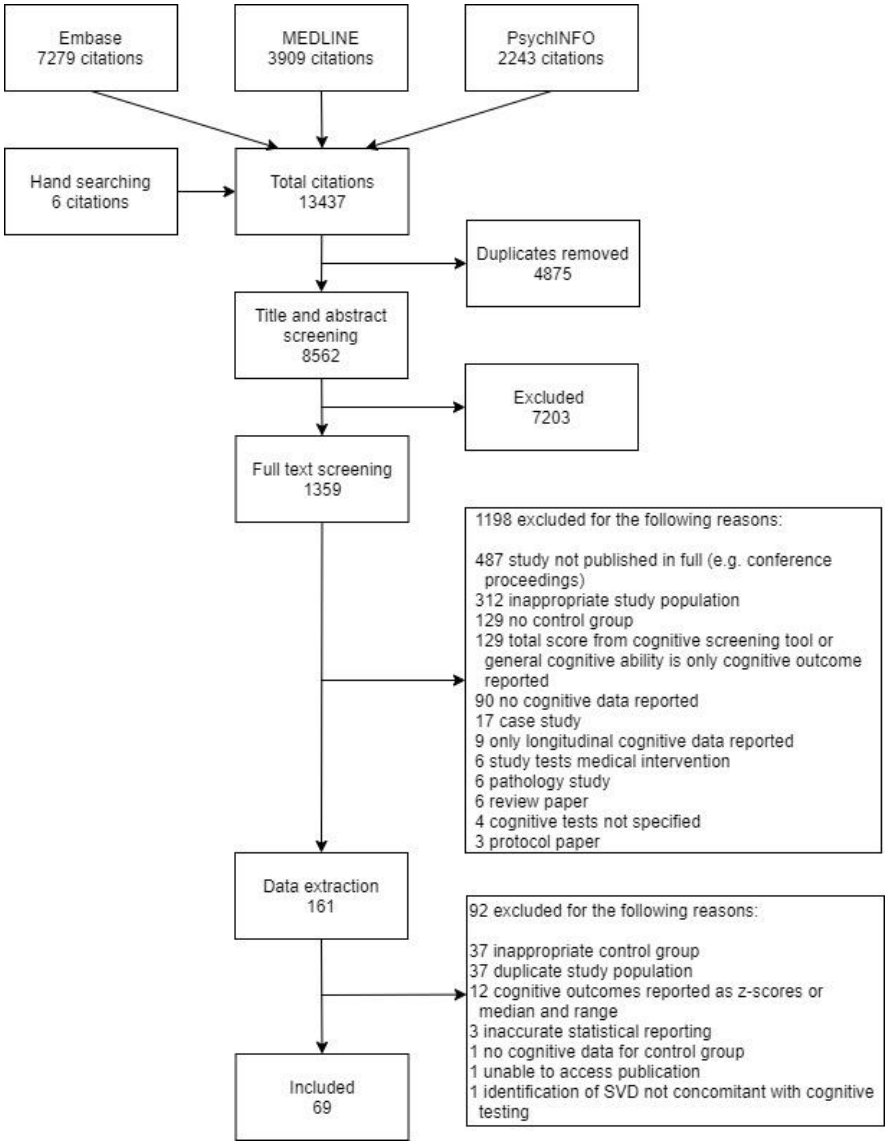
Methods

We performed this systematic review and meta-analysis in accordance with PRISMA guidelines. The review protocol is registered on the PROSPERO database (ID: CRD42017080215).

Search strategy and study selection criteria

We developed and tested a detailed search strategy (see Supplementary File 1) to identify studies reporting the results of cognitive testing in a cohort with SVD (performed contemporaneous with identification of SVD), and a control cohort with no history of neurological or psychiatric conditions. We searched OVID MEDLINE, Embase and PsycINFO, for human studies published in any language from 1st January 1985, when MRI became more widely available in clinical practice, to 6th October 2019. To identify additional studies, we checked the reference lists of relevant review articles and hand-searched the previous 7 years of Stroke and the Journal of Cerebral Blood Flow and Metabolism (see Figure 1). Study inclusion and exclusion criteria, are presented in Supplementary File 2.

Figure 1: Flow diagram of systematic review screening process



Data Extraction

Two authors (OH and EB) independently extracted key information, which included group-level demographic data for the SVD and control groups (age, sex, education); group-level data on vascular risk factors (% cohorts with hypertension, diabetes, hypercholesterolemia, and smoking status), group-level data on WMH burden, and group-level cognitive test scores for SVD and control groups. The vast majority of cognitive data were presented as mean and standard deviation. To avoid introducing additional heterogeneity into the meta-analysis dataset, we did not convert cognitive data presented as median and range to mean and standard deviation - instead these data are summarised in Supplementary File 3. Where

individual participant data were presented, we calculated the mean and standard deviation of the variables we extracted. Cognitive data were then categorised into seven domains of cognitive ability: information processing speed, executive function, delayed memory, attention, reasoning, visuospatial ability and language. However, it is important to note that subdomains of cognitive ability are not discrete, and that individual cognitive tests often engage abilities from multiple cognitive domains. To ensure that tests were reliably categorised according to the cognitive domain that they are considered to primarily assess, two authors experienced in neuropsychological testing (OH and AJ) independently categorised cognitive data into the seven domains listed above and resolved disagreements by consensus (see Supplementary File 4 for further information). Studies reported a wide range of memory tests, including tests of long-term, short-term and working memory. To reduce heterogeneity in the dataset we included only tasks featuring a delayed recall/recognition component, as these were the most frequently reported memory tasks. We excluded data for which we could not identify the specific test score (e.g. where authors reported results for a Trail Making task, but did not specify whether the score was for Trail Making A, Trail Making B, or Trail Making A-B). We also excluded data for which we could not discern whether a higher or lower score indicated better performance. Where studies reported multiple scores for one cognitive test (e.g. for the Wisconsin Card Sorting Test: number of perseverative errors, total number of errors, number of categories etc.), we included the score most commonly reported in the meta-analysis dataset. Due to the large number of included studies and the large number of variables used in our analyses (i.e. sociodemographic, cognitive, and vascular risk variables), we did not contact the authors of original publications to obtain missing data.

Statistical Analysis

We calculated a standardised mean difference (SMD) to represent the difference between performance of the SVD and control cohorts on each cognitive test. We multiplied the SMD by -1 for tests on which a lower score indicated better performance. We excluded three studies due to reporting of implausibly large effect sizes, which upon examination appeared to be due to statistical or reporting errors in the original publications. Whilst several larger effect sizes (SMD >3) remain in our meta-analyses, these effect sizes come from small study samples so are unlikely to affect results if omitted.

Meta-analysis models

We ran seven separate random effects meta-analyses to assess the difference in performance between SVD and control groups on cognitive tests in each cognitive domain. We conducted all meta-analyses using the robumeta package [13] in R version 3.6.1 [14]. robumeta permits the meta-analysis of multiple effect sizes from one study by employing robust variance estimation (RVE) to account for their statistical dependency. This approach maximises the amount of data included from a single study, increasing the statistical power of each meta-analysis. Dependency in our dataset arose from the inclusion of multiple effect sizes from the same study sample, and the inclusion of studies which used the same control group for comparison with multiple SVD groups. Covariance matrices for multiple outcomes arising from a single study are rarely published, therefore, robumeta imputes a user-specified value for the within-study effect size correlation. We were conservative in our choice of within-study effect size correlation - we specified rho as 0.8 and carried out sensitivity analyses in robumeta, which impute rho values at increments of 0.1 to test whether this alters the model results. For all analyses, we weighted effect sizes according to a correlated effects dependence structure within the robumeta package and used small sample size corrections. Small sample corrections, which correct both the residuals and df used in the RVE, increase the accuracy of models including fewer than 40 studies [13]. After correction, if the Satterthwaite df for the model are less than four, the p value is considered unreliable due to the probability of type I error being greater than 0.05. In our analyses, results of models with Satterthwaite df <4 were considered unreliable. We report I^2 and τ^2 as measures of heterogeneity.

Meta-regression models

We carried out two secondary analyses to examine the following study-level and cohort-level variables:

1) *SVD presentation*

To test whether the pooled study effect size differed according to SVD presentation, we grouped each SVD cohort into one of three categories according to the characterisation of the cohort and recruitment setting detailed in the original publication (see Supplementary File 5).

a) Stroke presentations

Cohorts in this category most commonly presented to stroke or neurology services with symptoms of lacunar syndrome, with or without evidence of corresponding vascular lesions. Other cohorts in this category had radiologically identified SVD, or subcortical ischaemic vascular disease.

b) Cognitive presentations

Cohorts in this category were identified on the basis of impaired cognitive ability ranging from MCI to VaD. Typically, cohorts presented with cognitive impairment (according to clinical diagnosis, objective cognitive testing, or subjective concern) and either radiological evidence supporting a vascular aetiology, or multiple risk factors for cerebrovascular disease.

c) Non-clinical presentations

Cohorts had radiological evidence of SVD (WMH or lacunes of presumed vascular origin), but no clinical diagnosis. Typically, cohorts were community-dwelling older individuals recruited within a defined geographical region, or via community advertising. Several cohorts in this category presented to clinical services with non-specific symptoms such as dizziness or headache, but received no diagnosis upon examination.

We then entered SVD presentation as an ordinal predictor in the meta-regression model for each cognitive domain, with the cognitive presentation category as the reference group.

3) Differences in the prevalence of vascular risk between the SVD and control cohorts

All extracted cognitive data were unadjusted for demographic or vascular risk factors. Therefore, to test whether differences in age, education, hypertension and diabetes between SVD and control cohorts accounted for study effect sizes, we calculated the difference in age, years of education, % sample with hypertension, and % sample with diabetes (e.g. difference in age = mean age of control cohort – mean age of SVD cohort), and entered these variables as predictors in separate univariate meta-regression models for each cognitive domain.

Quality Assessment

Quality assessment criteria (see Supplementary File 6) were devised according to STROBE guidelines. Two authors (OH and EJ) independently assessed the quality of included publications on a scale ranging from 0-8 and resolved disagreements by consensus. To assess whether the inclusion of lower quality studies affected the results of the meta-analyses, we re-ran meta-analysis models excluding studies with quality scores lower than the median quality score of the meta-analysis sample.

Results

We identified 69 studies for inclusion in the review (see Table 1; references 15–83), Included studies were from 18 countries in six continents, published in four languages. These studies reported data for 89 cohorts with SVD (n=3229), and 71 control cohorts (n=3679; demographic data for the SVD and control cohorts are presented in Table 2). Almost all studies reported participants' mean age and sex, but the reporting of educational level, vascular risk factors, and WMH burden was less complete; approximately half of all studies reported history of hypertension or diabetes, and only one third of studies reported smoking status, despite its known association with SVD progression. We did not pre-select literature that focused on a certain lesion type, or clinical, cognitive, or behavioural presentation of SVD, therefore, our dataset included SVD cohorts recruited from specialised cerebrovascular clinics, memory clinics, hospital-based stroke, dementia and general neurology services, non-specialist medical centres, a stroke research network, and also included several research cohorts of healthy community-dwelling individuals. Tests of executive function were the most commonly reported cognitive outcomes (58 studies reported 188 cognitive outcomes), followed by tests of delayed memory (41 studies, 98 outcomes), processing speed (37 studies, 88 outcomes), visuospatial ability (27 studies, 50 outcomes), language (24 studies, 42 outcomes), reasoning (16 studies, 25 outcomes), and attention (12 studies, 19 outcomes).

Table 1: Characteristics of all included studies

Study	SVD cohort described as	SVD n	Control n	SVD age mean (SD)	SVD % female	SVD years of Education mean (SD)	SVD % Hyperte-nsion	SVD % Diabetes	SVD % Ever smoking	Variables on which SVD & Controls are matched (blank cells=no matching, or data unavailable)	SVD Mean WMH/TIV (SD) *Mean Visual rating (SD)*
Anderson [15]	Lacunar syndrome	30	30	68.3 (16.8)	47%	9.7 (2.12)				1, 2	
Atwi, 2018 [16]	Fazekas ≥ 2	18	28	72 (5)	56%		22%	6%		1, 2, 3	9.2 ml (0.6)
Bella, 2016 [17]	VCI-ND	25	20	67.5 (6.7)	60%	7.6 (3.9)	88%		28%	1, 3	
Boone, 1992 [18]	1) WMH ≤ 1cm^2 2) WMH >1cm^2 - 10cm^2 3) Total WMH > 10cm^2	27 21 6	46 † †	63.6 (9.9) 69.2 (6.8) 72.0 (4.9)		15.0 (1.9) 14.2 (3.1) 12.8 (1.3)				3 3 3	
Brookes, 2014 [19]	SVD	45	80	69.7 (8.2)	44%	Highest formal qualification: None: 51% Secondary: 11% Further education.: 27% Degree: 9% Higher degree: 0% Unavailable: 2%	84%	21%	69%	1, 2	Modified Fazekas n (%): Fazekas 0: 6 (13%) Fazekas 1: 12 (27%) Fazekas 2: 12 (27%) Fazekas 3: 12 (27) Unavailable: 3 (6%)
Brookes, 2015 [20]	SVD	196	303	63.5 (9.9)	32%	13.7 (3.8)	75%	23%	44%	1, 2, 4	
DeCarli, 1995 [21]	WMH volume > 0.5% TIV	5	17	74 (14)			0%			1	WMH/TIV 0.80 (0.24)
Deguchi, 2013 [22]	Lacunar infarction	76	105	73.4 (8.9)	34%	12.5 (2.3)	68%	30%	13%*	1, 2	
Fang, 2013 [23]	1) silent brain infarct 2) Microbleeds 3) silent brain infarct + microbleeds	46 41 49	91 † †	70.9 (6.4) 70.6 (5.2) 72.1 (5.0)	57% 42% 47%	8.11 (2.3) 8.24 (1.9) 8.20 (2.3)	83% 81% 82%	22% 27% 25%	20% 22% 25%	1, 2, 5 1, 2, 5 1, 2, 5	

Fernández, 2011 [24]	MCI with subcortical vascular damage	19	19	72.2 (7.6)	32%	3.6 (3.5)					
Gainotti, 2008 [25]	MCI + multiple subcortical infarcts	41	65	71.7 (5.9)	41%	Reporting unclear				1, 3	
Garrett, 2004 [26]	VCI-ND	18	25	78.4 (6.4)	44%	13.6 (2.5)					
Gonçalves 2017 [27]	Subcortical vascular dementia	16	40	74.94 (5.4)	38%	3.2 (1.8)				1,2	
Graham, 2004 [28]	VaD	19	19	71.2 (7.8)	26%	11.6 (3.1)				1, 3	
Hassan, 2010 [29]	Symptomatic lacunar infarction	30	12	59.1(9.5)	40%	Able to read and write: 53% Educated to between primary and university level: 46.7%	100%	47%	53%	1	
Hsu, 2016 [30]	MCI due to SIVD	20	30	68.5 (10.8)	30%	7.6 (4.17)	40%	25%		1,2,3	*23.9 (9.9) Scheltens*
Ishii, 2007 [31]	1) CDR 0, non-strategic CVD 2) CDR 0, strategic CVD 3) CDR 0.5, non-strategic CVD 4) CDR 0.5, strategic CVD	68 38 21 21	234 † † †	74.9 (7.9) 73.0 (6.3) 79.1 (6.9) 80.7 (6.5)		8.3 (1.5) 8.4 (2.1) 7.3 (2.2) 7.6 (1.7)	84% 92% 76% 86%	10% 16% 14% 5%			
Jokinen, 2009 [32]	SIVD	89	524	73.6 (4.9)	48%	8.8 (4.2)	80%	18%	15%*	1, 2	*WMH severity ratings:* *Mild: 0* *Moderate: 10* *Severe: 79*
Kim, 2018 [33]	Subcortical VCI	61	19	78.7 (6.3)	72%	7.3 (5.1)				1,2,3	
Kramer, 2002 [34]	SIVD	12	27	73.7 (6.2)		15.3 (2.6)				1, 3	
Kuriyama, 2018 [35]	1) dWMH Fazekas grade 1 2) dWMH Fazekas grade 2 3) dWMH Fazekas grade 3	134 62 16	68 † †	69.3 (5.7) 71.5 (6.3) 73.8 (6.6)	31% 36% 38%	Reporting unclear	47% 57% 81%	12% 15% 6%	16%* 7%* 13%*	2	*PWMH ≥ grade 2 (de Groot classification), n (%):* *4 (3%)* *17 (27%)* *11 (69%)*

Ledesma-Amaya, 2014 [36]	Lacunar infarction	16	16	63 (9.4)	38%	7.1 (4)	13%	8%		1,3	
Lee, 2014 [37]	Subcortical vascular mild cognitive impairment	67	75	73.7 (6.7)	61%	9.0 (5.2)	75%	25%		2	34.9ml (17.8)
Lewine, 1993 [38]	1) Men with WMH 2) Women with WMH	4 6	4 6	35.2 (11.8) 43.3 (8.4)	0% 100%					1 1	
Li, 2001 [39]	Leukoaraiosis	29	25	64.9 (6.8)		7.5 (6.8)				1, 2, 3	
Li, 2012 [40]	Lacunar stroke with ischaemic leukoaraiosis	20	20	65.8 (8.4)	45%	Reporting unclear	60%		60%		
Li, 2015 [41]	Symptomatic lacunar infarction	19	23	66 (12.0)	37%	8.5 (3)	68%	37%	11%*	3	
Li, 2017 [42]	Leukoaraiosis	13	13	63 (6)	39%	10.3 (3.3)	69%			1, 2, 6	
Liu, 2008 [43]	Subcortical small vessel infarction	60	52	73 (8)	47%		27%	14%		1, 2, 3	
Liu, 2015 [44]	WMH	30	30	78.2 (5.7)		8.4 (2)	23%	11%		1, 3	
Liu 2019a [45]	1) Pre-subcortical vascular cognitive impairment vascular disease (pre-SVCI) 2) Subcortical vascular cognitive impairment (SVCI)	25 29	27 †	70.5 (3.5) 70.5 (5.8)	36% 45%	10.6 (2.6) 9.4 (1.7)	56% 59%	40% 37%	20% 24%	1, 2, 3 1, 2, 3	12.6ml (5.0) 19.8ml (8.8)
Liu 2019b [46]	1) SVD without cognitive impairment 2) SVD with cognitive impairment	21 20	25 †	64.6 (10.9) 66.5 (7.9)	52% 50%	10.5 (3.6) 13.1 (3.8)				1, 2, 3 1, 2, 3	3.2ml (3.0) 3.4ml (4.1)
Maeshima, 2002 [47]	1) Silent brain infarct 2) pWMH	21 14	63 70	49.4 (5.6) 51.4 (6.6)	62% 57%	12.5 (2.1) 12.4 (2.1)	24% 21%	14% 29%		1, 2, 3 1, 2, 3	

Nebes, 2013 [48]	WMH	26	40	75.1 (5.8)	65%	14.5 (2.7)				1, 2, 3	
Nordahl 2005 [49]	MCI + severe WMH	11	20	77.6 (3.6)	55%	13.5 (1.5)	82%	27%		1, 3	WMH/TIV 3.9 (1.3)
Nordlund, 2007 [50]	Vascular MCI	60	60	67.0 (7.3)	63%	11.2 (3.2)				1, 2, 3	
Oguro, 2000 [51]	PWMH	18	9	73.6 (4.2)	61%	9.3 (3.2)			Scale unclear	1, 2, 3	
Pascual, 2010 [52]	1) Vascular white matter disease without dementia 2) Vascular white matter disease with dementia	12 12	12 (cognitive data for 10 only) †	80.7 (5.2) 79.5 (4.6)	50% 50%					1, 2, 3 1, 2, 3	
Pinkhardt, 2014 [53]	Small vessel cerebrovascular disease	25	19	75 (58–91)	68%						*Fazekas pWMH 2.36; Fazekas dWMH 2.2 SD not reported*
Price, 2009 [54]	Dementia with: 1) mild leukoaraiosis 2) moderate leukoaraiosis 3) severe leukoaraiosis	73 44 27	24 † †	78.5 (5.7) 81.0 (5.0) 79.4 (4.4)	82% 66% 81%	12.6 (2.8) 12.2 (2.8) 11.9 (2.1)				2, 3	*Junque score* *4.0 (2.8)* *12.0 (2.3)* *22.3 (4.4)*
Quinque, 2012 [55]	Early cerebral microangiopathy	11	21	61.4 (6.3)	40%	13.8 (3.0)				1, 2, 3, 4	*8.3 (4.0) ARWMC*
Rao, 1989 [56]	Leukoaraiosis	10	40	47.1 (7.8)	90%	14 (1.9)				1, 2, 3	
Schmidt, 1993 [57]	WMH	74	76	61.3 (6.6)		11.4 (2.6)	4%			3	
Seo, 2010 [58]	1) Subcortical vascular MCI 2) Subcortical VaD	34 (cognitive data for between 30-34 only) 20 (cognitive data for between	96 (cognitive data for 63 only) †	70.6 (6.4) 74.2 (6.1)	44% 55%	10.1 (4.8) 7.2 (5.5)	84% 100%	29% 30%		2, 3	

		15-18 only)									
Sierra, 2004 [59]	Hypertensive with WMH	23	37	55.2 (4.2)	39%	11.2 (3.7)	100%		22%	1, 2, 3	
Squarzoni, 2017 [60]	Silent brain infarct	57	187	72.1 (3.4)	56%		68%	33%		1	
Sudo, 2013 [61]	Vascular MCI	15	11	74.1 (8.1)	60%	8.9 (4.0)				1, 2, 3	*Fazekas rating, n (%)* *Fazekas 0: 0 (0%)* *Fazekas 1: 0 (0%)* *Fazekas 2: 7(47%)* *Fazekas 3: 8 (53%)*
Sun, 2014 [62]	Mild WMH	51	49	65.3 (7.2)	55%	10.3 (3.4)	16%	10%	8%	1, 2, 3	
Tupler, 1992 [63]	dWMH	48	18	69.9 (10.1)	69%	13.9 (4.2)					
van Swieten, 1991 [64]	Hypertensive with confluent WMH	10	18	67.8 (5.3)	32%		100%	50%		1, 2	*Normal white matter=20; focal lesions=12; confluent lesions=10*
van Zandvoort, 2003 [65]	Lacunar infarct in brainstem	17	17	60.1 (11.6)	29%	<6 years primary school: 0% 6 years of education (YoE): 6% 8 YoE: 0% 9 YoE: 47% 10-11 YoE: 23.5% 12-18 YoE: 23.5% >18 YoE: 0%				1, 2, 3	
van Zandvoort, 2005 [66]	Supratentorial lacunar infarct	26	14	60.5 (12.3)	38%	Scale unclear				1, 3	
Villeneuve, 2011 [67]	MCI with confluent WMH	21	27	73.4 (5.1)	48%	12.4 (5.2)				1, 2, 3	*10.0 (3.1)* *Wahlund*
Wolfe, 1990 [68]	Multiple lacunar infarcts	11	11	64.6 (6.0)	No info	10.1 (3.1)				1, 3	
Wong, 2007 [69]	Stroke associated with SVD	32	42	72.8 (10.0)	44%	Scale unclear				1, 2, 3	56.9 ml (8.7)

Yamauchi, 2000 [70]	Lacunar infarct	28	34	69.3 (6.3)	32%	8.9 (1.3)	21%	11%		1, 3	*Anterior WMH 3.6 (3.1)* *Posterior 3.6 (2.8)* *Scale – see publication*
Yang, 2015 [71]	Vascular MCI	15	15	61.7 (6.2)	73%	9.3 (2.4)				1, 2, 3	
Yang, 2016 [72]	Lacunar infarct	60	30	67.0 (7.0)	42%	7.2 (2.3)	58%	18%	38%*	1, 2, 3	
Yi, 2012 [73]	Subcortical vascular MCI	26	28	66.7 (9.5)	58%	9.9 (4.4)				1, 2, 3	
Yu, 2019 [74]	Extensive SIVD	29	25	71.8 (11.0)	52%	14.4 (3.2)	75%	10%	58%	1, 2, 3	DWMH 2.55 (2.5)cm^3 PWMH 29.0 (21.6)cm^3
Yuan, 2012 [75]	Leukoaraiosis	46	38	72.0 (6.0)	70%	8 (4)	74%	61%		1, 2, 3	
Yuan, 2017 [76]	Leukoaraiosis	50	50	71.7 (5.5)	58%	7.5 (4.3)	67%	50%	26%	1, 2, 3	
Yuspeh, 2002 [77]	SVaD	29	38	74.1 (8.2)	35%	13.2 (4.4)				1, 2, 3	
Zhang 2019a [78]	SVD	77	39	70 (11)	40%	Educational level: Low = 45% Medium = 35% High = 20%	64%	16%	25%	1, 2	WMH/TIV 0.014 (0.002)
Zhang, 2019b [79]	Amnestic MCI with Fazekas >1	30	90	68.33 (5.3)	47%	12.30 (2.6)				1, 2	
Zhao, 2016 [80]	1) Lacunar infarct 2) WMH 3) Lacunar infarct + WMH	62 60 61	55 † †	73.2 (4.7) 71.9 (4.2) 73.9 (3.8)	42% 38% 33%	10.7 (3.2) 10.9 (3.6) 10.5 (3.2)	76% 75% 78%	37% 33% 43%	31%* 23%* 34%*		
Zhou, 2009 [81]	MCI due to SVD	56	80	67.3 (6.2)	36%	9.6 (3.1)				2, 3	
Zhou, 2014 [82]	1) Subcortical vascular MCI 2) Subcortical vascular disease	79 82	77 †	72.2 (7.1) 74.1 (7.1)	53% 51%	9.9 (3.3) 7.4 (3.3)	63% 73%	29% 22%	32%* 42%*	2	
Zi, 2014 [83]	pWMH	16	16	62.0 (4.9)	56%	8 (6.3–10.3)	63%	19%	19%*	1, 2, 3	

Table 1 note: Data are presented as mean (SD) or median (range), unless otherwise stated; CVD: cerebrovascular disease; dWMH: deep white matter hyperintensities; MCI: mild cognitive impairment; pWMH: Periventricular white matter hyperintensities; SIVD: subcortical ischaemic vascular disease; SVaD: subcortical ischaemic vascular dementia; SVD: cerebral small vessel disease; TIV: total intercranial volume; VaD: vascular dementia; VCI: vascular cognitive impairment; VCI-ND: vascular cognitive impairment – no dementia; WMH: white matter hyperintensities. Controls matched for: 1 Age; 2 Sex; 3 Education; 4 Premorbid IQ; 5 Vascular risk factors; 6 history of hypertension. Where cells are blank, no data were available. * Current smoker. † Same control group used as comparison for both/all SVD groups.

Table 2: Summary of socio-demographic and vascular risk data for SVD and control cohorts

	SVD cohorts		Control cohorts	
	cohorts (n=89)	mean (SD or 95% CI)	cohorts (n=71)	mean (SD or 95% CI)
mean age*	88	69.3 (67.8, 70.9)	70	66.4 (64.6, 68.2)
% female	76	49.0 (15.9)	63	50.9 (15.0)
mean years education*	67	10.3 (9.7, 10.9)	53	10.8 (10.1, 11.6)
% hypertension	48	66.7 (23.0)	34	37.8 (20.7)
% diabetes	45	25.5 (13.7)	31	17.1 (13.5)
% hypercholesterolemia	5	55.1 (20.0)	4	35.1 (12.3)
% history of smoking	28	28.3 (16.1)	16	25.6 (16.9)

Table 2 note: We did not test for differences in age, sex, level of education, or vascular risk factors between the SVD and control groups as some studies only reported these data for the SVD group, therefore, comparisons would not include all participants contributing cognitive data to the meta-analyses. * Mean age and mean years of education were calculated using random effects meta-analysis in the meta package in R version 3.6.1 (Schwarzer G. "meta: An R package for meta-analysis." R News 2007, 7(3), 40–45). Only studies that presented group level data for age and years of education as mean and standard deviation were included in these meta-analyses.

Meta-analyses

The pooled estimated effect size for each meta-analysis demonstrated that on average, control cohorts outperformed SVD cohorts on cognitive tasks in every domain examined (see Table 3 and forest plots in Figure 2 and Figures S1 – S6). I^2 values, which are an indicator of inconsistency between effect sizes in the meta-analyses, were high in each meta-analysis.

Table 3: Results of meta-analysis models for each cognitive domain

							Heterogeneity	
	Studies	Outcomes	Estimate (SE)	95% CI	Degrees of freedom	Uncorrected p value	τ^2	I^2
Processing Speed	37	88	-0.885 (0.14)	-1.17, -0.60	35.8	$2.3x10^{-7}$	0.6	91.4
Executive function	58	188	-0.936 (0.08)	-1.09, -0.78	56.1	$<2x10^{-16}$	0.4	87.6
Delayed memory	41	98	-0.898 (0.10)	-1.10, -0.69	39.6	$7.2x10^{-11}$	0.5	88.0
Attention	12	19	-0.622 (0.14)	-0.94, -0.31	10.6	0.001	0.2	80.8
Reasoning	16	25	-0.634 (0.14)	-0.93, -0.34	14.6	$4.2x10^{-4}$	0.2	76.5
Visuospatial ability	27	50	-0.720 (0.11)	-0.96, -0.48	25.3	$1.3x10^{-6}$	0.3	77.6
Language	24	42	-0.808 (0.10)	-1.01, -0.60	22.7	$3.2x10^{-8}$	0.3	81.2

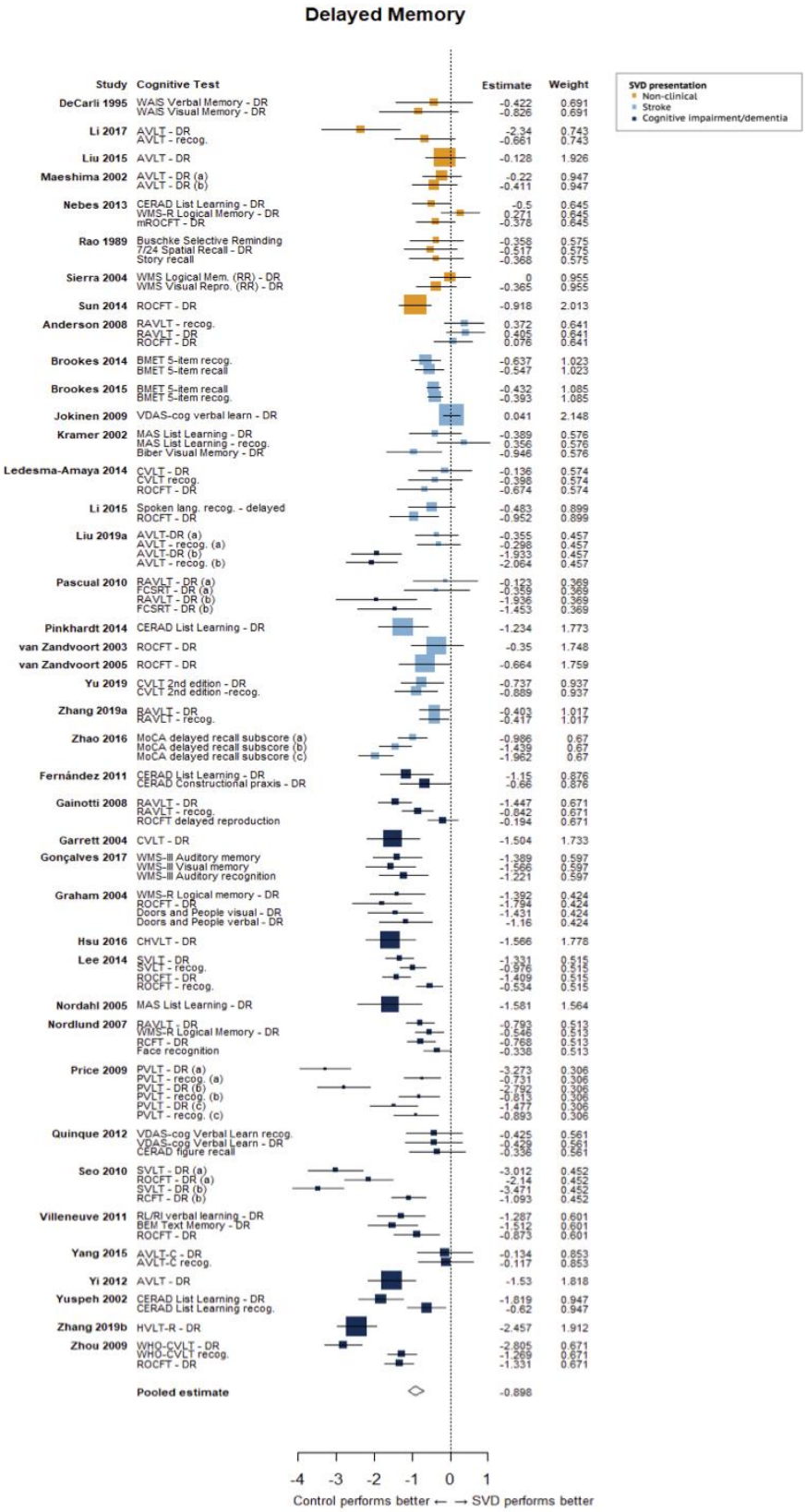


Figure 2: Forest plot of meta-analysis of tests of delayed memory

Note for Figure 2: The size of the squares reflects the weight given to the effect size. Letters in brackets indicate different SVD cohorts in a given study.

Meta Regression analyses

Our meta-analysis dataset included 26 cohorts with stroke presentations of SVD, 31 cohorts with cognitive impairment or dementia, and 32 cohorts with non-clinical presentations of SVD. There were no differences in years of education, or prevalence of hypertension or diabetes between the three SVD presentation categories, but cohorts with cognitive impairment/dementia were significantly older than those with non-clinical presentations of the disease (p=0.002; see Table 4).

Table 4: Demographics of non-clinical, cerebrovascular and cognitive SVD presentation categories

	Non-clinical		Cerebrovascular		Cognitive		
	% cohorts (n=32)	mean (SD or 95% CI)	% cohorts (n=26)	mean (SD or 95% CI)	% cohorts (n=31)	mean (SD or 95% CI)	Uncorrected p value†
mean age*	100	66.1 (62.8, 69.4)	96.2	69.0 (67.0, 71.1)	100	72.8 (70.9, 74.7)	0.002[a]
% female	71.9	53.2 (20.8)	92.3	42.0 (8.5)	93.5	51.6 (14.6)	0.027
mean years education*	68.8	10.6 (9.5, 11.7)	61.5	10.6 (9.4, 11.8)	93.5	9.9 (8.8, 10.9)	0.515
% hyper-tension	62.5	60.3 (28.7)	65.4	68.6 (17.6)	35.5	75.1 (16.4)	0.214
% diabetes	59.4	23.4 (16.4)	61.5	28.6 (12.7)	32.3	24.4 (9.1)	0.524

Table 4 note: *mean age and mean years of education were calculated using random effects meta-analysis in the meta package in R version 3.6.1. (Schwarzer G. "meta: An R package for meta-analysis." R News 2007, 7(3), 40–45). Only studies that presented group level data for age and years of education as mean and standard deviation were included in these meta-analyses.
† p value refers to comparisons made by one-way ANOVA.
[a] significant difference at p<0.01 between non-clinical and cognitive groups.

We did note, however, that vascular risk data were least often reported for cohorts with a cognitive presentation of SVD (see Table 5), which could suggest that these factors are perceived as being less relevant to cohorts with MCI or dementia. Additionally, tests of processing speed, executive function, attention and reasoning were most frequently carried out in cohorts with stroke and tests of delayed memory, visuospatial ability and language were most commonly carried out in cohorts with cognitive impairments (see Table 6).

Table 5: Percentage of included studies (total studies, and by SVD presentation) that report demographic data and vascular risk data

	% all studies (n=69)	% studies with non-clinical SVD cohorts (n=23)	% studies with stroke cohorts (n=24)	% studies with cognitive impairment/dementia cohorts (n=26)
Socio-demographic				
Age	100%	100%	100%	100%
Sex	89.9%	73.9%	91.7%	96.2%
Education (level or years)	88.4%	82.6%	83.3%	96.2%
Vascular risk				
Hypertension history	53.6%	60.9%	62.5%	30.8%
Diabetes history	46.4%	56.5%	58.3%	26.9%
Hypercholesterolemia history	7.2%	0%	16.7%	3.8%
Smoking status*	30.4%	30.4%	50%	11.5%
Cognitive				
Premorbid/peak cognitive function	4.1%	0%	16.6%	7.7%

Table 5 note: Pascual [52], Liu [45], and Liu [46] have cohorts in both the stroke and cognitive impairment/dementia groups, and Ishii [31] has cohorts in the non-clinical and cognitive impairment/dementia groups, so these studies are represented twice. *includes current, ever or never smoking.

Table 6: Percentage of cohorts in each SVD presentation category reporting cognitive outcomes in each domain

	Non-clinical		Stroke		Cognitive impairment/dementia	
	% cohorts (n=32)	number of outcomes	% cohorts (n=26)	number of outcomes	% cohorts (n=31)	number of outcomes
Processing Speed	50.0	36	69.2	31	45.2	21
Executive function	84.4	68	88.5	57	77.4	63
Delayed memory	28.1	16	65.4	30	74.2	52
Attention	15.6	5	23.1	8	16.1	6
Reasoning	12.5	6	30.8	9	22.6	10
Visuospatial ability	34.4	14	34.6	10	48.4	26
Language	9.4	4	38.5	14	54.8	24

Table 6 note: Pascual [52], Liu [45], and Liu [46] have cohorts in both the stroke and cognitive impairment/dementia groups, and Ishii [31] has cohorts in the non-clinical and cognitive impairment/dementia groups, so these studies are represented twice.

Meta-regression models investigating differences in cognitive effect sizes of the three SVD presentation groups indicated that the effect size for delayed memory was 0.83 standard deviations greater for the stroke cohorts (95% CI: 0.44, 1.21; p<0.001) and 0.85 standard deviations greater for non-clinical cohorts (95% CI: 0.40, 1.29; p=0.001), than cohorts with a cognitive impairment/dementia. We also found that the effect size was 0.49 standard deviations greater in the domain of executive function (95% CI: 0.10, 0.88; p=0.015), and 0.68 standard deviations greater in the domain of visuospatial ability (95% CI: 0.30, 1.01; p=0.002) for the non-clinical cohorts than the cohorts with a cognitive impairment/dementia (see Supplementary File 7 for full results). It is possible that the inclusion of samples with cognitive impairments (including MCI and dementia) could be driving the findings that SVD cohorts overall performed more poorly on tests of memory than control cohorts. However, visual inspection of forest plot for memory (Figure 2) suggests that this is unlikely to be the case as almost all cohorts in each presentation group show deficits relative to control cohorts in the domain of memory. Including SVD presentation as a predictor in meta-regression models had little effect on study heterogeneity.

Meta-regression models investigating the impact of differences in age, education and the prevalence of vascular risk factors between SVD vs. control groups on cognitive effect sizes, indicated that the difference in cognitive performance between SVD and control groups could be due to lower levels of education in SVD cohorts (see Supplementary File 8 for full results). For every 1 year of difference in education between SVD and control groups, the cognitive effect size decreased (indicating superior performance of the control groups) by an estimated 0.23 standard deviations in the domain of executive function (95% CI: -0.37, -0.09; p=0.004), 0.28 standard deviations in the domain of visuospatial ability (95% CI: -0.46, -0.10; p=0.009), and 0.31 standard deviations in the domain of language (95% CI: -0.46, -0.16; p=0.001). Including education as a predictor in meta-regression models reduced I^2 values by approximately 13% in the domain of visuospatial ability and language, suggesting that education may account for some of the variability in cognitive effect sizes in these domains. Overall however, I^2 values remained high. This could be due to our use of group-level demographic and vascular risk data, which may limit power to detect interactions between individual-level covariates and cognitive effect sizes. Meta-analytic approaches utilising individual patient data are increasingly popular, but rely upon the availability of patient-level datasets, which in our sample were rare.

The majority of the meta-regression models assessing the influence of age on cognitive effect size produced df <4, suggesting that model results were unreliable. Therefore, we further investigated the potential influence of age by re-running meta-analysis models excluding studies in which SVD and control groups were not matched for age. In these analyses magnitudes of estimated effect sizes were similar to the initial meta-analysis models and all models remained significant. Meta-regression models investigating the impact of hypertension and diabetes on cognitive effects also produced degrees of freedom <4 suggesting that model results were unreliable, likely due to the limited availability of vascular risk data.

Study Quality

The mean study quality score was 4.97 (median 5, range 2-8). The magnitudes estimated effect sizes were comparable to those using the full meta-analysis dataset, and all models remained significant (see Supplementary File 9). I^2 values reduced by a small amount in the domains of executive function, visuospatial ability, attention and language, but increased in the other domains.

Discussion

Based on 3229 individuals with SVD and 3679 control participants from 69 studies, our meta-analyses demonstrated that on average individuals with SVD perform more poorly than controls on cognitive tests in the domains of executive function, delayed memory, processing speed, language, visuospatial ability, reasoning, and attention. These findings support the notion that SVD-related cognitive impairment is global, affecting all examined cognitive domains, and mirrors the global effects of SVD seen on brain imaging [84,85]. This global cognitive impairment was present for cohorts with cerebrovascular, cognitive, and non-clinical presentations of SVD, although cohorts with a cognitive presentation of SVD had greater deficits in executive function, delayed memory, and visuospatial ability.

Our findings concur with those of a recent meta-analysis of 27 studies by Vasquez and Zakzanis [86], which compared cognitive abilities of participants with vascular cognitive impairment without dementia (n=794) and control subjects (n=1750), finding deficits (from largest to smallest) in processing speed, immediate memory, delayed memory, general

cognitive ability, language, executive function, visuospatial ability and working memory. Together with our meta-analysis, these results suggest that cognitive changes associated with SVD extend beyond impaired executive function and slowed processing speed to include multiple other domains, which often remain untested due to the perception that they are less affected in vascular cognitive impairment.

Results of our meta-regression analyses suggested that differences in years of education between SVD and control groups account for a proportion of the differences in cognitive test scores in the domains of memory, executive function, and visuospatial ability. All other cognitive domains showed a similar direction of effect (albeit non-significant) except processing speed, which could support the suggestion that processing speed might be less amenable to beneficial effects of education than other cognitive abilities [87]. A recent meta-analysis of early life risk factors in cerebrovascular disease found that fewer years of education was associated with increased MRI markers of SVD [88]. Similarly, our findings also highlight education as a (potentially modifiable) risk factor for SVD-related cognitive impairment, emphasising the importance of accounting for an individuals' level of education in analyses of cognitive change over time, or comparisons of cognitive ability between groups.

An estimation of cognitive ability prior to the onset of decline is another potential confound in assessments of cognitive decline, as any change in cognitive ability will be relative to an individuals' prior level [89]. Despite this, prior cognitive ability is seldom considered in clinical studies. Of the 69 studies included in our meta-analysis, only seven [15,19,20,27,29,55,72] estimated prior cognitive ability using a test such as the National Adult Reading Test (NART), and only two of these studies included this score as a covariate in their analyses. As the NART is a vocabulary task, it was included as a cognitive outcome in our meta-analysis of language. Therefore, our finding that individuals with SVD score more poorly on tests of language than control cohorts could reflect lower premorbid cognitive ability in the SVD cohorts, in addition to any decline in language abilities as a result of SVD.

A key strength of this study is that we did not pre-select literature that focuses on a certain lesion type, or clinical, cognitive, or behavioural presentation of SVD. Additionally, we included studies published in any language, which enabled us to analyse data from 18

countries in six continents. This broad approach to the characterisation of SVD aimed to capture a range of cohorts that represent the diversity of SVD presentations in different cultural and ethnic groups, and enable us to apply our findings to a range of clinical contexts. However, our study also has several important limitations. We observed high levels of heterogeneity in our meta-analyses. Whereas including SVD presentation and differences in demographic and vascular risk factors between SVD and control cohorts as predictors in meta-regression analyses reduced the I^2 values of some models, we were unable to account for the vast majority of the heterogeneity we observed. One reason for this could be our use of group-level demographic and vascular risk data, which may limit the power to detect interactions between individual-level covariates and cognitive effect sizes. Meta-analytic approaches utilising individual patient data are increasingly popular, but rely upon the availability of patient-level datasets, which in our sample were rare. Incomplete reporting of vascular risk data also limited our assessment of their impact on cognitive effect sizes. Approximately half of all included studies reported history of hypertension and diabetes, but only one third of studies reported smoking status, despite its known association with SVD progression [1]. Similarly, we were unable to assess whether age at presentation to clinical services accounted for apparent differences in performance on memory tests between cohorts with a cognitive presentation of SVD and other SVD presentations - very few studies reported data on disease duration, with the exception of eight studies of stroke populations that reported average/minimum/maximum duration since stroke onset [29,40,65,68,69,74,78]. We were also limited by our reliance on the quality of study reporting; our literature search identified three studies whose results were inaccurately reported, or were statistically implausible and so, were excluded from our analyses [90-92].

SVD-related cognitive impairment extends beyond deficits in processing speed and executive function - it affects a broader range of cognitive domains than previously considered. Our findings support the use of cognitive test batteries that cover a range of cognitive domains to fully investigate the extent of SVD-related cognitive impairment. Future investigations should include individuals with varying presentations of SVD, to represent the diversity of its clinical and non-clinical manifestations, and to enable more accurate characterisation and comparison of SVD subtypes. Accounting for educational level, or estimates of premorbid cognitive ability is essential for accurate assessment of SVD-related cognitive ability, and

more complete reporting of vascular risk data will enable further exploration of the relative contributions of vascular risk factors to vascular cognitive impairment.

Contributors

The study was designed by OH and supervised by JMW and IJD. OH conducted the literature search and OH, EB, TR, AS, and CM screened papers for inclusion in the review. OH, EB, XL and EJ extracted data from eligible papers. OH and AJ categorised cognitive test data into domains. OH analysed and interpreted the data with contributions from JMW and IJD. OH wrote the first draft of the manuscript – all authors contributed to later versions.

Declaration of interests

The authors declare no conflicts of interest.

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4.3 Summary

Based on 3229 individuals with SVD and 3679 control participants from 69 studies, the meta-analyses presented above demonstrated that on average, cohorts with SVD demonstrated impaired performance (relative to controls) on cognitive tests in all domains examined. Thus, contrary to recent consensus statements that emphasise impairments in executive function and processing speed, SVD-related cognitive impairments appear to affect all major domains of cognitive ability. In order to accurately assess the full extent of SVD-related cognitive impairments, future studies should use a comprehensive cognitive test battery that covers a wide range of domains.

Results of meta-regression analyses indicated that cohorts with cognitive presentations of SVD (i.e. SVD-related MCI or dementia) performed more poorly than cohorts with non-clinical presentations of the disease on tests of delayed memory, executive function and visuospatial ability; and more poorly than cohorts with stroke presentations on tests of delayed memory. Despite the differences in these effect size magnitudes, SVD cohorts demonstrated impaired cognitive performance across all domains, regardless of whether they presented with SVD-related stroke, MCI or dementia, or did not present clinically. This finding suggests that SVD associates with global cognitive changes across the spectrum of SVD presentations, from relatively healthy individuals, to those with dementia.

Finally, the results of meta-regression analyses indicated that level of education is associated with the severity of SVD-related cognitive impairments, such that fewer years of education in the SVD cohorts contributed to their poor cognitive performance in certain domains. A further conclusion, therefore, is that future studies examining cognitive ability in SVD should collect information about educational level or premorbid cognitive ability and include it, where appropriate, as a covariate in analyses.

After examining the pattern of cognitive impairments associated with SVD on a meta-analytic level, the next chapter will zoom in on the structure of SVD-related cognitive change in a cohort of community-dwelling older individuals, with the benefit of being able to account for potential confounding factors, such as vascular risk and childhood cognitive ability.

Chapter 5 Examining cross-sectional associations between the radiological burden of SVD and cognitive abilities

5.1 Introduction

In recent years a handful of studies have attempted to more accurately represent the total brain burden of SVD by constructing an SVD burden score (see Chapter 3, section 3.3). In several studies, a greater SVD burden score was found to associate with poorer cognitive test scores, and in some cases was found to be a stronger predictor of cognitive outcomes than individual radiological markers of SVD. The study presented in this chapter further develops the work of Staals and colleagues (2015), who, using data from the LBC1936, combined visual ratings of WMH, visible PVS, lacunes and microbleeds to construct a continuous latent variable representing the total brain burden of SVD. Also using data from the LBC1936, in the present study, I test whether it is feasible to include continuous measures of WMH and PVS in the total SVD variable, and whether doing so increases the strength of its cross-sectional associations with domain-specific cognitive measures.

However, as discussed in Chapter 2, scores from a diverse range of cognitive tests typically correlate positively with one another, owing to the construct of general cognitive ability. This means that if an individual scores poorly on a given cognitive test, they are also likely to perform poorly on a wider battery of tests. On a typical battery of cognitive tests, general cognitive ability is found to account for approximately 40% of the variability in individual cognitive test scores and approximately 60% of the variability in broader domains of ability (Carroll, 1993). As discussed in Chapter 3, SVD is commonly considered to affect the domains of processing speed and executive function, whilst abilities such as memory and language remain relatively unaffected. This study presented in this chapter investigates whether SVD does indeed have a specific association with slowed processing speed, or whether this association may be due to SVD's overall association with poorer general cognitive ability.

This study has been submitted to *Neurobiology of Aging* and is available on the *medRxiv* preprint server at https://doi.org/10.1101/2021.02.02.21250986. Supplementary files for this chapter are presented in Appendix C.

Associations between total MRI-visible small vessel disease burden and domain-specific cognitive abilities in a community-dwelling older-age cohort

Running head: SVD burden and domain-specific cognitive abilities

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Abstract

Cerebral small vessel disease (SVD) is a leading cause of vascular cognitive impairment, however the precise nature of SVD-related cognitive deficits, and their associations with structural brain changes, remain unclear. We combined computational volumes and visually-rated MRI markers of SVD to quantify total SVD burden, using data from the Lothian Birth Cohort 1936 (n=540; age:72.6±0.7 years). We found negative associations between total SVD burden and general cognitive ability (standardised β: -0.363; 95%CI: [-0.49, -0.23]; p(FDR)<0.001), processing speed (-0.371 [-0.50, -0.24]; p(FDR)<0.001), verbal memory (-0.265; [-0.42, -0.11]; p(FDR)=0.002), and visuospatial ability (-0.170; [-0.32, -0.02]; p(FDR)=0.029). Only the association between SVD burden and processing speed remained after accounting for covariance with general cognitive ability (-0.325; [-0.61, -0.04]; p(FDR)=0.029). This suggests that SVD's association with poorer processing speed is not driven by, but is independent of its association with poorer general cognitive ability. Tests of processing speed may be particularly sensitive to the cognitive impact of SVD, but all major cognitive domains should be tested to determine the full range of SVD-related cognitive characteristics.

Keywords: Cerebral small vessel disease; cerebrovascular disease; vascular cognitive impairment; white matter hyperintensities; cognitive aging; magnetic resonance imaging

Introduction

Cerebral small vessel disease (SVD) is a leading cause of vascular cognitive impairment, contributing to multiple neurological disorders ranging from stroke, to mild cognitive impairment and dementia. Whereas current neuroimaging methods lack the spatial resolution to visualise the brain's small vessels themselves, the downstream impact of their dysfunction is visible on brain imaging as white matter hyperintensities (WMH) and lacunes of presumed vascular origin, visible perivascular spaces (PVS) and cerebral microbleeds (Wardlaw et al., 2019). The presence and progression of radiological markers of SVD are frequently used as outcome measures in trials of interventions and treatments for SVD, however, the nature and extent of their associations with domain-specific cognitive outcomes remains unclear.

The majority of the literature examining SVD-related brain changes and cognitive ability focuses on individual radiological markers of SVD (most commonly WMH volume), thus fails to account for their potentially cumulative impact on cognitive performance. There is evidential support for considering the 'total' burden of SVD as a variable: different types of SVD lesions commonly occur together, are aetiologically related (Wardlaw et al., 2013), and associate with one another across a range of patient and healthy ageing populations (Ghaznawi et al., 2019, Potter et al., 2015). In recent years, studies have quantified the total burden of SVD with a 0-4 score, which allocates one point for the presence of WMH, PVS, lacunes or microbleeds (Al Olama et al., 2020, Banerjee et al., 2018, Del Brutto et al., 2018, Huijts et al., 2013, Uiterwijk et al., 2016). Whereas the 0-4 score can be calculated quickly from visual inspection of a brain scan, it lacks sensitivity to the range or severity of the individual SVD markers. To increase the fidelity of SVD burden quantification, two recent studies have developed continuous total SVD scores (Jokinen et al., 2020, Staals et al., 2015), finding negative associations between the continuous SVD burden score and domain-specific cognitive abilities. These studies also found that the magnitudes of these associations surpassed those of models using a simple 0-4 SVD burden score (Staals et al., 2015) or individual MRI markers of SVD (Jokinen et al., 2020) as predictors of cognitive performance. However, research on cognitive ageing has established that age-related cognitive decline is not only observed across different domains of cognitive ability, but is shared between them owing to an overall decline in general cognitive ability (Salthouse, 2010, Tucker-Drob et al., 2019). A key outstanding question, therefore, is whether poor cognitive performance in

certain cognitive domains is associated with general cognitive decline, or whether SVD has additional independent associations with specific domains of cognitive ability.

In this study we extend the work of Staals and colleagues (2015) by constructing a variable representing the total MRI-visible burden of SVD. We use structural equation modelling to combine continuous computational measures of white matter hyperintensities (WMH) and visible perivascular spaces (PVS), as opposed to previous studies that have employed ordinal measures derived from visual rating scales. We test whether the inclusion of these continuous SVD markers increases the sensitivity of the SVD score in its associations with general and domain-specific cognitive abilities. We then test whether poor performance in certain cognitive domains is associated with general cognitive decline, or whether SVD has additional independent associations with specific domains of cognitive ability. By gaining insight into the nature of the associations between the total brain burden of SVD and cognitive abilities, we aim to better characterise SVD-related cognitive impairment and facilitate its accurate measurement in trials and in clinical management.

Materials and Methods

Study cohort

Participants were members of the LBC1936, which has been described previously (Taylor et al., 2018). Briefly, the LBC1936 is a longitudinal follow-up to the Scottish Mental Survey of 1947, which assessed the cognitive ability of 70,805 11 year-old children, who were born in 1936 and were attending school in Scotland (Scottish Council for Research in Education, 1949). The present study includes participants from Wave 2 of the study, the first wave at which neuroimaging was carried out (usable neuroimaging data were available for n=680). Visible PVS are extremely small on neuroimaging (≤3 mm), therefore their computational detection is highly sensitive to noise and motion artefacts. Because of this, quality requirements for the MR images used in this study were high and images for 140 participants with available neuroimaging data could not be processed through the PVS pipeline (Ballerini et al., 2020). Reasons for this were failed registration of the centrum semiovale, noise or motion artefacts (which can have a similar appearance to PVS), or where small WMH were misclassified as PVS (Ballerini et al., 2020). Lack of computational PVS segmentation was the only factor that prevented inclusion in the study, thus the remaining 540 participants constitute our final sample. Approval for the LBC1936 was obtained from

the Scotland A Research Ethics Committee for Scotland (07/MRE00/58). All participants gave written, informed consent.

MRI acquisition and radiological markers of SVD

Details of the MRI acquisition protocol have been published previously (Wardlaw et al., 2011). Briefly, participants were scanned using a GE Signa Horizon HDx 1.5 Tesla clinical scanner (General Electric, Milwaukee, WI) operating in 'research mode', equipped with a self-shielding gradient set (33 mT/m maximum gradient strength) and manufacturer supplied eight-channel phased-array head coil. Sequences acquired were T1-weighted (T1W), T2-weighted (T2W), T2*-weighted (T2*W) and fluid attenuated inversion recovery-weighted (FLAIR) images. MRI markers of SVD (WMH, PVS, lacunes and microbleeds) were measured using a combination of computational and visual rating methods, all performed blind to clinical and cognitive data (see Table 1; Wardlaw et al., 2011, 2013). In all analyses we divide WMH volume by total intracranial volume (TIV) to account for differences in head size.

Cognitive data

Participants completed the Moray House Test No.12 (MHT), a test of general intelligence, at the age of 11 as part of the Scottish Mental Survey of 1947 (Scottish Council for Research in Education, 1933). In later life, participants completed a comprehensive battery of cognitive tests as part of the LBC1936, which we have grouped into three domains (processing speed, verbal memory, and visuospatial ability) according to prior work characterising their correlational structure (Tucker-Drob et al., 2014). The domain of processing speed includes Digit Symbol Substitution and Symbol Search from the Wechsler Adult Intelligence Scale-III (WAIS-IIIUK; Wechsler, 1998a) and two experimental tasks: Four Choice Reaction Time (Deary et al., 2001) and Inspection Time (Deary et al., 2004). Four Choice Reaction Time scores were multiplied by -1 so that higher scores indicated better performance. The domain of verbal memory includes Verbal Paired Associates (total score) and Logical Memory from the Wechsler Memory Scale IIIUK (WMS-IIIUK; Wechsler, 1998b), and Digit Span (WAIS-IIIUK). Visuospatial ability includes Block Design, Matrix Reasoning (both WAIS-IIIUK) and Spatial Span (average of forwards and backwards; WMS-IIIUK). Scores on the ten cognitive tests included these domains were considered together as an indicator of general cognitive

ability, given the well-replicated shared covariances of test scores across domains (Deary et al., 2010).

Table 1: Definitions of key imaging features of SVD on structural MRI

SVD feature	Definition and acquisition
White matter hyperintensities (WMH)	Visual rating: Periventricular and deep WMH were rated on the Fazekas scale (range 0-3) using FLAIR- and T2-weighted sequences (Fazekas et al., 1987). Computational volume: WMH and total intracranial volumes (TIV) were measured using MCMxxVI (Valdés Hernández et al., 2010), a validated multispectral image processing method that combines T2, T2*W and FLAIR sequences for segmentation. All slices of all scans were checked by a trained observer and manually corrected, if necessary, to ensure that no true WMH had been omitted and to avoid including erroneous tissues in the WMH.
Visible perivascular spaces (PVS)	Visual rating: PVS in the basal ganglia were quantified using a previously described visual rating scale (Doubal et al., 2010) and were defined as small punctate or linear hyperintensities, in axial and longitudinal section respectively, on T2W that are <3mm in diameter. Larger PVS may be visible on T1W as decreased signal, but not visible on T2W or FLAIR (Wardlaw et al., 2011, 2013). Computational count: PVS were computationally segmented in the native T2W space in the centrum semiovale using a recently validated technique (Ballerini et al., 2018, 2020) and are presented as total number of PVS. After segmentation of the PVS, all binary PVS masks (superimposed on T2-weighted images) were visually checked for the accurate quantification of PVS by a trained operator and were accepted or rejected blind to all other data. Where ambiguity arose, FLAIR and T1-weighted sequences were also checked (Ballerini et al., 2020).
Lacunes	Lacunes were classified as being present or absent and were defined as small (>3mm and <2cm in diameter) subcortical lesions of CSF-equivalent signal on T2W and decreased signal on T1W and FLAIR images in the white matter, basal ganglia, and brainstem (Wardlaw et al., 2011, 2013).
Cerebral microbleeds	Cerebral microbleeds were classified as being present or absent and were defined as small (<5mm), homogenous, round foci of low signal intensity on T2*W images in the white matter, basal ganglia, brain stem, cerebellum, and cortico-subcortical junction (Wardlaw et al., 2011, 2013).

Table 1 note: Visual ratings were made by an experienced, registered neuroradiologist and a random 20% sample and any uncertain cases were independently checked by a second neuroradiologist, with disagreements resolved by consensus.

Covariates

Cognitive and neuroimaging data were acquired on two separate occasions. To account for variation in time intervals between these two occasions across the cohort, we adjusted the manifest cognitive variables for the difference in days between imaging and cognitive data acquisition outside of the SEM models (residualised using linear regression). We included age in years at the time of MRI, sex, vascular risk, the depression sub-score from the Hospital Anxiety and Depression Scale (HADS-D), and MHT score at age 11 (subsequently referred to as age-11 IQ) as covariates in all of our models. Vascular risk variables included self-reported history of hypertension (yes/no), diabetes mellitus (yes/no) and smoking status (ever/never); blood-derived glycated haemoglobin (% total HbA1c); blood-derived total cholesterol (mmol/l); and systolic and diastolic blood pressure (average of six readings: three seated and three standing), which were measured by trained nurses. We used confirmatory factor analysis (CFA) to construct a latent variable representing vascular risk as previously modelled in this cohort (Wardlaw et al., 2014) and extracted its factor score for inclusion as a covariate.

Statistical analysis

Measurement models

We used CFA to construct a computationally-derived latent variable representing the total MRI-visible burden of SVD. This CFA assumed that the covariance among its indicators (WMH volume/TIV, PVS, lacunes, and microbleeds) was due to a single underlying factor (SVD), which is separate from unique and error variance in the four contributing variables. WMH volume/TIV and centrum semiovale PVS count were continuous computationally-derived variables, and lacunes and microbleeds were binary variables (i.e. present/absent), derived from visual assessment.

We also used CFA to reconstruct the latent total SVD variable based on ordinal visual scores used by Staals et al. (2015), which included deep and periventricular Fazekas scores as measures of WMH (both range 0-3), a visual rating scale for the assessment of PVS in the basal ganglia (range 0-4; Doubal et al., 2010), and counts of cerebral microbleeds and lacunes, which we converted to binary variables (present/absent) due to the low frequency of values greater than one.

Multivariable SEM models

First, we specified separate linear regressions between the computationally-derived SVD burden variable (independent variable) and latent variables of general cognitive ability, processing speed, verbal memory, and visuospatial ability. These models tested the association between total SVD burden and the cognitive factors as described in the measurement models above. We included age, sex, vascular risk (extracted factor score), HADS-D score, and age-11 IQ as covariates in a step-wise manner to assess their impact on any associations. Covariates were free to correlate with one another and with total SVD burden, and were also regressed on the cognitive factor. To assess the extent to which these associations might be driven by the contribution of WMH to the SVD burden score, we also ran these models with WMH/TIV as the predictor and compared the effect size magnitudes from both sets of models using the Williams test (Williams, 1959), implemented in the cocor package (Diedenhofen and Musch, 2015) in R version 4.0.1 (R Core Team, 2020).

Next, we ran these analyses using the reconstructed total SVD variable as created by Staals et al. (2015) as the predictor. We compared the effect size magnitudes of these models with those of models including the computationally-derived SVD variable as a predictor, again using the Williams test.

General cognitive ability accounts for approximately 40% of the variability in performance on diverse batteries of cognitive tests (Carroll, 1993). Thus, given that cognitive domains are all substantially and positively correlated, in order to generate a domain-specific cognitive score, one must account for its covariance with other cognitive domains (i.e. general cognitive ability). To account for the confounding effects of general cognitive ability, we next tested associations between the computationally-derived SVD burden variable and a bifactor model of general cognitive ability (Fig. 1), which partitions variance in the cognitive test scores into that which contributes to general cognitive ability, and that which uniquely contributes to the domain-specific factors. The results of this model will indicate whether total SVD burden associates with any of the domain-specific cognitive scores independently of the variance that the domain-specific scores share (i.e. general cognitive ability). In this model we included age, sex, vascular risk HADS-D score, and age-11 IQ simultaneously as covariates.

Figure 1: Diagram illustrating a bifactor model of general cognitive ability

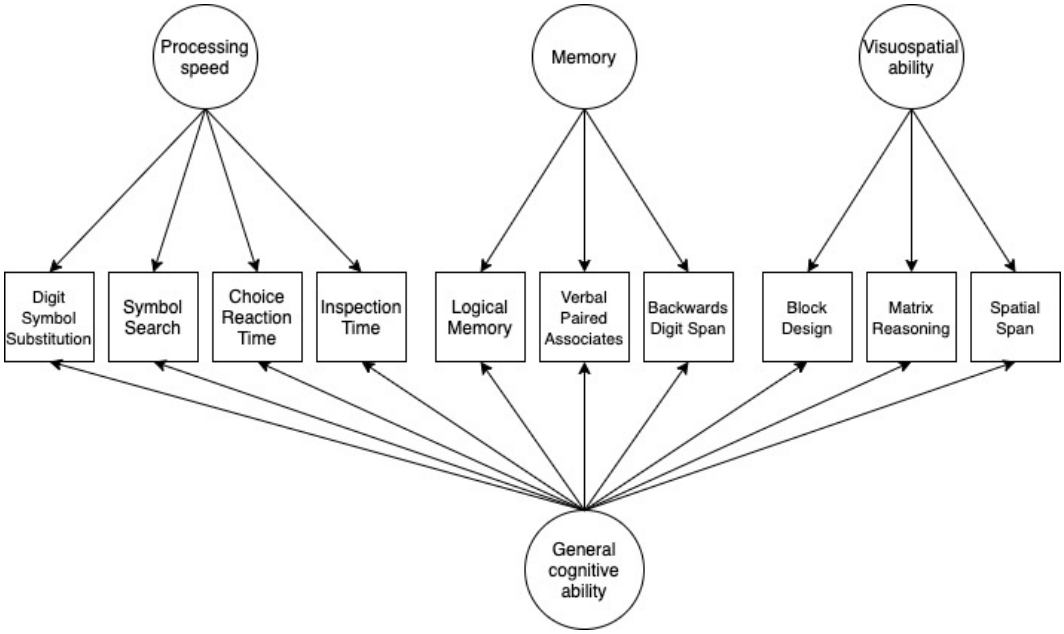

Figure 1 note: Following conventional SEM notation, variables in squares were observed and measured, and variables in circles represent unmeasured latent variables. In this diagram, arrows indicate relationships between the underlying latent variables and the observed manifest variables.

The estimator for all multivariable SEM analyses was weighted least square mean and variance adjusted (WLSMV), which does not make distributional assumptions about observed variables. WLSMV uses logit link for continuous, and probit link for categorical variables. Model fit was assessed using four absolute fit indices: Root Mean Square Error of Approximation (RMSEA; <0.06 considered acceptable), Comparative Fit Index (CFI; >0.95 acceptable), Tucker-Lewis Index (TLI; >0.95 acceptable), and Standardized Root Mean Square Residual (SRMR; <0.08 acceptable). Pairwise present data were analysed due to the small amount of missing data (all cognitive variables had n ≥530). Data were analysed in MPlus version 8.3 (Muthén and Muthén, 1998-2017). We corrected p-values for multiple comparisons using the False Discovery Rate adjustment (FDR; Benjamini and Hochberg, 1995) with p.adjust in R version 4.0.1 (R Core Team, 2020).

Data availability

Data supporting this study are available upon reasonable request from the corresponding authors.

Results

Participant characteristics and SVD burden quantification

Characteristics of the study participants are presented in Table 2. The four MRI markers of SVD loaded significantly onto the computationally-derived SVD burden variable (Fig. 2) and the model fitted well (RMSEA=0.00; CFI=1.00; TLI=1.02; SRMR= 0.019). The four marker variables had moderate to large loadings on the latent SVD variable, which accounted for 25% of the variance in WMH/TIV, 10% of the variance in PVS, 32% of the variance in lacunes, and 18% of the variance in microbleeds.

Table 2: Characteristics of the study sample

	n	Mean (SD) unless otherwise stated
Sociodemographic		
Age, years	540	72.6 (0.7)
Female, n (%)	540	252 (46.7%)
Education, years	540	10.9 (1.2)
Vascular risk		
Hypertension history (yes), n (%)	540	259 (48.0%)
Systolic blood pressure mmHg	534	146.5 (18.0)
Diastolic blood pressure mmHg	534	79.7 (18.0)
Diabetes history (yes), n (%)	540	54 (10.0%)
HbA1c % total	518	5.7 (0.6)
Cholesterol, mmol/l	521	5.2 (1.1)
CVD history, n (%)	540	154 (28.5%)
Smoking status, n (%)	540	Ever = 274 (50.7%) Never = 266 (49.3%)
Neurological/psychiatric		
Self-reported dementia, n (%)	540	0 (0%)
Self-reported stroke, n (%)	534	37 (10.5%)
HADS-D score	540	2.5 (2.1)
Neuroimaging		
Total WMH volume/TIV	536	0.008 (0.009)
PVS count	540	258.7 (94.6)
Lacunes, n (%)	540	Present = 28 (5.1%) Absent = 512 (94.9%)
Microbleeds, n (%)	540	Present = 65 (12.0%) Absent = 475 (88.0%)
Cognitive		
Moray House Test score age-11 (max. 76)	511	50.2 (11.9)

Table 2 note: CVD: Cardiovascular disease; HADS-D: depression sub-score of the Hospital Anxiety and Depression Scale; PVS visible perivascular spaces; TIV: total intracranial volume; WMH: white matter hyperintensities of presumed vascular origin.

Figure 2: CFA diagram of latent variable representing total MRI-visible SVD burden

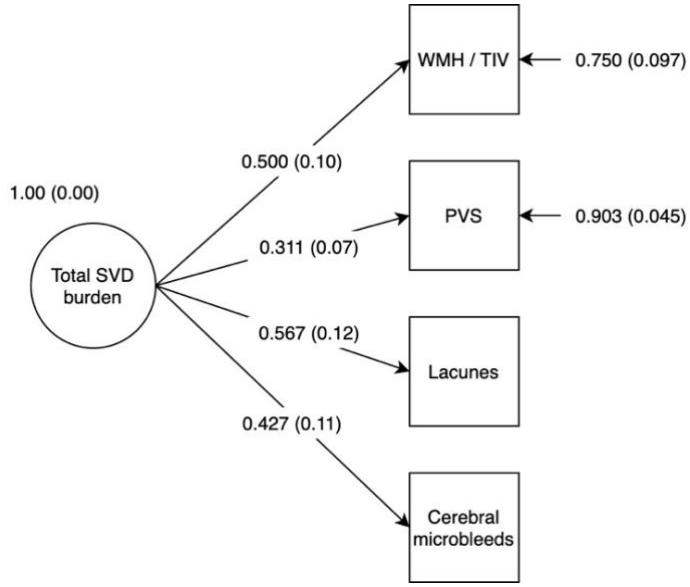

Figure 2 note: Latent variable representing total MRI-visible SVD burden. Estimator: WLSMV; RMSEA=0.00; CFI=1.00; TLI=1.02; SRMR=0.019. All indicators loaded significantly onto the factor at p<0.001. Standard errors are given in parentheses. For continuous variables (WMH and PVS) factor loadings represent standardised linear regression coefficients. For the binary variables (lacunes and microbleeds) factor loadings represent standardised probit regression coefficients. Factor loadings were freed for their interpretation. Following conventional SEM notation, variables in squares were observed and measured, and variables in circles represent unmeasured latent variables. Single headed arrows represent a relationship between two variables – in this model, this is either a linear or probit regression, with the arrow pointing towards the dependent variable.

Computationally-derived SVD burden score associates negatively with all cognitive domains

Total SVD burden demonstrated negative associations with all cognitive domains (Table 3). These associations remained significant after the inclusion of age, sex, vascular risk HADS-D score and age-11 IQ as covariates; covariate-adjusted absolute effect sizes range from -0.17 to -0.37. The latent variable representing total SVD burden accounted for 13% of the variance in general cognitive ability, 14% of the variance in processing speed, 7% of the variance in verbal memory, and 3% of the variance in visuospatial ability. Williams tests indicated that the magnitudes of these models (including all covariates) were significantly greater than those specifying WMH/TIV as the predictor: general cognitive ability (Williams' one-sided t-value=-7.38; p<0.001), processing speed (t=-7.28; p<0.001); verbal memory (t=-5.06; p<0.001), visuospatial ability (t=-2.81; p=0.0051). Results of associations between WMH/TIV and cognitive factors are presented in Table S3.

Similarly, the reconstructed total SVD burden variable used by Staals et al. (2015) associated negatively with all cognitive domains (Table 4). Williams tests indicated that the magnitudes of these models (including all covariates) were significantly smaller than those using the computationally-derived SVD burden variable as the predictor: general cognitive ability (Williams' one-sided t-value=-6.25; $p<0.001$), processing speed (t=-6.11; $p<0.001$); verbal memory (t=-4.48; $p<0.001$), visuospatial ability (t=-2.51; p=0.0123).

Table 3: Associations between the computationally-derived total SVD burden variable and cognitive domains (Table 3 note overleaf)

	Standardised β (SE)	95% CI	Uncorrected p value	FDR corrected p value	RMSEA	CFI	TLI	SRMR
General cognitive ability	-0.438 (0.08)	-0.595, -0.282	<0.001	<0.001	0.031	0.971	0.962	0.039
+ age	-0.467 (0.09)	-0.647, -0.287	<0.001	<0.001	0.028	0.974	0.966	0.038
+ age + sex	-0.467 (0.09)	-0.647, -0.287	<0.001	<0.001	0.054	0.895	0.867	0.051
+ age + sex + vascular risk	-0.459 (0.09)	-0.639, -0.279	<0.001	<0.001	0.057	0.871	0.837	0.053
+ age + sex + vascular risk + depression	-0.407 (0.08)	-0.569, -0.245	<0.001	<0.001	0.054	0.879	0.846	0.052
+ age + sex + vascular risk + depression + age-11 IQ	-0.363 (0.07)	-0.493, -0.233	<0.001	<0.001	0.056	0.873	0.836	0.052
Processing speed	-0.442 (0.08)	-0.589, -0.296	<0.001	<0.001	0.024	0.991	0.987	0.031
+ age	-0.430 (0.08)	-0.587, -0.273	<0.001	<0.001	0.013	0.997	0.995	0.029
+ age + sex	-0.426 (0.08)	-0.581, -0.272	<0.001	<0.001	0.053	0.933	0.903	0.043
+ age + sex + vascular risk	-0.455 (0.08)	-0.619, -0.291	<0.001	<0.001	0.050	0.933	0.901	0.043
+ age + sex + vascular risk + depression	-0.443 (0.08)	-0.601, -0.284	<0.001	<0.001	0.046	0.940	0.908	0.041
+ age + sex + vascular risk + depression + age-11 IQ	-0.371 (0.07)	-0.502, -0.240	<0.001	<0.001	0.046	0.940	0.905	0.040
Verbal memory	-0.329 (0.09)	-0.498, -0.160	<0.001	<0.001	0.000	1.000	1.000	0.026
+ age	-0.318 (0.09)	-0.496, -0.139	<0.001	<0.001	0.000	1.000	1.000	0.027
+ age + sex	-0.310 (0.09)	-0.485, -0.136	<0.001	<0.001	0.035	0.949	0.921	0.039
+ age + sex + vascular risk	-0.331 (0.09)	-0.511, -0.151	<0.001	<0.001	0.031	0.955	0.927	0.039
+ age + sex + vascular risk + depression	-0.324 (0.09)	-0.505, -0.143	<0.001	<0.001	0.029	0.959	0.931	0.038
+ age + sex + vascular risk + depression + age-11 IQ	-0.265 (0.08)	-0.418, -0.112	0.001	0.002	0.031	0.962	0.934	0.038
Visuospatial ability	-0.247 (0.08)	-0.412, -0.081	0.003	0.004	0.000	1.000	1.000	0.027
+ age	-0.221 (0.09)	-0.399, -0.043	0.015	0.018	0.000	1.000	1.000	0.026
+ age + sex	-0.231 (0.09)	-0.410, -0.052	0.011	0.015	0.031	0.966	0.947	0.037
+ age + sex + vascular risk	-0.226 (0.09)	-0.407, -0.044	0.015	0.018	0.028	0.968	0.949	0.037
+ age + sex + vascular risk + depression	-0.215 (0.09)	-0.393, -0.036	0.018	0.021	0.025	0.972	0.954	0.036
+ age + sex + vascular risk + depression + age-11 IQ	-0.170 (0.08)	-0.319, -0.020	0.026	0.029	0.022	0.982	0.968	0.034

Table 3 note. N=540 for all analyses. CFI: Comparative Fit Index; RMSEA: Root Mean Square Error of Approximation; SRMR: Standardized Root Mean Square Residual; TLI: Tucker Lewis Index. After the inclusion of sex as a covariate in the models, the TLI and/or CFI fell below conventional thresholds (both >0.95). Off-diagonal values of the residual correlation matrix indicated that there were correlations between sex and the residuals of several manifest cognitive variables, which were unaccounted for in our model. When we specified regressions between sex and these residuals, the TLI and CFI reached acceptable levels. Combined with the good fit of our initial measurement models, this indicates that the lower CFI and TLI values of these models are due to unspecified correlations between sex and cognitive variables and are not due to model mis-specification.

Table 4: Associations between the reconstructed SVD burden variable used by Staals et al. and cognitive factors

	Standardised β (SE)	95% CI	Uncorrected p value	FDR corrected p value	RMSEA	CFI	TLI	SRMR
General cognitive ability	-0.254 (0.05)	-0.360, -0.148	<0.001	<0.001	0.032	0.97	0.962	0.045
+ age	-0.242 (0.05)	-0.348, -0.135	<0.001	<0.001	0.030	0.969	0.961	0.046
+ age + sex	-0.244 (0.05)	-0.350, -0.139	<0.001	<0.001	0.048	0.915	0.893	0.054
+ age + sex + vascular risk	-0.236 (0.05)	-0.341, -0.130	<0.001	<0.001	0.051	0.895	0.869	0.056
+ age + sex + vascular risk + depression	-0.230 (0.05)	-0.332, -0.128	<0.001	<0.001	0.049	0.899	0.873	0.054
+ age + sex + vascular risk + depression + age-11 IQ	-0.202 (0.04)	-0.286, -0.117	<0.001	<0.001	0.051	0.892	0.864	0.055
Processing speed	-0.263 (0.05)	-0.398, -0.159	<0.001	<0.001	0.034	0.981	0.973	0.045
+ age	-0.251 (0.05)	-0.355, -0.146	<0.001	<0.001	0.034	0.977	0.969	0.048
+ age + sex	-0.257 (0.05)	-0.358, -0.156	<0.001	<0.001	0.047	0.950	0.931	0.051
+ age + sex + vascular risk	-0.245 (0.05)	-0.347, -0.144	<0.001	<0.001	0.044	0.951	0.932	0.050
+ age + sex + vascular risk + depression	-0.239 (0.05)	-0.337, -0.141	<0.001	<0.001	0.040	0.954	0.934	0.048
+ age + sex + vascular risk + depression + age-11 IQ	-0.214 (0.05)	-0.304, -0.124	<0.001	<0.001	0.041	0.952	0.928	0.048
Verbal memory	-0.171 (0.06)	-0.293, -0.050	0.006	0.008	0.000	1.000	1.000	0.038
+ age	-0.167 (0.06)	-0.289, -0.045	0.007	0.008	0.021	0.989	0.984	0.044
+ age + sex	-0.180 (0.06)	-0.297, -0.063	0.003	0.005	0.030	0.975	0.963	0.046
+ age + sex + vascular risk	-0.179 (0.06)	-0.297, -0.062	0.003	0.005	0.027	0.976	0.964	0.045
+ age + sex + vascular risk + depression	-0.177 (0.06)	-0.295, -0.060	0.003	0.005	0.026	0.974	0.960	0.045
+ age + sex + vascular risk + depression + age-11 IQ	-0.145 (0.05)	-0.248, -0.042	0.006	0.008	0.029	0.971	0.953	0.044
Visuospatial ability	-0.163 (0.05)	-0.269, -0.056	0.003	0.005	0.000	1.000	1.000	0.034
+ age	-0.152 (0.06)	-0.259, -0.045	0.005	0.007	0.010	0.998	0.997	0.040
+ age + sex	-0.139 (0.06)	-0.247, -0.030	0.013	0.015	0.021	0.988	0.984	0.042
+ age + sex + vascular risk	-0.131 (0.06)	-0.241, -0.022	0.019	0.021	0.019	0.990	0.985	0.042
+ age + sex + vascular risk + depression	-0.127 (0.06)	-0.235, -0.019	0.021	0.022	0.018	0.989	0.983	0.042
+ age + sex + vascular risk + depression + age-11 IQ	-0.101 (0.05)	-0.194, -0.008	0.034	0.034	0.017	0.991	0.985	0.040

Table 4 note. N=540 for all analyses. CFI: Comparative Fit Index; RMSEA: Root Mean Square Approximation; SRMR: Standardized Root Mean Square Residual; TLI: Tucker Lewis Index.

Computationally-derived SVD burden score shows a specific and independent association with processing speed

The multivariable bifactor model, performed to test associations between the computationally-derived SVD burden score and domain-specific cognitive abilities independently of general cognitive ability, fitted well (Fig. 3; RMSEA=0.030; CFI=0.970; TLI= 0.952; SRMR=0.044). Total SVD burden was negatively associated with general cognitive ability (standardised β: -0.224; 95%CI: [-0.40, -0.05]; p(FDR)=0.016) and processing speed (-0.325; [-0.61, -0.04], p(FDR)=0.029), and accounted for 5% of the variance in general cognitive ability and 11% of the variance in residual processing speed. There were no significant associations between total SVD burden and verbal memory (-0.133, [-0.32, 0.05], p(FDR)=0.166) or visuospatial ability (0.075; [-0.25, 0.40], p(FDR)=0.654). The latter result may be due to the heavy loading of the visuospatial tests onto general cognitive ability, which left relatively little variance for the independent visuospatial factor.

Figure 3: SEM diagram illustrating associations between SVD burden and a bifactor model of general cognitive ability

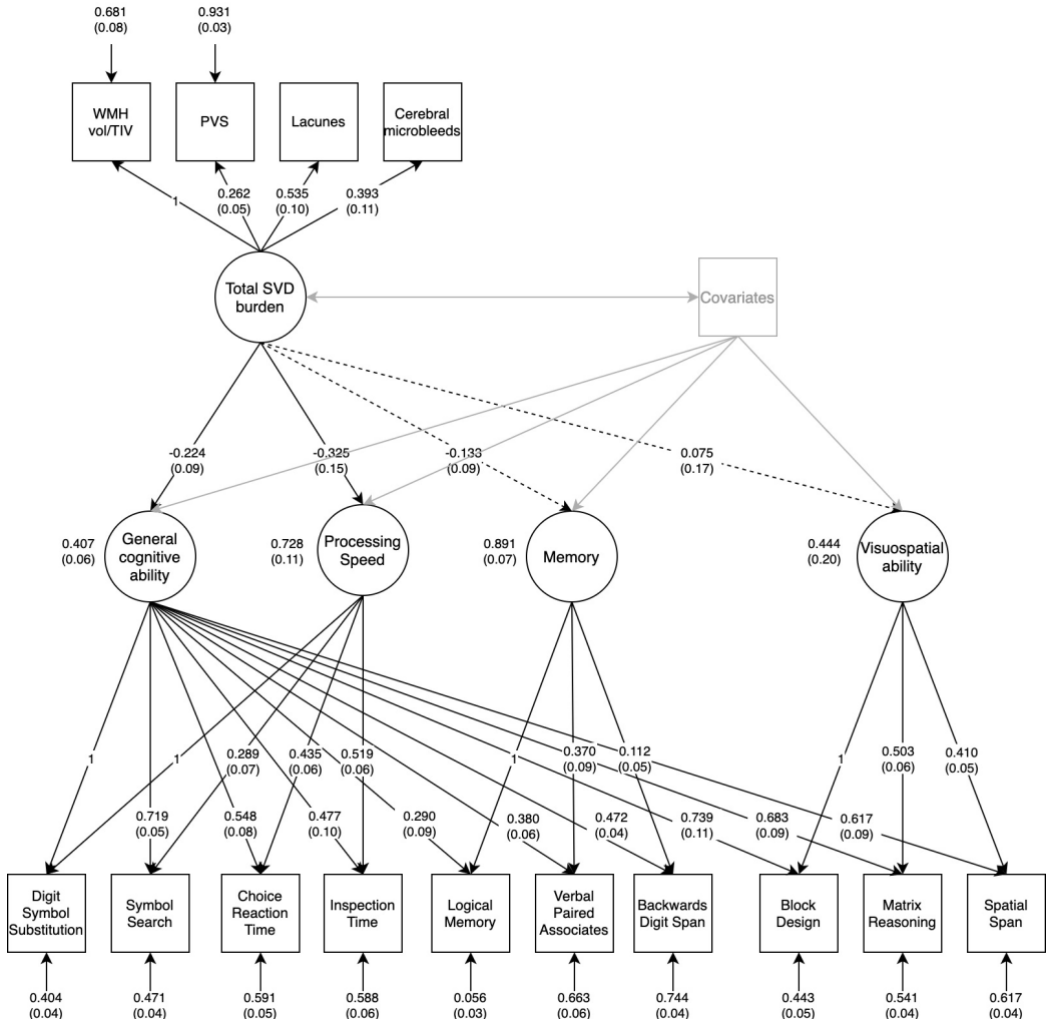

Figure 3 note: Associations between total SVD burden and a bifactor model of cognitive ability (n=540). Estimator: WLSMV. Fit indices: RMSEA=0.030; CFI=0.970; TLI=0.952; SRMR=0.044. Solid black lines between total SVD burden and cognitive factors represent significant associations and dashed lines represent non-significant associations after FDR correction. Factor loadings of these four associations are standardised linear regression coefficients and standard errors are shown in parentheses. Age at time of MRI, sex, vascular risk, HADS depression sub-score, and age-11 IQ were included as covariates and were free to correlate with one another.

Discussion

To date, the majority of studies have used individual MRI markers of SVD, or a simple 0-4 sum score to quantify SVD burden. In this study of 540 community-dwelling older adults, we combined computational and visually-rated MRI markers of SVD (including for the first time, a continuous measure of PVS) to estimate a continuous latent variable representing total MRI-visible SVD burden. In doing so, we were able to increase the fidelity with which SVD burden is quantified, relative to a previous method which relied on visually-rated SVD markers only. The results of our analyses indicated that a higher SVD burden was not only associated with poorer general cognitive ability and processing speed, as current consensus statements suggest (Peng et al., 2019, Rosenberg et al., 2016), but also with poorer memory and visuospatial ability. We then accounted for the covariance between cognitive domain scores and general cognitive ability in a bifactor model, finding that total SVD burden was associated with processing speed not only due to, but in addition to its association with poorer general cognitive ability. A comparison of the covariate-adjusted effect sizes for associations between total SVD burden and processing speed before accounting for general cognitive ability (simple regression model standardised β: -0.371) and after accounting for general cognitive ability (bifactor model standardised β: -0.325), suggests that approximately 12% of the variance in processing speed is accounted for by general ability. Therefore, failing to account for covariance with general cognitive ability could lead to an overestimation of effect sizes between SVD burden and processing speed.

Slowed processing speed and poor executive function are often considered to be the hallmark cognitive features of SVD, with little attention given to other cognitive domains. However, our results suggest that alongside slowed processing speed, SVD burden is also related to poorer performance on tests of memory and visuospatial ability, even in a cohort of individuals with mild, non-clinical presentations of SVD. We found associations between SVD burden and verbal memory and visuospatial ability in separate regression models, but not in the bifactor model. This suggests that negative associations between SVD and both memory and visuospatial ability may be a consequence of the negative association between SVD and general cognitive ability. It has been suggested that poor performance on tests of memory and visuospatial ability (two cognitive abilities subtended by specific cortical areas) could result from the disruption of white matter connections between cortical and

subcortical regions (Tuladhar et al., 2015). Our data support this notion and suggest that damage to these connections may be part of a more general, diffuse process.

Slowed information processing speed is recognised as a key feature of SVD. However, processing speed test scores are a chimera; that is, part of the variation in processing speed is due to its association with general cognitive ability. Therefore, it was previously unknown whether the apparent association between SVD and slowed processing speed was due to SVD's impact on general cognitive ability, or whether SVD may have specific and independent effects on processing speed. Here, we have removed the general cognitive ability variance from processing speed (and other cognitive domains), which affords a better test of any SVD-processing speed association. Our results suggested that the association between SVD burden and processing speed was independent of general cognitive ability, thus favouring the latter hypothesis. To the best of our knowledge, this is the first study to demonstrate an association between SVD burden and processing speed independently of the shared variance between cognitive test scores, which acts as a confound. Typically, this confound remains unaccounted for, thus previous studies that have reported associations between SVD and scores from tests of processing speed could be misleading. Processing speed is often regarded as having a special status among the domains of cognitive ability; it is typically the first domain affected by age, and as performance on tasks in a variety of cognitive domains relies on information processing, its early decline may lead change in other domains (Finkel et al., 2007). It follows that networks supporting processing speed appear to be distributed throughout the brain: previously in the LBC1936, poorer processing speed was associated with age-related reductions in white matter microstructural integrity across the whole brain, and in broad regions of interest (Deary et al., 2006, Kuznetsova et al., 2016, Penke et al., 2010). That total SVD burden may have a specific impact on processing speed, independent of its effect on general cognitive ability, further suggests that SVD-related brain changes are widespread, rather than tract-specific.

Previously, in 680 participants from the LBC1936 Staals et al. (2015) found no associations between their total SVD burden score (derived from visual rating scales of individual MRI markers of SVD) and a composite score of processing speed. This composite score of processing speed was extracted from a bifactor model of general cognitive ability, so as in our study, was independent of general cognitive ability. There are several key differences

between the present study and that of Staals et al. (2015), which may account for our differing results. First, we were unable to include 140 of Staals' 680 participants due to MRI noise or motion artefacts, which precluded the quantification of the computational PVS measure. As a higher burden of imaging artefacts likely reflect poorer brain health, the range of SVD severity is potentially reduced in our sample. The anticipated effect of this would be a reduction in the magnitude of observed effect sizes between SVD burden and cognitive outcomes, however this was not the case, so our smaller, less noisy sample is unlikely to be responsible for our differing results. Second, we used continuous as opposed to ordinal MRI data for two key SVD features (WMH and PVS) of our total SVD burden variable. In separate regression models, the reconstructed SVD variable used by Staals et al. was negatively associated with all cognitive domains that we tested, but the effect size magnitudes of these models were significantly smaller than those using the computationally-derived SVD score as a predictor. This suggests that incorporating continuous measurements of WMH and PVS into the original total SVD burden score increased the fidelity of the SVD burden measure, revealing associations with cognitive outcomes which were previously unobserved. The computationally-derived SVD variable also demonstrated greater predictive power in its associations with cognitive outcomes than WMH/TIV, suggesting that some of these effects may be missed when using WMH volume as the sole predictor of cognitive performance.

Whereas tests of processing speed may be particularly sensitive to, and possibly an early indicator of, the cognitive impact of SVD (Deary et al., 2019), our findings suggest that SVD burden also associates with poorer performance on tests of verbal memory and visuospatial ability. Future research studies and clinical trials assessing domain-specific cognitive outcomes in SVD should also assess all major domains of cognitive ability in order to capture a more accurate picture of SVD-related cognitive impairments. We have also demonstrated the benefit of constructing a computationally-derived variable of total SVD burden, over one constructed using visually-rated MRI data alone. A latent variable of SVD burden using continuous MRI data may be useful in a research setting for testing associations between SVD burden and clinically-relevant outcomes, however, further interrogation of the latent SVD burden variable is required before it could be considered for use as a marker of SVD severity in a clinical trial setting. We are yet to examine, for example, how the latent SVD variable might change over time, or whether it can be constructed in clinical populations with more substantial burden of SVD or more complex multi-morbidities, such as

Alzheimer's disease. The consistency of latent SVD variables using computationally-derived data might also vary according to scanning parameters or methods used to quantify the radiological markers of SVD.

Strengths of this study include our large sample size, extensive cognitive testing, and detailed assessment of biomarker variables, which enabled us to account for a broad range of vascular risk factors. Additionally, as childhood IQ accounts for approximately 50% of the variance in cognitive ability in later life (Deary, 2014), a further strength of this study is our ability to account for this confound by including age-11 IQ as a covariate in our analyses. Age-11 IQ had the greatest impact of any of the covariates we included, attenuating the standardised betas of the associations between total SVD burden and later-life cognitive abilities by an average of about .04. Limitations of this study include our reliance on binary measurements of lacunes and microbleeds, which were used due to the scarcity of participants in our sample with more than one lacune or microbleed. In a sample of participants with more substantial SVD pathology, it might be desirable to model these variables as count data, as the reduction of highly variable data into binary outcomes results in the loss of information. Computational continuous measures of lacunes and microbleeds are also feasible, however, it is not yet clear whether these should be expressed as a total volume or count; microbleeds may be contaminated with other mineral deposits, and as the least frequent SVD lesions, their contribution to the total SVD burden is well captured in a binary score. A valid computational measure would likely further increase the sensitivity of the latent SVD variable and should be tested in future, especially in more diseased populations likely to have more lacunes and microbleeds. A further limitation of this study is that the computationally-derived SVD variable incorporated a measure of PVS in the centrum semiovale, whereas the reconstructed SVD score used by Staals et al. (2015) incorporated a measure of PVS in the basal ganglia. Whereas PVS in the centrum semiovale are related to cerebral amyloid angiopathy (CAA) pathology, they are also present in sporadic SVD; in the LBC1936, visual ratings of PVS in the centrum semiovale and basal ganglia correlate with one another (r=0.40; $p<0.001$) and strong associations between computational PVS count and other markers of SVD, such as Fazekas scores and WMH volumes, have previously been reported (Ballerini et al., 2020). However, the associations that we observed between SVD burden and cognitive ability in the domains of processing

speed, verbal memory and visuospatial ability in the LBC1936 support the suggestion that SVD affects multiple cognitive domains before clinical presentation.

We constructed a computationally-derived variable representing the total MRI-visible burden of SVD using continuous scores of WMH and PVS and binary ratings of lacunes and microbleeds. SVD burden associated negatively with verbal memory and visuospatial ability, but this is likely due to SVD's association with general cognitive ability. SVD burden was also negatively associated with processing speed, but this association was found to be independent of poorer general cognitive ability. Future research studies and clinical trials monitoring cognitive outcomes in SVD should assess the domains of memory and visuospatial ability in addition to processing speed, in order to capture a fuller and more clinically-relevant picture of SVD-related cognitive abilities.

Declarations of interest

None.

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5.3 Summary

The study presented in this chapter tested cross-sectional associations between a continuous variable representing the total MRI-visible burden of SVD and cognitive abilities in the LBC1936, a relatively healthy, community dwelling cohort of older adults at the mean age of 73. Four key radiological markers of SVD contributed to the SVD burden variable: WMH volume/TIV, continuous computational count of visible PVS, and binary measures of lacunes and microbleeds. The construction of this continuous SVD measure was a development of work by Staals and colleagues (2015), whose latent SVD burden variable was derived from visual rating scores only. The computationally-derived SVD variable constructed in this study was negatively associated with measures of general cognitive ability, processing speed, verbal memory, and visuospatial ability. These associations remained significant after the inclusion of age, sex, vascular risk, depression score, and age-11 IQ as covariates. However, when accounting for the covariance between domain-specific cognitive scores (i.e. the shared variability represented by general cognitive ability), only the association between SVD burden and processing speed remained significant. These results suggest that SVD's association with poorer processing speed is not driven by, but is independent of its association with poorer general cognitive ability. In contrast, SVD appears to be associated with poorer verbal memory and visuospatial ability due to its overarching association with poorer general cognitive ability. Whereas tests of processing speed might be particularly sensitive to SVD-related cognitive deficits, future SVD studies should not neglect to test other major domains of cognitive ability such as memory and visuospatial ability – these domains also appear to be affected by SVD, but via SVD's association with poorer cognitive ability more generally.

The continuous SVD burden constructed in this study was more strongly associated with cognitive outcomes than either Staals' SVD burden variable (2015), or WMH volume alone. This suggests that there is utility in the inclusion of continuous MRI markers of SVD in a score of total SVD burden – the additional variability incorporated by the inclusion of continuous MRI markers of SVD might better reflect the underlying pathological burden of SVD.

Chapter 6 presents a further development of these analyses by examining associations between the total SVD burden variable and change in cognitive abilities between the ages of 73 and 82.

Chapter 6 Examining associations between the radiological burden of SVD and longitudinal cognitive decline

6.1 Introduction

In Chapter 5, I examined cross-sectional associations between a latent variable representing the total MRI-visible burden of SVD and cognitive abilities in the LBC1936. Results of that study suggested that greater total SVD burden associates with slowed processing speed, independently of SVD's association with poorer general cognitive ability. However, these cross-sectional analyses estimate a static association between two dynamic processes, namely the progression of SVD and the process of cognitive decline. Therefore, in this chapter I will extend the work presented in Chapter 5 by examining associations between total SVD burden at the age of 73, and *change* in cognitive abilities between the ages of 73 and 82, in the same LBC1936 sample.

This work is currently under review at *Molecular Psychiatry* and a copy has been uploaded to the *medRxiv* preprint server (available at https://doi.org/10.1101/2021.03.28.21254499). Supplementary materials for this study are presented in Appendix D.

Cerebral Small Vessel Disease Burden and Longitudinal Cognitive Decline from age 73 to 82: the Lothian Birth Cohort 1936

Running title: Cerebral small vessel disease and cognitive decline

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Abstract

Slowed processing speed is considered a hallmark feature of cognitive decline in cerebral small vessel disease (SVD), however, it is unclear whether SVD's association with slowed processing might be due to its association with overall declining general cognitive ability. We quantified the total MRI-visible SVD burden of 540 members of the Lothian Birth Cohort 1936 (age:72.6±0.7 years; 47% female). Using latent growth curve modelling, we tested associations between total SVD burden at mean age 73 and changes in general cognitive ability, processing speed, verbal memory, and visuospatial ability, measured at age 73, 76, 79 and 82. Covariates included age, sex, vascular risk, and childhood cognitive ability. In the fully-adjusted models, greater SVD burden was associated with greater declines in general cognitive ability (standardised β: -0.201; 95%CI: [-0.36, -0.04]; pFDR=0.022) and processing speed (-0.222; [-0.40, -0.04]; pFDR=0.022). SVD burden accounted for between 4 and 5% of variance in declines of general cognitive ability and processing speed. After accounting for the covariance between tests of processing speed and general cognitive ability, only SVD's association with greater decline in general cognitive ability remained significant, prior to FDR correction (-0.222; [-0.39, -0.06]; p=0.008; pFDR=0.085). Our findings do not support the notion that SVD has a specific association with declining processing speed, independent of decline in general cognitive ability (which captures the variance shared across domains of cognitive ability). The association between SVD burden and declining general cognitive ability supports the notion of SVD as a diffuse, whole-brain disease and suggests that trials monitoring SVD-related cognitive changes should consider domain-specific changes in the context of overall, general cognitive decline.

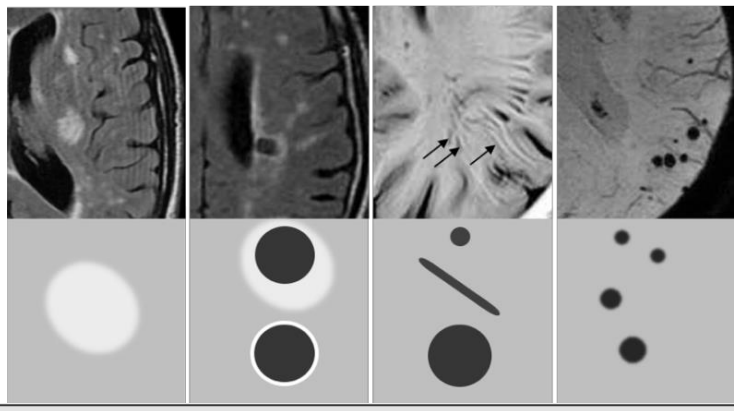
Introduction

Cerebral small vessel disease (SVD) is a major cause of cognitive impairment in older adults. It causes approximately 25% of all strokes and is the second most common cause of dementia after Alzheimer's disease, either on its own or through mixed pathologies (1,2). Caused by dysfunction of the brain's arterioles, capillaries, and venules, the downstream effects of SVD are visible on neuroimaging as white matter hyperintensities (WMH) and lacunes of presumed vascular origin, cerebral microbleeds, and visible perivascular spaces (PVS; 3; see Figure 1). In most individuals, these radiological markers do not result in overt clinical symptoms, however, their presence doubles the risk of stroke, and increases the risk of dementia and death in the general population (4). Despite its contribution to cognitive decline and to the development of associated co-morbidities (4,5), the precise nature of the associations between the radiological burden of SVD and decline in domain-specific cognitive abilities remains unclear.

Current consensus statements suggest that SVD is associated with declining processing speed and executive function, alongside relative preservation of memory and language abilities (6,7). However, previous studies examining domain-specific cognitive decline in SVD have not accounted for the well-replicated phenomenon in psychological research that cognitive test scores typically correlate positively with one another, such that an individual who performs well on a given cognitive test, is likely to perform well on a broader range of tests (8). This common variance among test scores can be accounted for by general cognitive ability, often termed 'g'. General cognitive ability also accounts for the majority of variance in domain-specific cognitive decline; a recent meta-analysis estimated that, on average, 60% of the variance in cognitive changes were shared across abilities (9). It follows, therefore, that any domain-specific measure of cognitive ability will be influenced not only by an individual's ability in that specific domain, but by their overall level of general cognitive ability. To be clear: if one finds an association between a biomarker, or any other exposure, and scores on a domain of cognitive ability or changes in a cognitive domain, there are three possible reasons for the result. First, the association might be wholly accounted for by an association with general cognitive ability (on which all cognitive domains load substantially); second, the association might be partly with general cognitive ability and partly with the cognitive domain; and, third, the association might indeed be exclusively with the cognitive domain. Thus, it is necessary to test formally whether previously-reported associations

between SVD and processing speed are indeed specific to that domain, rather than confounded by the phenomenon of general cognitive ability.

Figure 1: Key radiological markers of SVD examined in this study



	White matter hyperintensity	Lacune	Perivascular space	Cerebral microbleeds
Usual diameter	variable	3 -15 mm	≤2mm	≤10 mm
Comment	located in white matter	usually have hyperintense rim	usually linear without hyperintense rim	detected on GRE seq., round or ovoid, blooming
DWI	↔	↔/(↓)	↔	↔
FLAIR	↑	↓	↓	↓
T2	↑	↑	↑	↓
T1	↔/(↓)	↓	↓	↔
T2* / GRE	↑	↔ (↓ if hemorrhage)	↔	↓↓

Figure 1 note: Examples and schematic representations of key radiological features of SVD, according to STRIVE guidelines (3). Adapted with permission from Wardlaw et al. *The Lancet Neurology* 2013; 12(8): 822-38 [licence number 5010341055200, dated 15th February 2021]. DWI: diffusion-weighted imaging; GRE: gradient-recalled echo.

To date, most studies investigating the relationship between SVD brain changes and cognitive decline have focused on individual radiological markers of SVD. WMH are the most frequently investigated SVD marker, perhaps due to their prevalence which is estimated at 64-94% in 82-year olds (10). Recent meta-analyses report associations between greater baseline WMH burden and steeper decline in both general and domain-specific cognitive abilities, and greater risk of incident dementia (4,11). Similarly, the presence of lacunes and microbleeds have been associated with cognitive decline (12–14), but associations between PVS and poorer cognitive ability, either cross-sectionally or longitudinally, are more variable (12). In recent years, several studies have quantified the 'total brain burden' of SVD using a

simple 0-4 score, which allocates one point for the presence of each SVD marker (15–18). Whereas this approach goes some way towards considering the potential cumulative impact of different SVD markers on cognitive ability, the 0-4 score lacks sensitivity to subtle differences in the severity of the individual markers, and hence to their relative associations with cognitive abilities.

To improve the fidelity of SVD burden quantification, two previous studies (one using the same sample as the present study) utilised continuous neuroimaging variables to construct continuous SVD burden scores (19,20). In the first of these studies, Jokinen and colleagues (19) demonstrated associations between SVD burden (the average of standardised WMH, lacune, grey matter, and hippocampal volumes) and declining processing speed, executive function, memory, and general cognitive ability over a 3-year period. In a subsequent study from our own research group, using data from the LBC1936 (20), a continuous latent variable of SVD burden was negatively associated with latent variables of processing speed, verbal memory and visuospatial ability, in a structural equation modelling framework (SEM). However, after accounting for the shared variance between domain-specific scores (i.e. the variance attributable to general cognitive ability), only the association with processing speed remained. These findings suggest that the apparent associations we observed between SVD burden and domain-specific scores of verbal memory and visuospatial ability, were largely due to the confounding associations between SVD burden and general cognitive ability.

Longitudinal associations between SVD burden and declines in specific domains of cognitive ability, independent of their associations with general cognitive ability, have yet to be examined. Here, in a sample of relatively-healthy older individuals, we investigate associations between total MRI-visible SVD burden at age 73 and longitudinal cognitive decline between the ages of 73 and 82, a period that coincides with a substantial increase in dementia risk (21). Using growth curve modelling in a SEM framework, we separate the variance in cognitive test scores attributable to general cognitive ability from the variance attributable to the important, ageing-relevant domains of processing speed, memory, and visuospatial ability. This enables us to test whether SVD-related decline in specific cognitive domains are attributable to or independent of declining general cognitive ability.

Methods

This study uses data from the Lothian Birth Cohort 1936 (LBC1936), a longitudinal study of cognitive, brain, and general ageing (22). In brief, the LBC1936 is an ongoing follow-up study to the Scottish Mental Survey 1947 (SMS1947; 23), which tested the cognitive abilities of 70,805 11-year-old children who were born in 1936 and were attending school in Scotland in 1947. Between 2004 and 2007, 1091 individuals, most of whom had taken part in the SMS1947, were recruited to the LBC1936. They have contributed to up to five waves of data collection at mean ages of about 70 (n=1091), 73 (n=866), 76 (n=697), 79 (n=550), and 82 (n=431) years. The present study includes data from Waves 2 to 5 of the LBC1936 (there was no MRI at Wave 1). Wave 2 MRI data were unusable for 51 of the 731 participants who underwent neuroimaging. Images belonging to a further 140 participants exhibited noise or motion artefacts that precluded the computational quantification of PVS, which due to the small size of the PVS (<3mm), is highly sensitive to such artefacts. Therefore, the remaining 540 participants constitute the baseline sample of this study (see Figure 2). Approvals for Waves 2 to 5 of the LBC1936 were obtained from the Scotland A Research Ethics Committee for Scotland (07/MRE00/58). All participants gave written, informed consent.

MRI data and the quantification of total SVD burden

The neuroimaging protocol for the LBC1936 has been published previously (24). Briefly, participants were scanned using a GE Signa Horizon HDx 1.5 Tesla clinical scanner (General Electric, Milwaukee, WI) operating in 'research mode', equipped with a self-shielding gradient set (33 mT/m maximum gradient strength) and manufacturer supplied eight-channel phased-array head coil. Sequences acquired were T1-weighted (T1W), T2-weighted (T2W), T2*-weighted (T2*W) and fluid attenuated inversion recovery-weighted (FLAIR) images. Scanner stability was monitored throughout with a detailed quality assurance programme.

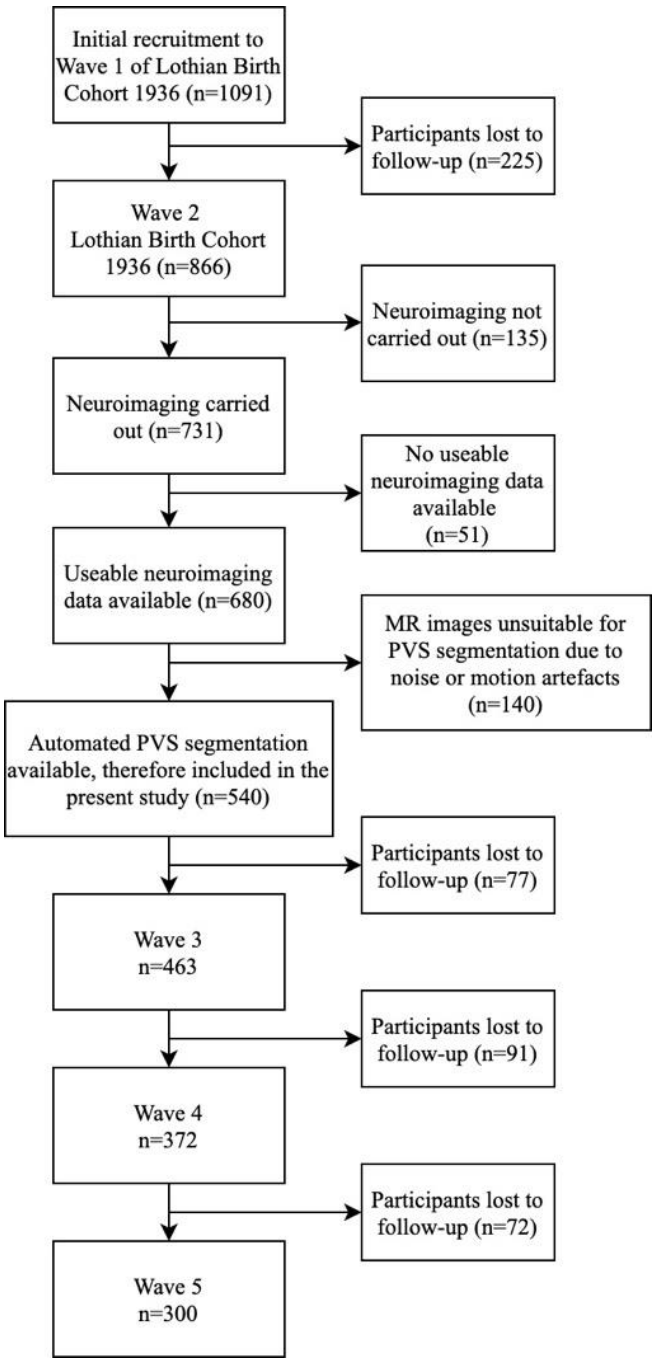


Figure 2: Consort diagram illustrating selection of the study sample

As previously reported, we used confirmatory factor analysis (CFA) to construct a latent variable representing total MRI-visible SVD burden (20). This latent variable comprised continuous WMH volume (divided by total intracranial volume (TIV) to account for differences in head size), continuous computationally-derived PVS count, and binary visual ratings of lacunes and microbleeds (i.e. present/absent). Total WMH volume and TIV, were measured semi-automatically using a validated multispectral image processing method that

combines T2*W and FLAIR sequences in the colour space for enhanced feature discrimination in the segmentation (25), available from https://sourceforge.net/projects/bric1936/ . All slices of all scans were checked by a trained observer and manually corrected, if necessary, to ensure that no true WMH had been omitted and to avoid including erroneous tissues in the WMH. PVS were computationally segmented in the native T2W space in the centrum semiovale using a recently validated technique (26,27) and are presented as total number of PVS. All binary PVS masks (superimposed on T2W images) were visually checked for the accurate quantification of PVS by a trained operator and were accepted or rejected blind to all other data. Where ambiguity arose, FLAIR and T1W sequences were also checked. Lacunes and microbleeds were rated by an experienced, registered neuroradiologist. Lacunes were classified as being present or absent and were defined as small (>3mm and <2cm in diameter) subcortical lesions of cerebrospinal fluid-equivalent signal on T2W and decreased signal on T1W and FLAIR images in the white matter, basal ganglia, and brainstem (3,24). Cerebral microbleeds were classified as being present or absent and were defined as small (<5mm), homogeneous, round foci of low signal intensity on T2*W images in the white matter, basal ganglia, brain stem, cerebellum, and cortico-subcortical junction (3,24). A random 20% sample of visual-ratings and any uncertain cases were independently checked by a second neuroradiologist, with disagreements resolved by consensus.

Cognitive data

Participants completed the same series of cognitive tests at each wave of data collection, in the same location, administered using the same instructions. According to previous work examining their correlational structure (28), we grouped cognitive tests into the following domains:

1) Processing speed was measured using Digit Symbol Substitution and Symbol Search from the Wechsler Adult Intelligence Scale-III (WAIS-IIIUK; 29) and two experimental tasks: Inspection Time (30) and Four Choice Reaction Time (31). The Inspection Time task requires participants to select the longer of two vertical lines that are flashed on a computer screen for between 6 and 200 milliseconds. The measure used here was the number of correct responses out of a total of 150 trials. Four Choice Reaction Time scores were multiplied by -1 so that higher scores indicated better performance.

2) Memory consisted of Verbal Paired Associates (total score) and Logical Memory (total score) from the Wechsler Memory Scale III UK (WMS-IIIUK; 32), and Backward Digit Span (WAIS-IIIUK).

3) Visuospatial ability included Block Design and Matrix Reasoning (WAIS-IIIUK) and Spatial Span (average of forwards and backwards; WMS-IIIUK).

Our measure of general cognitive ability encompassed each of the above-mentioned tests. The Moray House Test Number 12 (MHT), a 71-item test of general cognitive ability, was also administered at the age of 11 as part of the Scottish Mental Survey 1947. In this study, we use the raw MHT score, which can range from 0-76 and subsequently refer to this variable as childhood cognitive ability.

Covariates

We included age in years, sex, vascular risk, and childhood cognitive ability in all models, in a stepwise manner. Vascular risk variables included self-reported history of hypertension (yes/no); diabetes mellitus (yes/no); smoking status (ever/never); blood-derived glycated haemoglobin (% total HbA1c); blood-derived total cholesterol (mmol/l); and systolic and diastolic blood pressure (average of six readings: three seated and three standing), which were measured by trained nurses. We observed very little change in vascular risk variables over the four waves of testing (see Table 2), possibly as vascular risk factors such as hypertension and diabetes are relatively well managed in the LBC1936. Therefore, we considered baseline (Wave 2, age 73) vascular risk to be a sufficient representation of participants' vascular status over the study period. We used CFA to construct a latent variable representing vascular risk as previously modelled in the LBC1936 (33) and extracted its factor score for inclusion as a covariate. Childhood cognitive ability accounts for approximately half of the variance in later life cognitive ability (34). In part, this association might be mediated by increased SVD risk, which has also been found to associate with lower childhood cognitive ability (35,36). Therefore, as we expect childhood cognitive ability to attenuate the association between SVD burden and cognitive abilities measured at the age of 73 (Wave 2), we included MHT score measured at the age of 11 as a further covariate in our analyses. Time-invariant covariates (sex, baseline vascular risk, and childhood cognitive ability) were regressed on the outcomes of interest (the general and domain-specific

cognitive intercepts and slopes) and were allowed to covary with one another and with the latent SVD burden variable. We specified time-variant covariates (age in years at each wave) as direct predictors of the observed cognitive and MRI variables.

Statistical Analysis

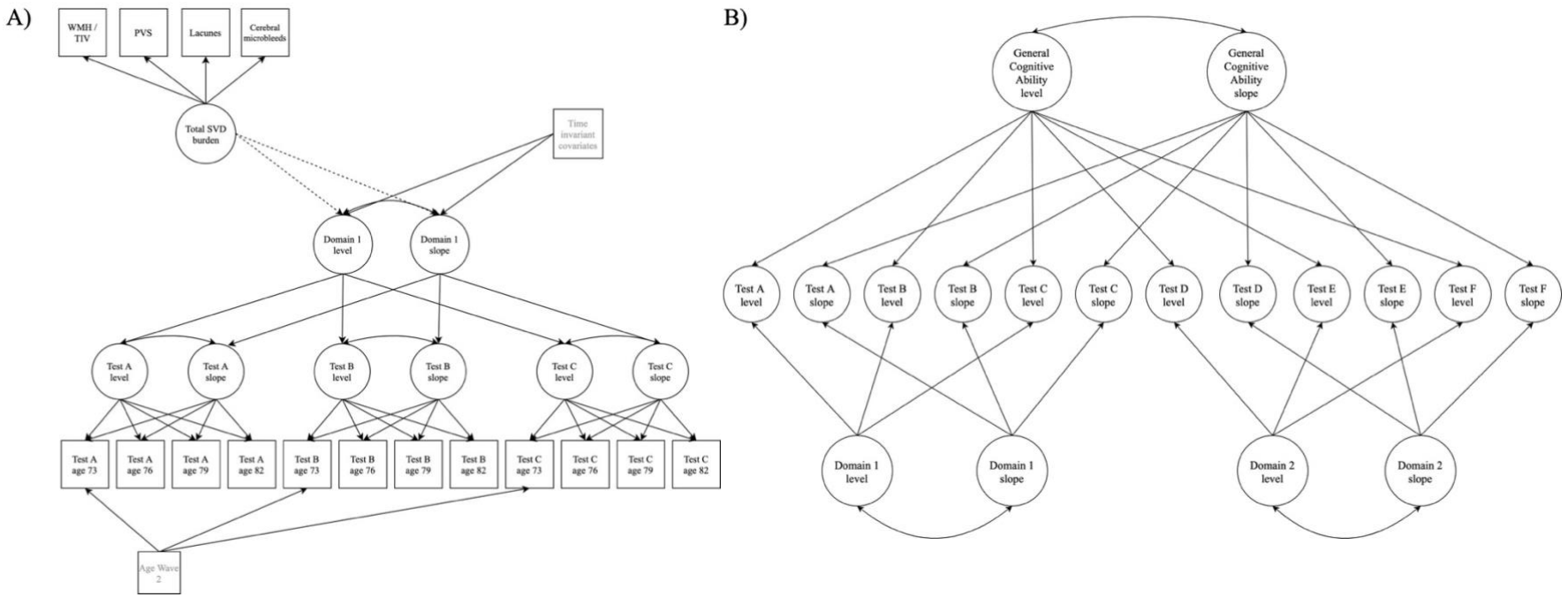
Measurement models

First, we used hierarchical 'factor-of-curves' models (FoC) within a SEM framework (37), as has been done previously in this cohort (38,39), to examine the initial level and subsequent decline in general cognitive ability, processing speed, memory, and visuospatial ability between mean ages 73 (Wave 2), 76 (Wave 3), 79 (Wave 4), and 82 (Wave 5). A FoC model estimates the initial level of each cognitive test (intercept) and its trajectory across all four waves of testing (slope). The latent intercepts and slopes of each cognitive test load onto superordinate latent intercepts and latent slopes of their respective cognitive domains (see Figure 3A). This permits analysis of the initial level and trajectory of each cognitive domain as if they were directly observed.

Hierarchical factor-of-curves models of SVD-cognitive ability associations

Next, we specified linear regressions between baseline SVD burden (independent variable) and the latent intercepts and slopes of general cognitive ability, processing speed, memory, and visuospatial ability (dependent variables). This was carried out in separate hierarchical FoC models: one for general cognitive ability, and one for each cognitive domain. Importantly, it should be noted that at this stage the cognitive domains will contain any variance actually attributable to general cognitive ability (i.e. common across cognitive domains). Associations between SVD burden and latent cognitive intercepts approximate the cross-sectional associations that we reported previously (20). Therefore, in this study we are primarily interested in the associations between SVD burden and the latent cognitive slopes.

Figure 3: Illustrations of a hierarchical 'factor-of-curves' model and a longitudinal bifactor model of cognitive ability



Note for Figure 3A: A hierarchical 'Factor-of-curves' (FoC) model of cognitive ability. For the hierarchical FoC models, a growth curve was estimated for each individual cognitive test, producing a latent intercept and slope. These test-specific latent intercepts and slopes in turn loaded onto an overall latent intercept and slope for the cognitive domain. Loadings on the slopes were set to 0, 3.78, 6.83, and 9.55, to reflect the average time lags between baseline and subsequent waves. In this illustration we also show how we specified associations between latent SVD burden and the intercept and slope of the cognitive factor (see dashed lines), and how we included additional time-invariant (sex, vascular risk, childhood cognitive ability) and time variant (age) covariates (see items in grey). Separate models were carried out for each cognitive domain (i.e. general cognitive ability, processing speed, verbal memory,

and visuospatial ability). Following conventional SEM notation, variables in squares were observed and measured, and variables in circles represent unobserved latent variables. Single headed arrows represent specified relationships between variables and double headed arrows represent correlations.

Note for Figure 3B: Longitudinal bifactor model. In the centre of the model are the latent intercept and slope of each cognitive test, which were constructed using latent growth curves of the originally observed test scores at each time point (as described in the panel A note). The variance in these test-specific latent intercepts and slopes is separated into that which contributes to the latent intercept and slope of each cognitive domain, and that which contributes to the latent intercept and slope of general cognitive ability. We tested associations between total SVD burden and the intercept and slope of each cognitive variable simultaneously (not shown in this illustration). Additional time-invariant and time-variant covariates were included as indicated for the hierarchical FoC model (not shown in this illustration, see panel A for details).

Longitudinal bifactor models of SVD-cognitive ability associations: accounting for covariance between domain-specific scores and general cognitive ability

Previous analyses in the LBC1936 have estimated that general cognitive ability explains approximately 50% of the variability in the decline of individual test scores between the ages of 70 and 76, and up to 70% of variability in their decline between 70 and 79(38,40). Owing to this shared variability, estimations of decline in any measure of domain-specific cognitive ability will contain both the amount of decline in that domain-specific ability and the amount of decline in general cognitive ability. Therefore, to assess decline in domain-specific cognitive abilities, the variance in test scores associated with general cognitive ability must be removed. To do this, we constructed a longitudinal bifactor model (in a SEM framework) in which the variance associated with general and domain-specific abilities is parsed into separate latent variables, so that the level and trajectory of general cognitive ability and those of the domain-specific abilities can be measured independently of one another (see Figure 3B). To test associations between SVD burden and the level and decline of domain specific-abilities independently of general ability, we specified linear regressions between SVD burden (independent variable) and the latent intercepts and slopes of the cognitive variables (general cognitive ability and the three cognitive domains) from the longitudinal bifactor model.

Examining the contribution of WMH to the total SVD burden-cognitive ability associations

Of the radiological markers of SVD examined here, WMH are the most regularly associated with poorer cognitive abilities. It is plausible, therefore, that any associations between the SVD burden variable and cognitive factors could largely be driven by WMH. To test whether this was the case, we repeated the hierarchical FoC analyses with WMH/TIV in the place of SVD burden as the predictor variable. As an indication of the relative utility of total SVD burden and WMH/TIV as predictors of cognitive outcomes, we examined the magnitude of standardised effect sizes and confidence intervals of models specifying WMH/TIV, and those of models specifying total SVD burden as the predictor.

As absolute fit indices are unavailable when using maximum likelihood to estimate models including binary measures, we assessed the fit of models specifying total SVD burden as the predictor (binary measures of lacunes and microbleeds contribute to the latent SVD variable) against a less-restrictive neighbouring model (i.e. one in which latent SVD burden, latent

cognitive intercepts and latent cognitive slopes were permitted to correlate with one another) using the likelihood ratio test statistic calculated as follows: -2 x (loglikelihood of the less-restrictive model – loglikelihood of full model). For models specifying WMH/TIV as the predictor, model fit was assessed using four absolute fit indices: Root Mean Square Error of Approximation (RMSEA; <0.06 considered acceptable), Comparative Fit Index (CFI; >0.95 acceptable), Tucker-Lewis Index (TLI; >0.95 acceptable), and Standardized Root Mean Square Residual (SRMR; <0.08 acceptable; 41).

All analyses were carried out in MPlus version 8.4 (42) and were estimated using Full Information Maximum Likelihood (FIML), which estimates model parameters based on all available data from our sample of 540 LBC1936 participants. We corrected p-values for multiple comparisons using the False Discovery Rate adjustment (FDR; 43), with p.adjust in R version 4.0.1(44). This correction was carried out separately for p values from three different groups of models: 1) associations between total SVD burden and the intercept and slopes of cognitive change from hierarchical FoC models; 2) associations between WMH/TIV and the intercept and slopes of cognitive change from hierarchical FoC models; 3) associations between total SVD burden and the intercept and slopes of cognitive change from bifactor models.

Results

Cohort characteristics

Sociodemographic and clinical characteristics of participants at each wave are presented in Table 1. The same characteristics at each wave for study completers only are shown in Table 2, highlighting changes in the same sample over the four waves. We included 540 participants at baseline and lost between 13 and 16% of participants to follow-up at each subsequent wave. Participants lost to follow-up had a higher baseline prevalence of diabetes (but slightly lower cholesterol levels), greater total WMH volume, fewer years of education, and slightly lower childhood cognitive ability than study completers (see Table S1).

Table 1: Characteristics of the study sample at each wave

	n	Wave 2 (n=540)	n	Wave 3 (n=463)	n	Wave 4 (n=372)	n	Wave 5 (n=300)
Sociodemographic								
Age, years	540	72.5 (0.5)	463	76.2 (0.7)	372	79.5 (0.6)	300	82.0 (0.5)
Female, n (%)	540	252 (46.7%)	463	217 (46.9%)	372	195 (52.4%)	300	147 (49.0%)
Education, years	540	10.9 (1.2)	463	10.9 (1.2)	372	10.9 (1.2)	300	11.0 (1.2)
Vascular risk								
Hypertension history, n (%)	540	259 (48.0%)	462	251 (54.3%)	372	218 (58.6%)	300	176 (58.7%)
Systolic blood pressure	534	146.5 (18.0)	458	147.4 (18.5)	366	144.2 (17.9)	294	147.2 (20.2)
Diastolic blood pressure	534	79.7 (18.0)	458	80.3 (9.8)	366	78.2 (9.7)	294	78.6 (10.5)
Diabetes history, n (%)	540	54 (10.0%)	463	52 (11.2%)	371	42 (11.3%)	300	33 (11.0%)
HbA1c mmol/mol	518	39.0 (6.4)	438	40.8 (7.1)	348	40.4 (8.0)	280	40.2 (8.0)
Cholesterol, mmol/l	521	5.2 (1.1)	426	5.0 (1.2)	360	5.0 (1.2)	284	4.9 (1.2)
Cardiovascular disease history, n (%)	540	154 (28.5%)	463	152 (32.8%)	372	135 (36.3%)	298	118 (39.6)
Smoking status, n (%)	540	Ever=274 (50.7%) Never=266 (49.3%)	462	Ever=218 (47.2%) Never=244 (52.8%)	372	Ever=204 (54.8%) Never=168 (45.2%)	300	Ever=167 (55.7%) Never=133 (44.3%)
Cognitive								
Moray House Test age 11 (raw score, max 76)	511	50.2 (11.9)	437	50.9 (11.6)	372	51.1 (11.7)	283	51.2 (11.5)
Neuroimaging								
WMH volume cm^3	537	12.22 (12.8)	387	16.37 (15.3)	309	20.49 (17.7)	241	22.41 (18.8)
Total brain volume cm^3	533	993.66 (88.4)	387	976.35 (88.5)	309	965.41 (87.0)	241	947.3 (85.5)
PVS count	540	258.7 (94.6)						
Lacunes, n (%)	540	Present=28 (5.1%) Absent=512 (94.9%)						
Microbleeds, n (%)	540	Present=65 (12.0%) Absent=475 (88.0%)						

Note for Table 1: Values are mean (SD) unless otherwise specified. PVS: visible perivascular spaces; WMH: white matter hyperintensities of presumed vascular origin.

Table 2: Characteristics at each wave of study completers only

	n	Wave 2	n	Wave 3	n	Wave 4	n	Wave 5
Sociodemographic								
Age, years	300	72.5 (0.7)	297	76.2 (0.7)	296	79.3 (0.6)	300	82.0 (0.5)
Female, n (%)	300	147 (49.0%)	300	145 (48.8%)	296	143 (48.3%)	300	147 (49.0%)
Education, years	300	11.0 (1.2)	297	11.0 (1.2)	296	11.0 (1.2)	300	11.0 (1.2)
Vascular risk								
Hypertension history, n (%)	300	135 (45.0%)	297	157 (52.9%)	296	172 (58.1%)	300	176 (58.7%)
Systolic blood pressure	297	145.6 (18.0)	293	146.4 (17.5)	291	144.2 (17.9)	294	147.2 (20.2)
Diastolic blood pressure	297	79.4 (9.2)	293	80.0 (9.4)	291	78.4 (9.5)	294	78.6 (10.5)
Diabetes history, n (%)	300	20 (6.7%)	297	26 (8.8%)	296	31 (10.5%)	300	33 (11.0%)
HbA1c mmol/mol	290	38.8 (5.8)	283	40.7 (7.1)	281	40.5 (7.9)	280	40.2 (8.0)
Cholesterol, mmol/l	291	5.3 (1.1)	275	5.1 (1.2)	287	5.1 (1.1)	284	4.9 (1.2)
Cardiovascular disease history, n (%)	300	83 (27.7%)	297	103 (34.7)	296	110 (37.2%)	298	118 (39.6)
Smoking status, n (%)	300	Ever=141 (47.0%) Never=159 (55.0%)	297	Ever=134 (45.1%) Never=163 (54.9%)	296	Ever=137 (46.3%) Never=159 (53.7%)	300	Ever=133 (44.3%) Never=167 (55.7%)
Cognitive								
Moray House Test age 11 (max 76)	283	51.2 (11.5)	280	51.2 (11.5)	279	51.3 (11.5)	283	51.2 (11.5)
Neuroimaging								
Total WMH volume cm3	298	10.47 (11.3)	258	14.76 (14.6)	252	19.17 (16.9)	241	22.41 (18.8)
Total brain volume cm3	300	991.9 (87.2)	258	976.0 (86.8)	252	964.4 (88.0)	241	947.3 (85.5)
PVS count	300	251.8 (92.5)						
Lacunes, n (%)	300	Present=13 (4.3%) Absent=287 (95.7%)						
Microbleeds, n (%)	300	Present=33 (11.0%) Absent=267 (89.0%)						

Note for Table 2: Values are mean (standard deviation) unless otherwise specified. PVS: visible perivascular spaces; WMH: white matter hyperintensities of presumed vascular origin. Three participants did not take part in Wave 3 only and four participants did not take part in Wave 4 only.

Cognitive decline effect sizes between age 73 and 82

We first modelled the mean change in general cognitive ability, processing speed, memory, and visuospatial ability between the ages of 73 and 82 in separate hierarchical FoC models. Note that, at this stage, the cognitive domains will still contain any variance due to general cognitive ability. Table S2 provides details of the initial levels (intercepts) and trajectories (slopes) for each cognitive domain. All cognitive domain scores showed a significant mean decline over the nine-year period (all $p<0.001$). In standard deviation units, the declines per year were: -0.13 (just under 2 IQ points, which each have a SD of 15) for general cognitive ability, -0.16 for processing speed, -0.005 for memory, and -0.08 for visuospatial ability.

Total SVD burden associations with declines in general cognitive ability and cognitive domains in separate factor-of-curves models

The key analyses in this study were associations between total SVD burden and trajectories of general cognitive ability, processing speed, verbal memory, and visuospatial ability. Note that in the hierarchical FoC models, the domains still contain any variance due to general cognitive ability. After the inclusion of covariates, total SVD burden was negatively associated with the slope of general cognitive ability (standardised β: -0.201; 95%CI: [-0.36, -0.04]; p=0.015; pFDR=0.022) and processing speed (-0.222; [-0.40, -0.04]; p=0.015; pFDR=0.022), but not with verbal memory or visuospatial ability (see Table 3). R^2 values indicated that total SVD burden accounted for approximately 4% of the variance in the slope of general cognitive ability, and 5% of the variance in the slope of processing speed (which still contains general cognitive ability variance). In line with our previously reported results (20), total SVD burden was negatively associated with the intercept of all cognitive variables after the inclusion of covariates: (standardised betas ranged between -0.322 to -0.173; pFDR ≤0.022; for full results see Table S3).

Table 3: Factor-of-curves models of associations between total SVD burden and the slope of latent cognitive variables between the ages of 73 and 82[a]

	Slope			
	Standardised β (SE)	95% CI	Uncorrected p value	FDR-corrected p value[b]
General cognitive ability	-0.191 (0.08)	-0.351, -0.031	0.019	0.026
+ age + sex	-0.200 (0.08)	-0.358, -0.042	0.013	0.022
+ age + sex + vascular risk	-0.198 (0.08)	-0.355, -0.041	0.013	0.022
+ age + sex + vascular risk + childhood cognitive ability	-0.201 (0.08)	-0.363, -0.039	0.015	0.022
Processing speed	-0.189 (0.09)	-0.364, -0.013	0.035	0.047
+ age + sex	-0.223 (0.09)	-0.399, -0.046	0.013	0.022
+ age + sex + vascular risk	-0.222 (0.09)	-0.397, -0.047	0.013	0.022
+ age + sex + vascular risk + childhood cognitive ability	-0.222 (0.09)	-0.401, -0.044	0.015	0.022
Verbal memory	-0.139 (0.10)	-0.340, 0.061	0.174	0.223
+ age + sex	-0.092 (0.11)	-0.302, 0.117	0.388	0.428
+ age + sex + vascular risk	-0.094 (0.11)	-0.304, 0.115	0.377	0.428
+ age + sex + vascular risk + childhood cognitive ability	-0.102 (0.11)	-0.315, 0.110	0.345	0.410
Visuospatial ability	-0.179 (0.22)	-0.602, 0.245	0.408	0.435
+ age + sex	-0.157 (0.22)	-0.579, 0.265	0.466	0.466
+ age + sex + vascular risk	-0.162 (0.22)	-0.589, 0.265	0.457	0.466
+ age + sex + vascular risk + childhood cognitive ability	-0.171 (0.18)	-0.527, 0.185	0.346	0.410

Note for Table 3 Four separate models were run for each cognitive factor, adding covariates in a stepwise manner. Likelihood ratio test statistic (LR) and degrees of freedom (DF) for each of the unadjusted models were as follows: General cognitive ability (LR=6.79; DF=30), processing speed (LR=0.22; DF=2), verbal memory (LR=2.95; DF=1), visuospatial ability (LR=1.54; DF=2). CI: confidence interval; FDR: false discovery rate; SE: standard error. SVD burden-cognitive intercept associations from these models are presented in Table S3. [a] Note that the cognitive domains will contain any variance due to general cognitive ability. [b]FDR correction was conducted across results presented in this table and in Table S3.

Total SVD burden associations with declines in general cognitive ability and specific cognitive domains, modelled simultaneously in a longitudinal bifactor model

We next tested associations between total SVD burden and cognitive variables using a bifactor model, which separates out the variance in cognitive test scores attributable to general cognitive ability and to domain-specific factors (see Table 4). Results of the fully-adjusted bifactor model indicated that total SVD burden was associated with greater decline (steeper downward slope) in general cognitive ability only prior to FDR correction (standardised β: -0.222; 95%CI: [-0.39, -0.06]; p=0.008; pFDR=0.085). We found no significant associations between total SVD burden and the slopes of any other cognitive variables (i.e. processing speed, verbal memory or visuospatial ability) in the bifactor model. In terms of SVD-cognitive intercept associations, total SVD burden was associated with the intercept of general cognitive ability only, but this association became non-significant after the inclusion of covariates and adjustment for FDR (see Table S4).

Finally, we tested whether the associations observed between SVD burden and cognitive decline were likely driven by the contribution of WMH to the SVD burden score. We re-ran the hierarchical FoC models with WMH/TIV in the place of total SVD burden as the predictor (for results see Tables S5 and S6). Note that in the hierarchical FoC models, the domains will still contain any variance due to general cognitive ability. In the fully-adjusted, FDR-corrected models, we observed significant associations between WMH/TIV and the slopes of general cognitive ability (standardised β: -0.149; 95%CI: [-0.26, -0.04]; p=0.008; pFDR=0.012) and processing speed (standardised β: -0.176; 95%CI: [-0.30, -0.05]; p=0.007; pFDR=0.012). Effect sizes of these models were 0.052 and 0.046 standard deviations smaller (for general cognitive ability and processing speed, respectively) than models specifying total SVD burden as the predictor, and confidence intervals from models using different predictors overlapped substantially. Differences in effect size magnitudes were more pronounced for the total SVD-cognitive intercept associations; effect sizes of models with WMH/TIV as the predictor were between 0.105 and 0.117 standard deviations smaller than models with total SVD burden as the predictor. Overlap between confidence intervals of these models was present but more modest than for slopes.

Table 4: Results of bifactor models of associations between total SVD burden and slope of latent cognitive variables between age 73 and 82

	Slope			
	Standardised β (SE)	95% CI	Uncorrected p value	FDR-corrected p value[a]
General cognitive ability	-0.204 (0.08)	-0.366, -0.042	0.014	0.112
+ age + sex	-0.224 (0.08)	-0.386, -0.062	0.007	0.085
+ age + sex + vascular risk	-0.223 (0.08)	-0.385, -0.062	0.007	0.085
+ age + sex + vascular risk + childhood cognitive ability	-0.222 (0.08)	-0.387, -0.057	0.008	0.085
Processing speed	0.057 (0.17)	-0.265, 0.380	0.728	0.971
+ age + sex	-0.067 (0.16)	-0.382, 0.249	0.678	0.943
+ age + sex + vascular risk	-0.071 (0.16)	-0.389, 0.248	0.664	0.943
+ age + sex + vascular risk + childhood cognitive ability	-0.087 (0.17)	-0.410, 0.236	0.599	0.943
Verbal memory	-0.078 (0.11)	-0.298, 0.141	0.483	0.871
+ age + sex	0.012 (0.12)	-0.223, 0.247	0.919	0.982
+ age + sex + vascular risk	0.012 (0.12)	-0.224, 0.247	0.922	0.982
+ age + sex + vascular risk + childhood cognitive ability	0.007 (0.12)	-0.231, 0.245	0.955	0.982
Visuospatial ability	0.191 (0.28)	-0.352, 0.734	0.490	0.871
+ age + sex	0.120 (0.27)	-0.399, 0.638	0.650	0.943
+ age + sex + vascular risk	0.125 (0.26)	-0.392, 0.642	0.636	0.943
+ age + sex + vascular risk + childhood cognitive ability	0.065 (0.26)	-0.444, 0.574	0.803	0.982

Note for Table 4: Each bifactor model estimates associations between SVD burden and the four cognitive variables simultaneously. Four bifactor models were run: one without covariates, then three further models including covariates in a stepwise manner. Likelihood ratio test statistic (LR) and degrees of freedom (DF) for the unadjusted model was as follows: LR=55.3; DF=9. CI: confidence interval; FDR: false discovery rate; SE: standard error. SVD burden-cognitive intercept associations from these models are presented in Table S4. [a]FDR correction was conducted results presented in this table and in Table S4.

Discussion

In this longitudinal study of 540 community-dwelling older adults, we investigated associations between the total MRI-visible burden of cerebral SVD and the nine-year trajectory of cognitive abilities between the ages of 73 and 82. We found associations between greater SVD burden and greater decline in both general cognitive ability and processing speed, after accounting for age, sex, vascular risk and childhood cognitive ability. We then separated the variance in cognitive test scores attributable to domain-specific abilities and to general cognitive ability (using a bifactor model), to test SVD's relationship with declining processing speed, independent of the influence of general cognitive decline. In the fully-adjusted bifactor model, the association between greater SVD burden and declining general cognitive ability was nominally significant (p=0.008), but became non-significant after FDR correction (pFDR=0.085). In contrast, in the bifactor model the negative association between total SVD burden and declining processing speed was non-significant both prior to and following FDR correction (p=0.599; pFDR=0.943). We were cautious in our use of FDR correction; smaller p-values in the bifactor models were heavily penalised due to the large number of p-values included in the correction. In addition to the non-zero-containing confidence intervals for this association, the overall results from this bifactor model suggest that SVD burden's association with declining processing speed might be accounted for by overall decline in general cognitive ability. By overlooking the shared variance among domain-specific cognitive tests, previously observed associations between radiological markers of SVD and decline in domain-specific abilities could be an artefact of the relationship between SVD markers and declining general cognitive ability. Alongside these main results, in the hierarchical FoC models we observed associations between total SVD burden and the initial levels of general cognitive ability, processing speed, verbal memory, and visuospatial ability at the age of 73. These results are in line with our previous analyses that used only cross-sectional data from age 73 (20).

Effect sizes for associations between total SVD burden and greater decline in general cognitive ability and processing speed (before accounting for their covariance), were medium sized (standardised betas were -0.201 and -0.222 respectively) (45). These relatively modest effect sizes are unsurprising considering the huge number of additional structural brain variables, such as decreasing white matter microstructural integrity and cortical volumes, that contribute to cognitive decline in later life (39,46). The addition of age, sex,

vascular risk, and childhood cognitive ability did not attenuate these effect sizes. The lack of attenuation is expected as it has been observed previously in the LBC1936 that childhood cognitive ability is strongly associated with levels of cognitive ability in later life, but not with cognitive decline (38). Additionally, combined vascular risk factors measured in later life only account for approximately 2% of the variance in WMH in the LBC1936 (47; see also 48), and individually, factors such as a diagnosis of hypertension, diabetes, or cerebrovascular disease have shown no unique association with cognitive decline in this sample (28,38).

That SVD burden appears to be associated with an overall decline in general cognitive ability (after accounting for covariance between general and domain-specific test scores) is consistent with the pattern of non-pathological, age-related cognitive decline. Previous studies have estimated that the majority of the variance in age-related decline across domain-specific cognitive abilities is shared, and that the proportion of shared variance increases with age (up to 70% by the age of 85) (9,38). This implies that to a large and increasing extent, different domains of cognitive ability will decline together with advancing age. As age is the most important risk factor for SVD, it follows that SVD-related decline in domain-specific cognitive abilities are likely attributable to cognitive decline more generally. When examining associations between SVD burden and cognitive decline, our results suggested that SVD burden was associated with decline in general cognitive ability and processing speed only. However, it would be inaccurate to conclude from this that SVD-related cognitive decline does not involve declining visuospatial and memory abilities, as variance associated with decline in memory and visuospatial tests is well represented in the latent slope of general cognitive ability.

The potential association between SVD burden and overall decline in general cognitive ability also supports the notion of SVD as a diffuse, whole-brain disease that disrupts or 'disconnects' regions of the brain that sub-serve our cognitive abilities (49,50). Diffusion imaging (dMRI), which quantifies the diffusion of water molecules, thus providing a measurement of the microstructural organisation of the brain's white matter, has demonstrated that SVD-related structural changes extend beyond visible radiological markers of the disease into the 'normal appearing' tissue that surrounds the visible lesion (51–53). Radiological markers of SVD are also known to have deleterious effects on areas remote from the lesion site; lacunes have been associated with thinning of the overlying

cortical area, possibly due to degradation of the connecting white matter fibres (54). Widespread alterations of white matter connections have been associated with poorer cognitive abilities directly (55,56), and have also been highlighted by studies applying graph theoretic approaches to dMRI tractography data as a potential determinant of cognitive impairments via reduced density of white matter connections and impaired efficiency of information transfer between different brain regions (57–59).

To test whether associations between total MRI-visible SVD burden and cognitive outcomes were driven primarily by the contribution of WMH burden to the total SVD burden variable, we re-ran our hierarchical FoC models specifying WMH volume as the predictor. WMH volume was associated with the intercept of all cognitive factors, however, the magnitudes of effect sizes of these models were smaller (by between 0.105 and 0.117 standard deviations, with 95% CIs slightly overlapping) than those from models specifying SVD burden as the predictor. This suggests that total SVD burden could be a more powerful predictor of cognitive performance cross-sectionally than WMH burden alone. Interestingly, this was not the case when modelling cognitive decline; differences between the effect sizes of models specifying total SVD burden vs. WMH/TIV as the predictor of decline in cognitive outcomes appeared to be more modest (differences of between 0.046 and 0.052 standard deviations, with 95% CIs largely overlapping). Whereas incorporating measurements of PVS, lacunes and microbleeds alongside WMH in a single SVD burden score appears to strengthen the prediction of cognitive outcomes cross-sectionally, doing so may provide limited predictive power beyond that of WMH volume alone in associations with cognitive change between the ages of 73 and 82. WMH on neuroimaging represent heterogenous changes in the underlying brain tissue and cerebral microvasculature, ranging from alterations in water content and the build-up of perivascular oedema, which can resolve over time, to demyelination and axonal degeneration, which likely cannot (2). On the one hand, even though WMH are dynamic in nature (60), as one of the earliest radiological features of SVD, extensive WMH could indicate a longer duration of disease processes, thus could be more strongly related to detectable clinical features such as cognitive decline. On the other hand, other radiological markers of SVD such as lacunes and cerebral microbleeds, which represent more established vascular damage, are relatively uncommon in our study sample; only 28 participants from our sample of 540 had lacunes, and only 65 had microbleeds at baseline. Therefore, in a population of individuals with more severe SVD pathology, a variable

representing total SVD burden may have more predictive power in relation to cognitive change. Additionally, the latent SVD burden variable represents only the shared variance between the four MRI markers of SVD. If the variance unique to each MRI marker of SVD also associates with cognitive change, the fact that it is not represented in our latent SVD burden variable may limit the magnitude of associations between the SVD burden variable and cognitive slopes.

This study benefits from the availability of multiple waves of in-depth cognitive testing in a relatively large sample of individuals, over almost a decade of time. In-depth biological and clinical phenotyping in the LBC1936 also enabled us to account for a broad range of vascular risk variables. A further strength of the LBC1936 is the availability of a measure of childhood cognitive ability. By including childhood cognitive ability as a covariate in our models, we were able eliminate its confounding effects on associations between SVD burden and later life cognitive abilities. Our study also has several limitations. Members of the LBC1936 are self-selecting, so represent a generally healthy, well-educated and highly-motivated sample and mostly have a mild non-clinical presentation of SVD. The main effect of this is probably a slight lowering of true effect sizes (61). It could be the case, therefore, that we are underestimating the associations between SVD burden and cognitive decline. However, that we observe associations between SVD burden and cognitive decline in a relatively healthy population of older individuals who are mostly free of overt cognitive impairment, demonstrates that SVD-related cognitive decline is present even before clinical presentation. A limitation of the longitudinal study design is that participants who dropped out of the study before Wave 5 may have done so due to poor health outcomes related to SVD (i.e. stroke or dementia). Indeed, study non-completers had significantly greater baseline WMH volumes than participants who remained in the study up to Wave 5 (see Table S1). To some extent, we have been able to mitigate this survivor bias by using FIML as our model estimator, thus including all available data from our sample of 540 LBC1936 participants and ensuring that our results were not overly biased by the healthier participants of the initial 540, who completed all waves.

In this study we observed associations between the total MRI-visible burden of SVD and decline in general cognitive ability. The association we observed between SVD burden and decline in processing speed appears to be due to the overarching association between SVD

burden and declining cognitive ability more generally. When monitoring SVD-related cognitive decline, trials of treatments or interventions for SVD should carry out an in-depth measure of general cognitive ability (i.e. as opposed to a brief screening instrument) alongside assessments of any specific cognitive domain that is of particular interest. In doing so, any domain-specific cognitive changes can be examined in the context of declining general cognitive ability.

Conflict of Interest

None.

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6.3 Summary

The study presented in this chapter tested associations between total MRI-visible SVD burden and change in cognitive abilities between the ages of 73 and 82, in a cohort of relatively healthy community-dwelling older adults. Results of these analyses indicated that greater SVD burden was associated with greater declines in general cognitive ability and processing speed. These associations remained significant after the inclusion of age, sex, vascular risk, and age-11 IQ as covariates. However, after accounting for the covariance between domain-specific cognitive scores (i.e. the shared variability represented by general cognitive ability), the association between SVD burden and declining processing speed was no longer statistically significant. Whereas the results of Chapter 5 suggested that SVD burden at the age of 73 had specific and independent effects on processing speed measured at the same age, the results of our longitudinal analyses suggest that SVD burden at age 73 associates with declining processing speed largely due to SVD's overarching association with general cognitive decline. Taken together, the findings of these two chapters do not support the notion that SVD has specific effects on processing speed, but that any such associations are likely due to SVD's overall association with declining general cognitive ability.

To test whether the associations observed between SVD burden and cognitive decline were likely driven by the contribution of WMH to the SVD burden score, I compared the results of the above models with those of models specifying WMH/TIV as the predictor of cognitive change. In contrast with the findings in Chapter 5, the total SVD burden appeared to provide limited predictive power beyond that of WMH volume alone. However, this could be due to the fact that lacunes and cerebral microbleeds, which represent more established vascular damage, are relatively uncommon in our study sample.

In Chapter 7, I will summarise the main results of the studies presented in Chapters 4, 5 and 6 of this thesis and will discuss how these findings add to what is currently known about the nature of SVD-related cognitive impairments. I will also consider potential mechanisms underlying SVD-related cognitive impairments, and how SVD contributes to what might be considered as 'typical' and 'pathological' cognitive ageing. Finally, I will discuss, the limitations of the studies presented in this thesis, and will make recommendations for future research.

Chapter 7 General discussion

The overall aim of this thesis was to advance current understanding of the cognitive changes associated with sporadic SVD. More specifically, the aims of this thesis were:

- *Primary aim:*
    - To assess which domains of cognitive ability are impaired in individuals with sporadic SVD
- *Secondary aims:*
    - To assess whether the pattern of SVD-related cognitive impairments varies between different presentations of the disease
    - To assess whether any SVD-related impairments in specific cognitive domains remain after accounting for their association with general cognitive ability.

7.1 Summary of findings

The aims of this thesis were investigated in a systematic review and meta-analysis, and two empirical studies. Chapter 4 presented the results of a systematic review and meta-analysis of the literature reporting cognitive test scores for cohorts with various clinical and non-clinical presentations of SVD. The systematic review included 69 relevant studies, which reported data for 3229 individuals with SVD and 3679 control participants. The results of the main meta-analyses indicated that, on average, control cohorts outperformed SVD cohorts on cognitive tests in all domains examined, which included executive function, processing speed, memory, visuospatial ability, language, attention, and reasoning. The effect sizes of these associations were very large; standardised mean difference values ranged from -0.622 to -0.936, suggesting that, across all domains, cognitive test scores of SVD cohorts were between 0.6 and 0.9 standard deviations lower than those of control groups. These very large effects could be due to the inclusion of several smaller, less accurate studies with larger effect sizes in the meta-analyses. Additionally, the data contributing to the meta-analyses were raw cognitive test scores, uncorrected for differences in age, vascular risk, or education, which would be expected to attenuate effects. However, the effect sizes observed are comparable with those reported by Vasquez and Zakzanis (2015), who meta-analysed the cognitive performance of cohorts with VCI (without dementia) relative to

control cohorts, with standardised effect sizes ranging between -0.48 and -1.36. Taken together, these findings suggest that contrary to current consensus (Peng et al., 2019; Rosenberg et al., 2016), the cognitive impairments associated with SVD extend beyond processing speed and executive function to include several major domains of cognitive ability.

Chapter 4 also presented the results of a series of meta-regression analyses, aiming to assess the potential contributions of differences in age, education, and vascular risk between SVD and control cohorts, to cognitive effect sizes. Differences in age between SVD and control cohorts did not appear to contribute to differences in their cognitive performances. However, fewer years of education in SVD vs. control cohorts did contribute to the poorer performance of SVD cohorts on cognitive tests in the domains of executive function, visuospatial ability, and language (this result will be discussed further in section 7.4). There were insufficient data available on the prevalence of hypertension and diabetes to be able to assess associations between the vascular risk and cognitive effect sizes. In particular, vascular risk data were least often reported for cohorts presenting to memory clinics with SVD-related cognitive impairment or dementia, suggesting that these factors are perceived as less salient in the study of neurodegeneration, despite increasing recognition of the contributions of vascular disease to the development and progression of most major dementias (Hachinski et al., 2019).

The results of further meta-regression analyses indicated that SVD cohorts presenting with cognitive impairment or dementia performed worse (relative to controls) on tests of memory, executive function and visuospatial ability, than cohorts with stroke or non-clinical presentations of SVD. Greater severity of cognitive impairments in cohorts with cognitive impairment or dementia is to be expected, owing to the additional cognitive impact of more advanced neurodegenerative pathologies. Overall, however, the results of this study suggest that cohorts with SVD demonstrated cognitive impairments (relative to controls) in several major domains of cognitive ability, *regardless* of whether they presented with stroke, cognitive impairment or dementia, or had not presented clinically.

The analyses in Chapter 5 examined cross-sectional associations between the total MRI-visible burden of SVD and cognitive abilities at the age of 73 in the LBC1936, a cohort of

relatively healthy community-dwelling older adults. Within a SEM framework, I constructed a latent variable of SVD burden using computationally-derived measures of WMH and visible PVS, and visual ratings of lacunes and microbleeds. This was a development upon previous work by Staals and colleagues (2015), whose latent SVD burden variable was derived from visual rating scores only. I found that greater SVD burden was associated with poorer performance in general cognitive ability and in the domains of processing speed, verbal memory, and visuospatial ability. These associations remained after correcting for age, sex, vascular risk, depression score, and age-11 IQ. However, after accounting for the covariance in cognitive test scores attributable to general cognitive ability, only the association between SVD burden and processing speed remained statistically significant. Further analyses revealed that the computationally-derived SVD variable was a stronger predictor of cognitive outcomes than Staals' visually-derived SVD variable, or WMH volume alone.

In sum, the results of this study suggest that SVD's association with poorer processing speed in relatively healthy older adults is not driven by, but is *independent* of its association with poorer general cognitive ability. Results also suggest that incorporating continuous computational measures into the total SVD burden variable increases the strength of its associations with cognitive outcomes.

This work was further developed in Chapter 6, which examined associations between total SVD burden at the age of 73 and change in cognitive abilities across four waves of cognitive testing between the ages of 73 and 82, in the same LBC1936 sample. Results of these analyses indicated that, over a period of 9 years, greater SVD burden was associated with steeper declines in general cognitive ability and processing speed, but not with declines in verbal memory or visuospatial ability. These associations remained after correcting for age, sex, vascular risk, and age-11 IQ. However, after accounting for the covariance in cognitive test scores attributable to general cognitive ability, the association between SVD burden and steeper decline in processing speed was no longer significant. Contrary to the specific relationship between SVD burden and processing speed that was observed in the cross-sectional analyses (Chapter 5), these results suggest that SVD's association with declining processing speed is due to its overarching association with declining general cognitive ability.

The effect size magnitudes of these models were similar to those of models specifying only WMH volume as the predictor of cognitive decline. Once again, this finding contrasts with that of the cross-sectional analyses, in which total SVD burden was a stronger predictor of cognitive outcomes than WMH alone. Therefore, the SVD burden variable appears to provide only limited predictive power beyond that of WMH volume alone in associations with longitudinal cognitive change, although this result may be due to the relatively mild SVD burden of the study sample. These analyses also did not account for change in SVD burden over the 9-year period in which cognitive testing was done, during which time different SVD lesions types might accrue at different rates and have different impacts on co-varying cognitive change.

Overall, the findings of this final empirical study do not support the common perception that SVD has a specific association with declining processing speed, suggesting instead that SVD's association with declining processing speed is due to SVD's overarching association with declining general cognitive ability.

Importantly, in the latter two empirical studies, I was able to account for levels of childhood cognitive ability, which, as discussed in Chapter 2, owing to the stability of intelligence differences across the life course, account for approximately half of the variability in cognitive test scores in later life (Deary, 2014). By accounting for childhood cognitive ability, I am able to conclude that, after setting aside one of the largest known contributors to cognitive abilities in later life, greater SVD burden at the age of 73 associates both with poorer cognitive abilities at the same age, and with a greater rate of general cognitive decline between the ages of 73 and 82.

7.2 The global pattern of SVD-related cognitive impairments: potential mechanisms

As discussed in Chapter 3, there is a common perception that the cognitive symptoms of SVD are characterised by slowed processing speed and poor executive function, alongside relative preservation of memory and language abilities (Peng et al., 2019; Rosenberg et al., 2016). Results of the analyses carried out in this thesis do not fully support this notion, and instead suggest that SVD associates with impairments in several major domains of cognitive ability. The results of the systematic review and meta-analysis presented in Chapter 4 indicate that relative to controls, individuals with SVD demonstrate impairments in

processing speed, executive function, attention, memory, visuospatial ability, reasoning and language. Additionally, the results of analyses in Chapters 5 and 6, indicated that alongside slowed processing speed, a greater radiological burden of SVD associates with poorer memory and visuospatial abilities (albeit that these associations appear to be due to SVD's overarching association with poorer general cognitive ability). Why then, despite evidence to the contrary, does the notion that SVD selectively affects the domains of processing speed and executive function endure? Previous meta-analyses examining associations between radiological markers of SVD and cognitive abilities (discussed in Chapter 3) highlighted a dearth of literature examining visuospatial ability and language. Likewise, the vast majority of studies included in Chapter 4's systematic review and meta-analysis carried out tests of processing speed, executive function and memory only, with relatively few studies examining visuospatial ability, language, attention, or reasoning. This suggests that some SVD studies might only test for the cognitive deficits that they expect to observe, therefore, may be biased towards generating data that supports the notion of SVD as a primarily dysexecutive syndrome.

Growing evidence suggests that SVD-related cognitive impairments result from the disruption of white matter tract networks connecting brain regions that are critical for cognitive functioning (Biesbroek et al., 2017; ter Telgte et al., 2018). More specifically, it has been suggested that deficits in executive function, often referred to as "frontal" or "dysexecutive" symptoms, result from the disruption of long frontal-subcortical white matter connections (Biesbroek et al., 2017; O'Sullivan et al., 2001). The case for disruption of specific white matter tracts as a key mechanism through which SVD-related cognitive deficits arise, is supported by lesion symptom mapping (LSM) studies, which use statistical modelling to effectively 'map' cognitive impairments to affected brain regions (Biesbroek et al., 2017). Lesion-symptom mapping studies across a range of SVD presentations (including community-dwelling older adults, adults with arterial disease, memory clinical patients, and individuals with CADASIL) have commonly reported relationships between WMH or lacunes in the anterior thalamic radiation and the forceps minor, and poorer scores on tests of executive function and processing speed, independently of total lesion burden (Biesbroek et al., 2013, 2016; Duering et al., 2011, 2013, 2014). These findings are consistent with those of the studies discussed in Chapter 3, which report poorer executive function and slower

processing speed in individuals with lesions in the thalamus (Benisty et al., 2009; Benjamin et al., 2014; O'Brien et al., 2002; Szirmai et al., 2002).

However, visible radiological markers of SVD represent only the tip of the iceberg in terms of underlying SVD pathology. As described at various points throughout this thesis, white matter microstructural damage is commonly observed in SVD, both in areas of WMH and within normal appearing white matter (Muñoz Maniega et al., 2019). DTI measures of reduced microstructural integrity are associated with poorer cognitive abilities in SVD, independently of visible MRI markers of the disease (Jokinen et al., 2013; Tuladhar et al., 2015; van Norden et al., 2012); thus, in addition to the disruption of frontal-subcortical circuits (described above), more general disruption of the brain's white matter tract networks appears to contribute to cognitive dysfunction in SVD. Several studies have highlighted that slowed processing speed in particular, is associated with global microstructural changes, as opposed to tract-specific changes (Baykara et al., 2016; Deary et al., 2019; Kuznetsova et al., 2016).

One methodological approach that has provided additional insight into white matter connectivity in SVD, is the application of graph theoretic approaches to DTI tractography data (for a comprehensive review see ter Telgte et al., 2018). Using DTI data to reconstruct white matter tract networks, this method represents the brain as a series of nodes (brain regions) and edges (the white matter connections that link them together). Several studies adopting this approach have found reduced numbers of network connections, reduced strength of network connectivity, and decreased network efficiency, both in regional and global networks in SVD, and have observed associations between these network measures and poorer cognitive performance (Banerjee et al., 2018; Du et al., 2019; Lawrence, Chung, Morris, Markus, & Barrick, 2014; Tuladhar et al., 2016; Wiseman et al., 2018). It should be noted, however, that some caution is warranted when interpreting results of these studies; previously, different network connectivity metrics have been found to correlate extremely highly with one another (some $r > .99$; Buchanan et al., 2020), calling into question the extent to which they represent separate constructs. In one study of 225 individuals from a memory clinical population (mean age: 72.2±8), reductions in network efficiency were associated with cortical thinning, and both of these factors were found to mediate the relationship between greater total SVD burden (measured using the 0-4 sum score) and

poorer performance on tests of executive function and visuospatial ability (Banerjee et al., 2018), providing support for the role of SVD in widespread disconnection of brain regions that support cognitive functioning.

7.3 SVD associates with general as opposed to domain-specific cognitive impairments

Whereas cognitive impairments in SVD appear to affect several major domains of cognitive ability, from this observation alone it is unclear whether this multi-domain pattern of cognitive impairments could be due to SVD's association with general cognitive ability, or whether SVD might have specific and independent effects upon one or two specific cognitive domains. Owing to the universally-replicated phenomenon that all cognitive test scores correlate positively with one another (Carroll, 1993), measures of processing speed also contain variance that is shared across other cognitive domains (i.e. general cognitive ability). Therefore, associations between SVD and processing speed observed in previous publications could be largely due to SVD's association with general cognitive ability. The domain of processing speed is a cognitive chimera from which, in Chapters 5 and 6, I used SEM to distil the more specific variance in cognitive test scores attributable to processing speed. The results of the analyses presented in Chapter 5 demonstrated that SVD burden associates cross-sectionally with this 'purer' processing speed variable. In line with popular perception, this finding indicates that SVD burden may indeed have a specific relationship with processing speed. As described above, this association could reflect the fact that SVD causes the widespread disruption to the brain's white matter tract networks; as networks supporting processing speed appear to be distributed throughout the brain, tests of processing speed may be particularly selective to SVD's diffuse structural changes (Madole et al., 2020). However, there are several other explanations for this specific SVD-processing speed association. As described in Chapter 5, processing speed is also often considered to hold a special status among the domains of cognitive ability; many cognitive tasks appear to require speed of information processing for efficient performance, and tests of processing speed are among those most affected by aging. As a result, it has been suggested that processing speed drives age-related changes in other fluid cognitive abilities (Salthouse, 1996). Moreover, processing speed has been found to mediate, statistically, the association between brain white matter health and general cognitive ability in older people (Penke et al., 2012). However, it is important to note that there is currently a more agnostic attitude to

the place of processing speed; there is not considered to be definitive evidence about whether processing is the driver of age-related declines in other cognitive abilities, or whether it is just another domain of cognitive ability that declines on average with age (Salthouse, 2010c; Verhaegen, 2014).

Another potential explanation for the observed association between SVD burden and the variance in cognitive test scores uniquely attributable to processing speed, concerns the nature of the cognitive tests used to assess processing speed in the LBC1936. Two of the tasks that contribute to the latent processing speed variable (Four-Choice Reaction Time and Inspection Time) are qualitatively different from the other cognitive tasks used in the study. These two tasks involve either rapid response to, or rapid exposure to intellectually simple content (for a description see Chapter 2, Table 1), so are thought to measure more fundamental aspects of cognitive processing, as opposed to the more complex cognitive activities assessed by tasks requiring careful thought or reasoning (Deary, 2000). It is possible, therefore, that the association between SVD burden and the latent processing speed variable may partly reflect an association between SVD burden and poorer *fundamental* processing capabilities, which are thought to account for a proportion of variance in test scores measuring other more complex cognitive abilities (Johnson & Deary, 2011), and are hypothesised to contribute to producing intelligence differences more broadly (Jensen, 2006).

In the systematic review and meta-analysis presented in Chapter 4, lower levels of education in SVD cohorts (vs. control cohorts) contributed to their poorer cognitive performance in the domains of executive function, visuospatial ability, and language. The beneficial effect of educational attainment on cognitive performance in later life is discussed further below, but it is worth noting here that whereas previously, education has been found to associate with better cognitive performance in later life, this effect appears to be limited to certain domains of cognitive ability. For example, in the LBC1936, years of education were positively associated with later life IQ, but only very weakly, or not at all, with tests of processing speed (Ritchie, Bates, Der, Starr, & Deary, 2013; see also Ritchie, Bates, & Deary, 2015). As education does not appear to improve information processing abilities, the processing speed scores in the empirical studies presented in Chapters 5 and 6 may capture variation in cognitive performance that accounting for childhood cognitive ability 'washes out' of the

other cognitive domain scores, and could be another reason for the apparent unique association between SVD burden and processing speed.

The cross-sectional analyses presented in Chapter 5, present a snapshot of an association between two ongoing, dynamic processes, namely the progression of SVD and the process of cognitive decline. Therefore, the associations observed in these analyses are unlikely to accurately represent the relationship between SVD burden and cognitive abilities over time. The study presented in Chapter 6 attempted to (partly) address this limitation by examining associations between the total SVD burden variable at the age of 73 and change in cognitive abilities across four waves of testing between the mean ages of 73 and 82. Results of these analyses indicated that, greater SVD burden was associated with greater decline in both general cognitive ability and processing speed over the 9-year period examined. However, in contrast with the specific SVD-processing speed association that was observed in Chapter 5, after accounting for the covariance in the decline in cognitive test scores attributable to general cognitive ability, SVD burden was no longer associated with declining processing speed. In other words, whereas cross-sectionally, SVD was associated with processing speed independently of its relationship with general cognitive ability, this relationship was not borne out in the longitudinal analyses of cognitive decline. Rather, results of the longitudinal analyses indicated that SVD burden associates with declining processing speed via its overarching relationship with declining general cognitive ability. In addition to changing cognitive abilities over time, it is possible that the progression of SVD burden over the 9-year study period contributed to loss of the specific SVD-processing speed between the cross-sectional and longitudinal analyses. It could be the case that as the radiological burden of SVD progresses (increasing damage to local as well as global WM tract networks), general cognitive impairment predominates over any specific SVD-processing speed associations that were present at the beginning of the study period (i.e. at age 73).

To an extent, the pattern of general cognitive decline associated with SVD burden, resembles that observed in healthy cognitive ageing; as discussed in Chapter 2, fluid cognitive abilities tend to decline in concert, with approximately half of the variance in their decline accounted for by declining general cognitive ability (Tucker-Drob et al., 2019). This raises the question: to what extent might SVD-related cognitive decline represent an

advanced form of typical cognitive ageing in relatively healthy older populations such as the LBC1936? This question will be discussed further in section 7.4, below.

7.4 Cognitive impairments in clinical and non-clinical presentations of SVD

Age-related cognitive decline is thought to reflect the cumulative impact of a multitude of biological, lifestyle, socio-demographic, and environmental factors on our cognitive abilities. Whereas many different risk and protective factors for age-related cognitive decline have been proposed, very few factors associate with rates of cognitive decline on a meta-analytic level. A meta-analysis of data from 127 observational studies, 22 randomised controlled trials, and 16 systematic reviews, found current tobacco use, diabetes mellitus, and carriership of the *APOE* e4 genotype to be associated with greater rates of cognitive decline in heathy ageing (Plassman et al., 2010; see also Ritchie et al., 2016). It is possible that SVD pathology mediates some of these associations; SVD is an age-related disease, increasing in prevalence and severity over time, and is more common in those with increased vascular risk, including smokers and individuals with hypertension, hyperlipidemia, and diabetes (Wardlaw et al., 2019). Indeed, evidence from population-based studies indicates that the majority of older adults with evidence of SVD on neuroimaging do not present to clinical services with cognitive problems and experience rates of cognitive decline within the bounds of what might be considered 'healthy cognitive ageing' (Das et al., 2019). This observation aligns with the idea that SVD pathology could be a part of a continua linking typical 'healthy' cognitive ageing and pathological cognitive ageing. BBB leakage, for example, is observed in middle and older aged adults in the absence of cognitive disturbances or major neurological disease (Verheggen et al., 2020). However, whereas the majority of individuals with evidence of SVD on neuroimaging will experience a relatively benign trajectory of cognitive decline, other individuals will experience a steeper decline in their cognitive abilities, resulting in presentation to clinical services. However, radiological markers of SVD are also known to associate with adverse clinical outcomes. For example, in a meta-analysis, extensive WMH were associated with increased risk of incident stroke (in both the general population and in those with increased risk for vascular disease or dementia), increased risk of dementia (in the general population), and increased mortality (in the general population and in higher risk groups; Debette et al., 2019). Similarly, another recent meta-analysis of 104 studies of ischaemic stroke patients found dose-response associations between WMH burden and risk of cognitive impairment, dementia, and mortality (both all-cause and cardiovascular;

Georgakis et al., 2019). These outcomes are not inevitable consequences of ageing and demonstrate that SVD contributes to cognitive decline in healthy and pathological cognitive ageing.

It was previously unknown whether the pattern of SVD-related cognitive impairments might differ between these clinical and non-clinical presentations of SVD. In the systematic review and meta-analysis presented in Chapter 4, cohorts with varying clinical and non-clinical presentations of the disease demonstrated similar cognitive impairments: SVD cohorts were impaired (relative to controls) in all cognitive domains examined, regardless of whether they presented with stroke, MCI or dementia, or did not present clinically. The three broad categories of SVD presentations examined in the meta-analysis are not distinct; individuals with radiological evidence of SVD but no overt clinical symptoms may go on to experience stroke and/or dementia. Additionally, owing to the inter-related nature of stroke and dementia, it is possible that cohorts in these three categories exhibit both vascular and neurodegenerative pathologies and that mixed pathologies may have contributed to the observed similarities in the cognitive deficits across the three SVD presentation groups.

7.4.1 Potential attenuating factors: cognitive reserve

In the prediction of cognitive and/or clinical outcomes associated with SVD, one factor that is important to consider (in addition to the radiological burden of the disease) is the potential resilience of the brain against SVD pathology. Various 'reserve' mechanisms, such as brain reserve or cognitive reserve, have been proposed to mitigate the impact of SVD-related brain changes on cognitive functioning (Satz, 1993; Stern, 2002). The hypothesis surrounding *brain reserve* suggests that favourable differences in brain structure (e.g. larger brain size), or better brain connectivity increases tolerance to pathological brain changes. According to this hypothesis, cognitive and other symptoms only become apparent after brain pathology reaches a certain threshold of severity (Jokinen et al., 2016; Murray et al., 2011). The hypothesis of *cognitive reserve* posits that experiential resources, such as educational attainment, occupational attainment or premorbid cognitive ability, moderate the association between pathological brain changes and cognitive decline (Ritchie & Tucker-Drob, 2018; Staff, Murray, Deary, & Whalley, 2004; Stern, 2002). Previously, it has been observed that educational attainment mediates the relationship between WMH burden and

cognitive outcomes in SVD (Backhouse et al., 2017; Pinter, Enzinger, & Fazekas, 2015), and shares a dose-response relationship with dementia risk (Xu et al., 2016).

Results of the systematic review and meta-analysis presented in Chapter 4 suggest that lower levels of education in SVD vs. control groups contributed to their poorer cognitive test scores in certain cognitive domains, supporting the cognitive reserve hypothesis. However, these associations should be interpreted carefully; previous studies have consistently reported associations between educational attainment and levels of cognitive ability in older age, but not with age-related cognitive changes (Seblova, Berggren, & Lövdén, 2020). This indicates that, rather than offering protection against age-related cognitive decline, it is possible that educational attainment positively influences the rate of cognitive development in childhood and adolescence, thus associates with a higher peak level of cognitive ability in adulthood, from which an individual has further to fall before developing notable cognitive symptoms (Tucker-Drob, 2019). This effect may be further compounded by the fact that lower levels of education, along with other inter-related early life factors such as childhood socioeconomic status and childhood IQ, associate with greater SVD burden in later life (Field et al., 2016).

7.4.2 Potential attenuating factors: vascular risk management

Another set of factors to consider when examining correlates of later-life cognitive abilities are traditional vascular risk factors, such as hypertension and hyperlipidemia. Although known to be key risk factors for the progression of SVD, the nature of their associations with structural brain changes and with cognitive outcomes are poorly understood. For example, traditional vascular risk factors have been found to account for up to only 2% of the variance in various indices of brain health, such as WMH volume, grey matter volumes, and white matter integrity (Cox et al., 2019; Wardlaw et al., 2014). To date, the majority of studies examining associations between vascular risk and cognitive abilities have focused on hypertension, but these studies have produced mixed results (see Iadecola et al., 2016 for a comprehensive review). Whereas evidence linking higher blood pressure (BP) levels in midlife to poorer cognitive abilities in later life is fairly consistent (Elias, Wolf, D'Agostino, Cobb, & White, 1993; Kilander, Nyman, Boberg, & Lithell, 2000; Launer, 1995; Nishtala et al., 2015; Swan, Carmelli, & La Rue, 1996), results of associations between later-life BP and later-life cognitive abilities are conflicting (Cerhan et al., 1998; Guo, Fratiglioni, Winblad, & Viitanen, 1997). Some evidence also suggests that high

BP levels may have age-dependent effects on cognitive abilities; in individuals over the age of 85, higher BP has been found to associate with *better* cognitive performance, possibly due to the need for higher BP to maintain adequate cerebral perfusion (Euser et al., 2009; Harrison, Stephan, Siervo, & Granic, 2015). The management of hypertension represents an important therapeutic target for SVD. In a meta-analysis of six observational studies with long-term follow-up, study participants who had a high baseline BP (≥140 mmHg) and used antihypertensive medications exhibited a 12% lower risk of dementia and a 16% lower risk of AD, compared with those not using antihypertensives (Ding et al., 2020). Despite such findings from observational studies, it has proved difficult to demonstrate the beneficial effects of BP lowering on slowing rates of cognitive decline, or reducing the prevalence of MCI or dementia in clinical trials (Bath et al., 2017; Diener et al., 2008; Pearce et al., 2014; Rapp et al., 2020; The SPRINT-MIND Investigators for the SPRINT Research Group, 2019b; Tzourio et al., 2003). For example, in one of the only studies to indicate positive effects of BP reduction on cognitive outcomes, SPRINT-MIND, intensive BP reduction to target levels had to be sustained over almost four years in order to show a benefit in reducing the incidence of the combined outcome of MCI or dementia (The SPRINT-MIND Investigators for the SPRINT Research Group, 2019b). Similarly, trials of lipid lowering treatments have produced mixed results for the impact of statins in ameliorating cognitive outcomes (Bath et al., 2017; Collins, Armitage, Parish, Sleight, & Peto, 2002; Shepherd et al., 2002). Multiple factors likely contribute to these disappointingly small effects, such as having limited periods of follow-up, cognitive outcomes not being specified as primary outcomes of trials, and measuring cognitive outcomes with brief screening tools, which are less sensitive to cognitive change. Findings from these clinical trials highlight that the complex interplay between vascular risk, brain health, and cognitive outcomes is not yet fully understood.

In the systematic review and meta-analysis presented in Chapter 4, I was unable to assess the potential impact of vascular risk on SVD-cognitive associations as very few papers reported vascular risk data for their study cohorts. Of the studies included in the meta-analysis, almost all reported data on the age, sex, and education of study cohorts, however, reporting of vascular risk data was less complete; approximately half of all studies reported history of hypertension or diabetes, and only one third of studies reported smoking status, despite its known association with SVD progression and the adverse effects of all three common risk factors on brain health. Vascular risk data were least often reported for cohorts

with a cognitive presentation of SVD, which could suggest that these factors are perceived as being less relevant to cohorts with MCI or dementia.

7.5 Limitations

In addition to the limitations that have been discussed in Chapters 4-6, there are some further limitations to the methods used in this thesis, which are discussed below.

The analyses presented in Chapters 5 and 6 used data from the LBC1936, a follow-up study to the SMS1947, which tested the cognitive ability of thousands of Scottish schoolchildren in 1947. However, as study participants are rarely lost to follow-up at random, the LBC1936 (like the majority of cohort studies) is liable to sample bias. Previously, older adults who did not respond to invitations to participate in a community-based study of later life cognitive abilities more often reported a history of psychiatric illness, had poorer physical health, and lower cognitive test scores than those who did participate (Launer, Wind, & Deeg, 1994). Indeed, the average childhood IQ of LBC1936 participants is higher than that of the general Scottish population: the mean (SD) age-11 MHT score for the LBC1936 is 49.0 (11.8), compared with 36.7 (16.1) for the whole of Scotland, and 40.3 for the Edinburgh region (Taylor et al., 2018). As a self-selecting group, members of the LBC1936 are a generally healthy, well-educated and highly-motivated sample, who are not fully representative of the general older population of Edinburgh (although members of the cohort do have good variation in social background and cognitive test scores). Additionally, all members of the LBC1936 are white, therefore the cohort is lacking in its representation of Black, Asian, and Minority Ethnic participants, whom make up a small but increasing proportion of the older adult population of Scotland (Walsh et al., 2019). Together, these factors may limit the generalisability of the results presented in Chapters 5 and 6, to other groups of older adults.

Attrition of the LBC1936 sample over time also introduces a further bias. As participants with poorer physical and cognitive health drop out of the study, later waves of the study become enriched for those who are healthier and more cognitively able. This effect has previously been reported for the wider LBC1936 sample between Waves 1-4 (Taylor et al., 2018); study completers (up to Wave 4) had higher MMSE scores and had better physical fitness than participants who dropped out of the study at any wave. Examining differences between participants who remained in the study and those who dropped out at specific waves, those

who remained in the study also demonstrated significantly higher older-age IQ, and higher socioeconomic status (as represented by more professional occupation types). Similar effects were observed in the smaller LBC1936 sample that was analysed in Chapter 6; participants who completed Wave 5 data collection had a lower prevalence of diabetes, lower WMH volumes and higher childhood cognitive test scores than participants who were lost to follow-up. To some extent, the use of FIML as the model estimator mitigated this survivor bias by including all available data from the sample of 540 LBC1936 participants, as opposed to basing analyses on participants who had data at all time points. However, the over-representation healthier and more able participants, both in the cohort in general and over time due to attrition, likely results in a slight lowering of true effect sizes when examining correlates of cognitive aging (Johnson, Corley, Starr, & Deary, 2011).

As outlined in Chapters 5 and 6, although 680 LBC1936 participants had available neuroimaging data, only 540 participants were included in the studies presented in these chapters due to the inability to carry out computational segmentation of visible PVS in images for 140 participants. Reasons for this were failed registration of the centrum semiovale, noise or motion artefacts (which can have a similar appearance to PVS), or where small WMH were misclassified as PVS. Whereas it would be possible to include individuals without visible PVS data in the study sample, their total SVD burden score would consist of only WMH volume and binary ratings of lacunes and microbleeds, thus would be substantively different from the SVD variable constructed for rest of the sample. Because of this, I chose to exclude participants for whom visible PVS quantification was unavailable. However, additional noise and other artefacts on neuroimaging could be an indication of poorer brain health, therefore, by excluding individuals with no PVS segmentation (i.e. those with noisier scans), the final study sample of 540 might be further enriched for healthier participants with fewer pathological brain changes. Despite this, associations between SVD burden and cognitive changes were observed in this sample, demonstrating that SVD-related cognitive decline is present even the presence of very mild SVD.

There are also limitations regarding the measures used to construct the total SVD burden variable in Chapters 5 and 6. As discussed in Chapter 3, several studies have suggested that the number or volume of lacunes and microbleeds, as opposed to a binary measure of their presence or absence, may better reflect the underlying pathological burden of SVD. Whereas

computational quantification of lacunes and microbleeds have not yet been carried out in the LBC1936, raw count data are available. However, in the dataset used in Chapters 5 and 6, only 18 of the 540 participants had >1 microbleed (3.3% of the sample) and only 8 participants had >1 lacune (1.5% of the sample). Therefore, due to the scarcity of participants with more than one lacune or microbleed, prior to analysis, I decided to present microbleeds and lacunes as binary data (i.e. present/absent). To test whether the use of raw counts as opposed to binary measures of lacunes and microbleeds changed the nature of the latent SVD construct, I constructed the total SVD burden variable using continuous measures of WMH and PVS, and raw counts of lacunes and microbleeds (these data were ordinal due to the low numbers of participants with values >1). The correlation between the factor score of this new latent SVD variable and that of the SVD variable used in this thesis was very high (r=0.85). It is likely, therefore, that the use of count (ordinal) data for lacunes and microbleeds would make little difference to the results presented in this thesis. However, in a participant sample with more substantial SVD pathology, it might be desirable to model microbleeds and lacunes as count data.

It is also important to note that whilst the latent total SVD burden variable used in Chapters 5 and 6 represents the shared variance of its four constituent SVD markers (WMH volume, visible PVS, lacunes and microbleeds), it does not account for the heterogeneity of the distribution, or severity (in the case of lacunes and microbleeds) of these markers in other SVD subtypes. For instance, the latent SVD variable does not incorporate a measure of *lobar* microbleeds, which are more commonly associated with CAA, thus the latent variable might not be as sensitive to the severity of SVD in CAA as it is to the severity of SVD in a sporadic form, secondary to arteriolosclerosis and lipohyalinosis. Owing to this, it could be the case that in SVD subtypes such as CAA, the latent SVD variable would show different patterns of association with cognitive abilities than have been observed in this thesis. The findings of Chapters 5 and 6, therefore, may be limited in the extent to which they can be generalised to other SVD subtypes. Replicating the total SVD burden–cognitive performance associations in other forms of SVD represents an important next step for this work.

One further limitation of this thesis is that the longitudinal study presented in Chapter 6 relied upon repeated measurements of the same cognitive tests over four waves of data collection. Whereas repeated measurements enable researchers to track cognitive abilities over time, estimates of cognitive change based on repeated measures also incorporate error

due to practice effects (i.e. improved performance due to participants becoming familiar with the test materials). As practice effects tend to be fairly evenly distributed among test-takers (i.e. demonstrating minimal between-person variation), they have little impact on individual differences in cognitive change (Salthouse & Tucker-Drob, 2008). Because of this, I would not expect practice effects to impact models examining associations between SVD burden and cognitive change in Chapter 6, however, I would expect some impact on the estimates of mean change in cognitive test scores. Typically, the largest practice effects are observed on tests of learning and memory (Salthouse & Tucker-Drob, 2008). Indeed, this could be the reason why verbal memory scores exhibited the least amount of decline in the longitudinal analyses presented in Chapter 6 (verbal memory scores declined by 0.005 standard deviations per year, compared with 0.13 for general cognitive ability, 0.16 for processing speed, and 0.08 for visuospatial ability). However, in longitudinal studies, the greatest practice effects are usually observed between the first and second sessions of testing – practice-related changes in test performance do persist at subsequent timepoints, but are typically much smaller (Bartels, Wegrzyn, Wiedl, Ackermann, & Ehrenreich, 2010). Although the measurement error associated with practice effects was likely present in the estimates of cognitive decline in Chapter 6, these effects will have been mitigated owing to the fact that we used data from the second session of testing (i.e. Wave 2) as baseline.

7.6 Implications, recommendations and avenues for future research

The findings of this thesis have implications for the assessment of cognitive abilities in individuals with SVD, both in clinical and research settings. A key finding of this thesis was that SVD associates with impairments in several major domains of cognitive ability, not just the domains of processing speed and executive function. Therefore, to capture the full range of SVD-related cognitive impairments, a comprehensive test battery covering a range of cognitive abilities should be used in clinical and research settings. One such test battery is that proposed by the National Institute for Neurological Disorders and Stroke (NINDS) and the Canadian Stroke Network (CSN), which is designed for use with participants with VCI (Hachinski et al., 2006). The full-length protocol takes approximately 60 minutes to administer, but can be shortened to 30 or 5 minutes, while still capturing information from several different domains of cognitive ability. Widespread use of a standard cognitive testing protocol would also facilitate more accurate cross-comparison and meta-analysis of cognitive data from different studies.

A key finding of the results presented in Chapters 5 and 6 is that a greater radiological burden of SVD associates with steeper decline in general cognitive ability, as opposed to declines in any domain-specific cognitive abilities. This further reinforces the suggestion that by only measuring one or two domains of cognitive ability, researchers and clinicians will gain only a partial view of the cognitive changes occurring in SVD. By failing to account for the positive correlation between cognitive test scores (i.e. general cognitive ability), researchers remain in the dark as to whether apparent associations between measures of SVD burden and domain-specific scores are due, either wholly or partly, to SVD's association with an overall decline in general cognitive ability. In particular, this has implications for clinical trials of treatments or interventions for SVD, which increasingly measure cognitive performance as a primary outcome. Whereas tests of processing speed may be particularly sensitive to the cognitive changes associated with SVD, the majority of the variance in SVD-related cognitive decline appears to be attributable to declining general cognitive ability. It may be beneficial, therefore, to include an in-depth measure, or ideally several diverse measures, of general cognitive ability (as opposed to a score from a cognitive screening tool) as a primary outcome in clinical trials examining the impact of treatments and interventions for SVD. Such measures could be constructed from other 'domain-specific' cognitive test scores via a principal components analysis, as described in Chapter 2.

A further important finding of this thesis is that cohorts spanning the full spectrum of SVD presentations, from non-clinical presentations to SVD-related dementia, demonstrated cognitive impairments in several major domains of cognitive ability. This may have implications for the assessment of patients with suspected SVD in clinical settings; deficits in cognitive domains such as memory, which are typically considered hallmark signs of dementia, may also flag those at increased risk of stroke due to underlying SVD pathology.

As discussed in Chapter 1, it is increasingly recognised that vascular and neurodegenerative pathologies co-occur and likely interact with one another. However, results of the systematic review presented in Chapter 4 indicated that studies of cohorts with SVD-related cognitive impairment and/or dementia infrequently report data on vascular risk factors. One recommendation for future SVD research is that where possible, data should be collected that is relevant to both vascular and neurodegenerative disease processes. In terms of

cognitive data, this would mean collecting data from a broad range of cognitive domains, as recommended above. In terms of neuroradiological data, this would mean considering radiological markers of SVD (WMH, visible PVS, lacunes, microbleeds, microinfarcts, altered dMRI metrics), and those more commonly associated with neurodegeneration such as cerebral atrophy and hippocampal volume. The collection of vascular risk data is also important. History of hypertension, diabetes, and smoking status are quick to ascertain and should be collected for all individuals with suspected SVD in clinical and research settings. The collection of vascular biomarkers at different stages throughout the development of dementia may also provide an indication of the changing contributions of vascular dysfunction to neurodegenerative disease processes over time.

Results of the meta-regression analyses presented in Chapter 4 indicated that educational attainment is associated with the severity of SVD-related cognitive impairments. A further recommendation, therefore, is that future studies account for educational level or peak cognitive ability when examining later life cognitive abilities, or comparing cognitive abilities between study groups. A range of methods can be used to estimate peak cognitive ability, some of which are free and have been validated in multiple languages (Bright & van der Linde, 2020).

Following on from the studies presented in Chapters 5 and 6, one promising avenue for future research is further investigation of the utility of constructing composite scores of total SVD burden. Prior to this thesis, only two studies had estimated continuous variables representing the total MRI-burden of SVD (Jokinen et al., 2020; Staals et al., 2015). In both of these studies, the magnitudes of associations between SVD burden and cognitive outcomes surpassed those of models using a simple 0-4 SVD burden score (Staals et al., 2015) or individual MRI markers of SVD (Jokinen et al., 2020) as predictors of cognitive performance. Further developing the work of Staals et al. (2015), the results of the studies presented in Chapters 5 and 6, suggest that the incorporation of computational measures of WMH and PVS into a continuous latent variable of SVD burden increased the strength of its cross-sectional associations with cognitive outcomes even further. As methods for the computational quantification of lacunes and microbleeds become more widely used, future studies might test whether incorporating these measures (or other variables such as

measures of microstructural integrity) into a variable of total SVD burden, further increases the fidelity with which the total brain burden of SVD can be measured.

If the incorporation of computational measures of SVD into a continuous SVD burden score does indeed increase the fidelity with which total SVD burden is measured, it is tempting to consider how continuous measures of SVD burden might be used in clinical practice. However, further work is required before these possibilities can be considered. The reproducibility and consistency of the total SVD variable with varying scanner parameters, methods of WMH and PVS quantification, and in different patient groups has not yet been tested. Additionally, associations between SVD burden and other clinically relevant outcomes such as recurrent stroke (a common primary outcome in trials of interventions or treatments for SVD), or how the SVD variable itself might change over time, have yet to be examined, and present avenues for future research.

Studying the genomics of SVD could also provide further insight into the relationship between SVD pathology and cognitive changes in later life. Over the last decade, results of genome-wide association studies (GWAS) studies have suggested that cognitive ability is a highly polygenic trait, in that large numbers of genetic variants contribute to variation in cognitive test scores (for an up-to-date summary see Deary, Cox, & Hill, 2021). More recently, multiple large-scale GWAS of SVD have been carried out, identifying genetic loci associated with radiological markers of SVD (Fornage et al., 2011; Hofer et al., 2015; Malik et al., 2018; Sargurupremraj et al., 2020; Traylor et al., 2016; Verhaaren et al., 2015). Interestingly, there is some evidence that these partly genetically-influenced traits of cognitive ability and SVD burden have some shared aetiologies. In a recent examination of GWAS data from 23 population-based studies from the CHARGE consortium (approximate n=48,000), a negative genetic correlation was observed between WMH volume and general cognitive ability (*rg* = -0.111; Sargurupremraj et al., 2020). Previously, genetic contributions to individual differences in cognitive ageing have been examined, but only in small sample sizes due to limited availability of long-term follow up data (Davies et al., 2014). As sample sizes of genetic consortia and large longitudinal studies such as the UK Biobank continue to grow, it might be possible to perform larger GWAS of cognitive change, in addition to GWAS of change in SVD biomarkers such as WMH, and samples permitting, potentially examine the genetic correlation between the two.

7.7 Final Summary

This thesis sought to gain a better understanding of the cognitive impairments associated with sporadic SVD. Taken together, the results of the systematic review and meta-analysis and the two empirical studies presented herein indicate that SVD associates with impairments in several major domains of cognitive ability. This appears to be the case for cohorts with non-clinical presentations of SVD, cohorts with SVD-related stroke, and cohorts with SVD-related cognitive impairment or dementia. Contrary to the popular perception that SVD promotes selective deficits in processing speed and executive function, the results of this thesis suggest that any apparent domain-specific cognitive impairments may be due to SVD's overarching association with declining general cognitive ability. These findings have implications for cognitive assessment in SVD, both in research and in clinical settings; in order to assess the full extent of SVD-related cognitive deficits, as many as is feasible of the major domains of cognitive ability should be tested.

Although SVD represents a common mechanistic pathway between stroke and dementia, the findings of this thesis have highlighted certain disconnections between the practices of stroke and dementia research. The clinical presentation of SVD cohorts appears to influence the cognitive domains that are assessed in research settings, and vascular risk factors are less frequently reported for study cohorts with SVD-related cognitive impairment or dementia. Likewise, patients presenting to stroke clinics or in community-dwelling cohorts are less likely to have a comprehensive assessment of diverse cognitive domains resulting in a perception that SVD affects processing speed and executive function primarily. Through a more complete exploration of the risk factors, brain changes, and cognitive consequences that are shared between stroke and dementia, more accurate characterisation of SVD subtypes and their precipitating factors might be possible.

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Appendix A: Published version of work presented in Chapter 4

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THEORETICAL ARTICLE

Cognitive impairment in sporadic cerebral small vessel disease: A systematic review and meta-analysis

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Abstract

This paper is a proposal for an update on the characterization of cognitive impairments associated with sporadic cerebral small vessel disease (SVD). We pose a series of questions about the nature of SVD-related cognitive impairments and provide answers based on a comprehensive review and meta-analysis of published data from 69 studies. Although SVD is thought primarily to affect executive function and processing speed, we hypothesize that SVD affects all major domains of cognitive ability. We also identify low levels of education as a potentially modifiable risk factor for SVD-related cognitive impairment. Therefore, we propose the use of comprehensive cognitive assessments and the measurement of educational level both in clinics and research settings, and suggest several recommendations for future research.

KEYWORDS
cerebral small vessel disease, cognitive ability, lacunar stroke, meta-analysis, systematic review, vascular cognitive impairment, vascular dementia

1 | CONTEXT FOR THE "HYPOTHESIS"

The term small vessel disease (SVD) refers to a collection of neuroimaging and neuropathological abnormalities found in the brain's white and deep gray matter. Visible radiological markers of the disease include white matter hyperintensities (WMH) and lacunes of presumed vascular origin, cerebral microbleeds, visible perivascular spaces, and cerebral microinfarcts. These markers likely reflect multiple pathological changes affecting the brain's small vessels, such as endothelial dysfunction, impaired cerebral blood flow, and reduced vessel pulsatility, although the relationships among these mechanisms are complex and not yet fully understood.[1,2] SVD is the primary cause of vascular cognitive impairment (VCI) in older age. The meaning of the term VCI has been refocused several times in recent years,[3-5] but broadly refers to cognitive impairments due to underlying vascular contributions, which can range in severity from subtle subclinical decline in cognitive ability, to mild cognitive impairment (MCI) and dementia.[7,8] In this review, we use the term "impairment" to denote any reduction in cognitive ability relative to an individual's typical ability, as opposed to a normative standard, or a diagnostic construct, unless otherwise stated.

1.1 | Why is SVD-related cognitive impairment important?

As life expectancies across the world continue to rise, so too does the predicted global burden of age-related cognitive impairment, including VCI. In all societies, the economic impact of cognitive impairment

is tremendous. Individuals with cognitive impairment use more healthcare services and require greater support with activities of daily living, either from unpaid family carers, or from paid care services.[9,10] In 2002, a review of the costs associated with VCI in Canada estimated the average annual cost per individual to be between CAD $15,022 (USD equivalent $9,313) for mild VCI, and CAD $34,515 (USD equivalent $21,399) for severe VCI.[10] Equally as striking is the personal impact upon individuals experiencing cognitive impairment, who are at greater risk of anxiety and depression and report having a lower quality of life.[11,12] A reduction in the incidence or progression of cognitive impairment, therefore, is a key target for clinical trials of treatments or interventions for SVD. Any intervention that improves cognitive outcomes in SVD has the potential to alleviate the burdens it places on individuals and on our societies, and would be a step toward reducing rates of VCI and multiple major dementias.

RESEARCH IN CONTEXT

1. Systematic review: We conducted systematic searches of MEDLINE, Embase, and PsycINFO. Identified literature contradicts current consensus statements on small vessel disease (SVD)–related cognitive impairments, which describe impaired information processing speed and executive functions, alongside preserved memory and language skills. Also, little is known about whether cognitive impairments vary between clinical presentations of SVD.
2. Interpretation: SVD-related cognitive impairments are global, affecting all cognitive domains examined. Global impairments were present regardless of SVD presentation (eg, stroke, mild cognitive impairment/dementia, or non-clinical cohorts). Our findings also highlight low levels of education as a potentially modifiable risk factor for SVD-related cognitive impairments.
3. Future directions: Future studies should test a broad range of cognitive domains, account for educational experience, and include multiple presentations of SVD, to examine vascular contributions to cognitive impairments and dementia.

1.2 | What kind of cognitive impairments are associated with SVD?

To accurately assess cognitive ability in SVD and how it might change in response to intervention, researchers must use cognitive tests that are sensitive to the cognitive impairments caused by SVD. However, despite a huge number of studies on the subject, the nature of cognitive impairments in SVD remains poorly characterized. Current consensus statements suggest that the disease primarily affects the domains of processing speed and executive function, but that memory and language abilities remain relatively well preserved.[13,14] Processing speed refers to the speed at which a person can understand and respond to information.[15] Executive function is a broader concept encompassing skills such as planning, organization, and switching attention, which enable goal-directed behaviors.[15] This profile of SVD-related cognitive impairments is frequently reported in the research literature, but the studies underpinning this suggestion are conflicting and require careful consideration. First, many of the studies examining SVD-related cognitive impairments have small participant samples, so could be insufficiently powered to detect cognitive deficits. Second, many of these studies focus on narrowly defined subtypes of SVD (ie, genetic SVDs), or on those with a high disease burden who may not represent the full spectrum of sporadic SVDs. We also anticipate that some studies may be influenced by expectations of the cognitive impairments they will observe. Based on the understanding that SVD causes deficits in executive function and processing speed, studies might carry out tests that measure only those abilities and neglect to test for impairments in other abilities such as memory, which are more typically associated with dementia.

To gain an unbiased overview of the nature of cognitive impairments associated with SVD, we carried out a systematic review and meta-analysis of studies reporting cognitive data for cohorts with clinical or radiological evidence of SVD, and control cohorts without SVD (see Figure 1; full details of the Methods and Results are provided in Section 2). As expected, the sample sizes of the SVD cohorts were small, ranging between 4 and 196 participants (median: 27). Four studies conducted power calculations,[52,57,71,85] but only one of these studies included a sample size sufficient to detect differences in cognitive performance between groups, according to their own calculations.[57] We carried out seven separate meta-analyses to examine differences in performance between SVD and control groups in seven cognitive domains: executive function, delayed memory, processing speed, language, visuospatial ability, reasoning, and attention. The results of our meta-analyses suggested that individuals with SVD performed more poorly than controls on cognitive tests in each cognitive domain that we examined. Our findings concur with those of a recent meta-analysis of 27 studies by Vasquez and Zakzanis,[16] which compared the cognitive abilities of participants with vascular cognitive impairment without dementia and control subjects, finding deficits in a similarly broad range of domains. Contrary to current consensus, our results suggest that the cognitive impairments associated with SVD extend beyond executive function and processing speed, to affect all major domains of cognitive ability.

Typically, multiple cognitive abilities are recruited to carry out an individual cognitive task. For example, a list learning task is broadly considered to be a test of memory, but performance of the task will also require language abilities to comprehend the words on the list, processing speed to process the verbal information, and so on. Therefore, deficits in a number of cognitive domains could result in poor performance on this memory task. Many cognitive tasks appear to require speed of information processing for efficient performance, and tests of processing speed are among those most affected by aging. As a

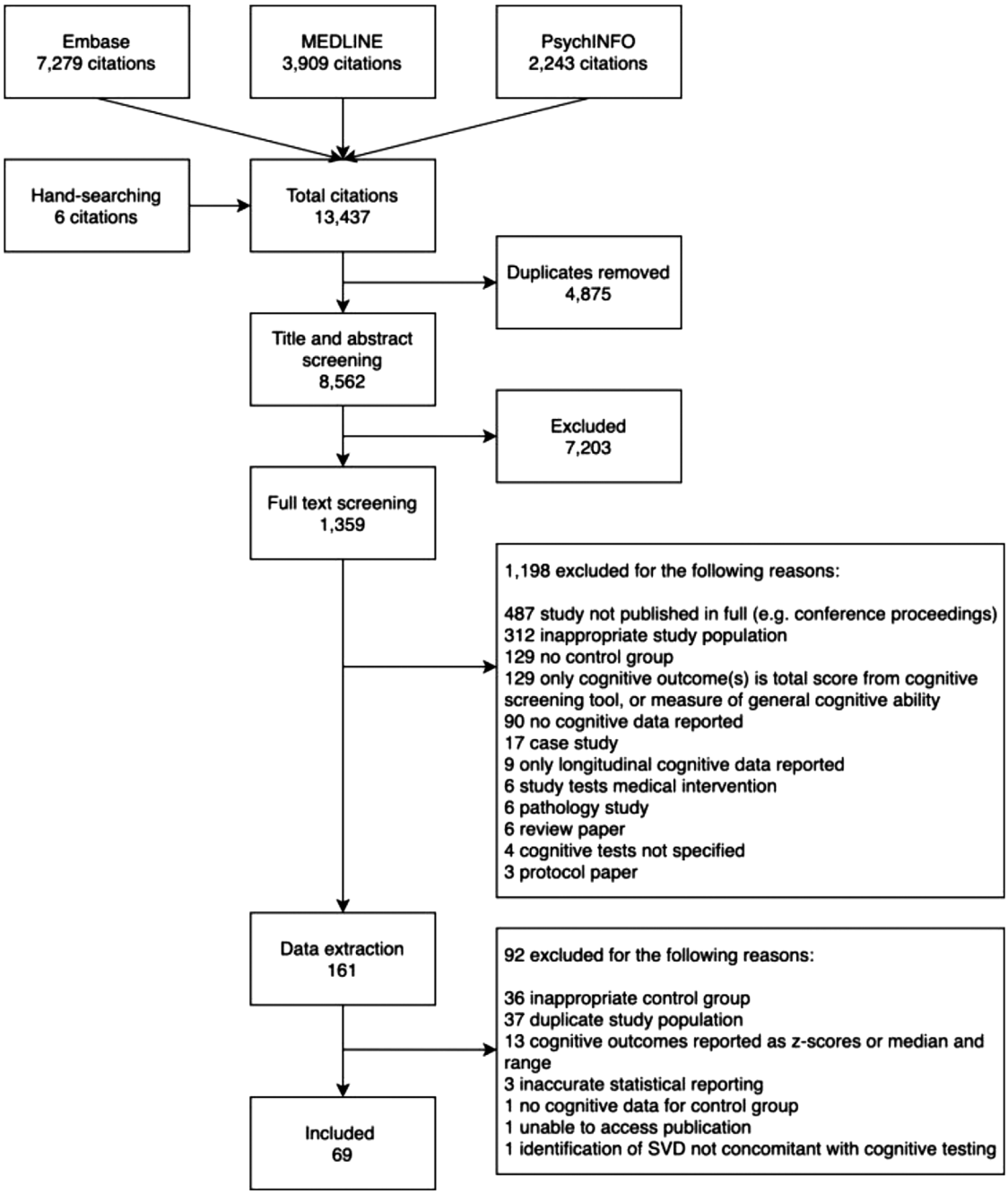

FIGURE 1 Flow diagram of systematic review screening process

result, it has been suggested that processing speed drives age-related changes in other fluid cognitive abilities.[17] Moreover, processing speed has been found to mediate, statistically, the association between brain white matter health and general cognitive ability in older people.[18] However, there is currently a more agnostic attitude to the place of processing speed; there is not considered to be definitive evidence about whether processing is the driver of age-related declines in other cognitive abilities, or whether it is just another domain of cognitive ability that declines on average with age.[19,20] Whereas the results of our meta-analyses suggest that relative to controls, cohorts with SVD have deficits in all major domains of cognitive ability, it remains to be examined whether these deficits could be the result of the early impairment of certain key domains of cognitive ability, or could be the result of impairment across multiple domains of cognitive ability more generally.

Growing evidence suggests that SVD-related cognitive impairments result from the disruption of white matter tract networks connecting regions of the brain that are critical for cognitive function.[21,22] Several cohort studies have suggested that the dysexecutive/slowed information processing profile typically associated with SVD could arise from strategic lesions that disrupt frontal-subcortical white matter projections, such as the anterior thalamic radiation and the forceps

minor.[23–26] However, visible infarcts represent only a proportion of the structural changes occurring in SVD. Microstructural alterations in WMH extend beyond the visible lesion, into the surrounding, normal-appearing peri-lesional tissue known as the "SVD penumbra".[27] Similarly, the impact of visible lesions can extend beyond local tissue, to affect distant brain regions.[28] Therefore, SVD-related structural brain changes are diffuse and likely affect white matter networks throughout the whole brain.[22,29] One analytic approach that has provided insight into the impact of SVD on the structural connectivity of the brain is the application of graph theoretic approaches to diffusion tensor imaging (DTI) tractography data. Whereas several studies adopting this approach have found reduced connectivity and efficiency of both local and global white matter networks, associations between these changes and impairments in specific cognitive domains remain unclear.[22]

1.3 | Do cognitive impairments vary according to the clinical presentation of SVD?

In the majority of cases, SVD manifests sub-clinically with few overt symptoms. However, SVD also contributes to, and in some cases is the primary cause of, a spectrum of disorders ranging from stroke, to MCI, and multiple major dementias. SVD causes ≈20% of all strokes, increases the risk of recurrent ischemic stroke, and associates with poorer functional outcomes post-stroke.[30,31] SVD also contributes to ≈40% of all dementias and increases the odds of developing incident dementia.[32,33] Whereas stroke and dementia are often considered separately, they convey mutual risk to one another. For example, stroke doubles the chance of developing dementia,[34] and poor cognitive performance increases the risk of stroke.[35] Additionally, increasing evidence supports the hypothesis that stroke and dementia share underlying mechanisms.[36,37] For example, dysfunction of the blood–brain barrier (BBB) has been identified as one of the earliest detectable mechanistic changes in the preclinical stages of dementia, occurring prior to the development and accumulation of typical Alzheimer's disease (AD) biomarkers such as amyloid beta (Aβ) and phosphorylated tau.[38] Arterial stiffness, another pathological hallmark of SVD, has also been associated with the deposition of Aβ and its accumulation over time.[39] Vascular pathologies are now considered to contribute substantially to the cognitive deficits observed in most major forms of dementia, including AD. In a recent study examining carriers of the E4 variant of apolipoprotein E (*APOE4*), the primary susceptibility gene for AD, BBB breakdown in the hippocampus and parahippocampal gyrus was associated with poorer cognitive ability independently of Aβ or tau accumulation.[40] Whereas these findings have yet to be replicated, they suggest that this gene variant might contribute to AD and its resultant cognitive decline through BBB dysfunction, rather than solely through more traditional AD biomarkers. In 2017 the World Health Organization highlighted the prevention of stroke via the management of traditional vascular risk factors (eg, smoking, high blood pressure, high cholesterol, diabetes) as a means of preventing dementia.[6] However, despite increasing recognition of cerebrovascular contributions to neurodegenerative disease processes,[41] little is known about how cognitive impairments might differ across different SVD presentations. Patients who experience stroke and dementia have differing routes into clinical care, are treated by different specialists, and are recruited into different research studies, often preventing direct comparison of their cognitive symptoms.

We categorized the SVD cohorts in our sample into three groups based on the clinical characterizations and recruitment settings detailed in the original publications. These three groups included: (1) non-clinical SVD cohorts (cohorts who exhibited radiological evidence of SVD, but had no specific clinical or cognitive symptomatology); (2) cohorts who presented with stroke; and (3) cohorts with subjective or objective cognitive impairments, or dementia (further detail on cohort categorization is provided in Section 2). To some extent, our three SVD presentation categories may represent a continuum; individuals with radiological evidence of SVD but no overt clinical symptoms may go on to experience stroke and/or dementia. Additionally, owing to the inter-related nature of stroke and dementia, it is possible that cohorts in these three categories exhibit both vascular and neurodegenerative pathologies. As expected, tests of processing speed, executive function, attention, and reasoning were most frequently carried out in cohorts with stroke and tests of delayed memory, visuospatial ability and language were most commonly carried out in cohorts with cognitive impairments (see File S1 in supporting information).

The results of meta-regression models investigating differences in cognitive performance of the three SVD presentation groups (relative to controls) indicated differences in the magnitude of cognitive effect sizes among the three groups, such that cohorts with cognitive impairment/dementia performed worse than non-clinical cohorts on tests of executive function, delayed memory, and visuospatial ability, and worse than stroke cohorts on tests of delayed memory only. It is possible that the inclusion of samples with cognitive impairments (including MCI and dementia) could be driving the findings that SVD cohorts overall performed more poorly on tests of memory than control cohorts. However, visual inspection of a forest plot for memory (Figure 2) suggests that this is unlikely to be the case as almost all cohorts in each presentation group show deficits relative to control cohorts.

1.4 | How do risk factors for SVD affect cognitive impairment?

Age is the primary risk factor for the development and progression of SVD. The prevalence of magnetic resonance imaging (MRI) markers of SVD increase with age and are found in the majority of individuals over the age of 60. In contrast, it is unclear whether biological sex may act as a risk factor for SVD,[42,43] although the under-recruitment of women in stroke research may limit knowledge,[44] and the lack of sex-disaggregated reporting limits the scope of meta-analyses on this topic. Owing to their potential for modification, traditional vascular risk factors (VRFs) such as hypertension, diabetes, and hypercholesterolemia have received a great deal of attention, alongside lifestyle factors such as smoking, lack of exercise, poor diet, and high salt intake.

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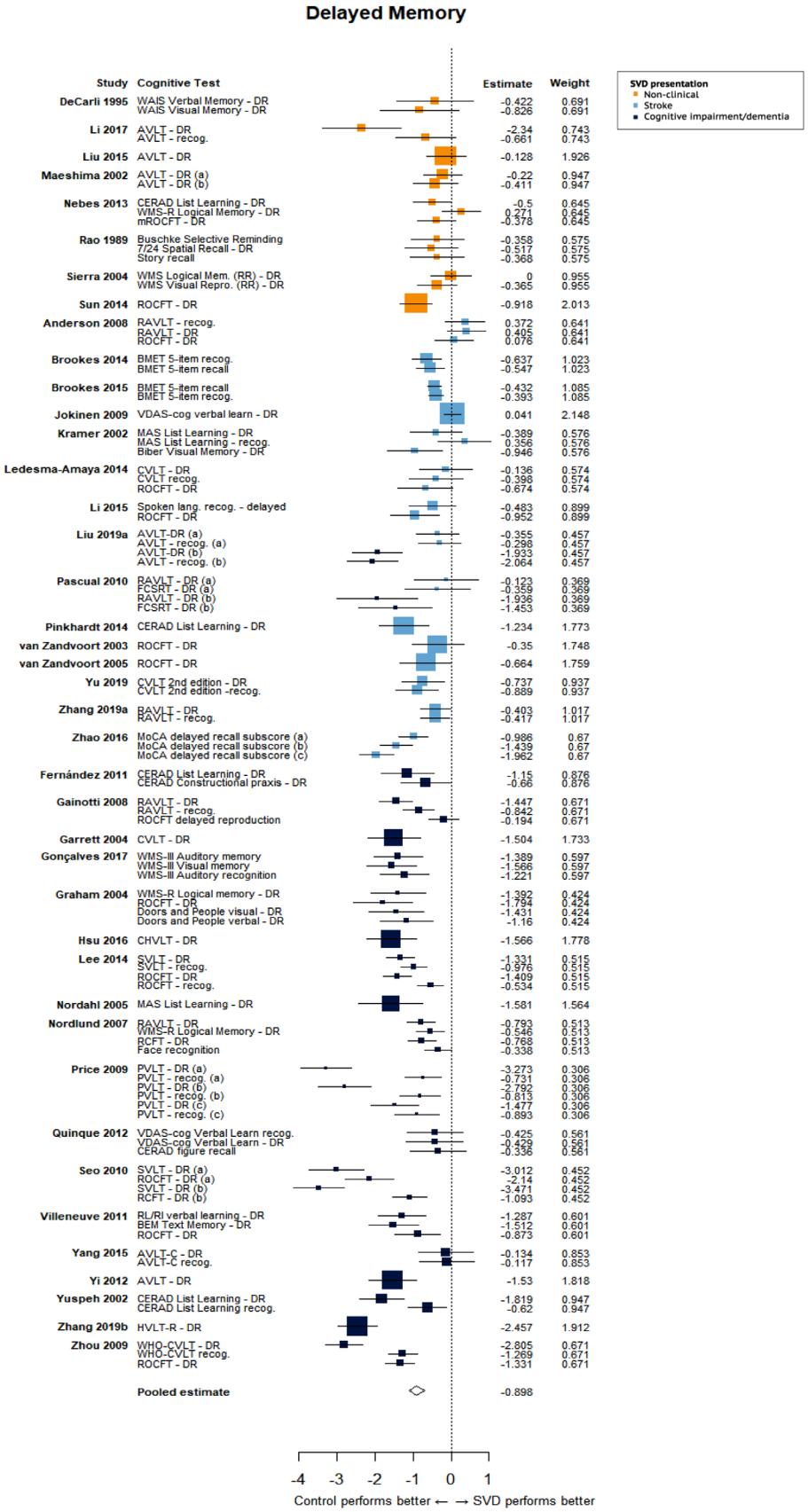

FIGURE 2 Forest plot of meta-analysis of tests of delayed memory. The effect size metric is a standardized mean difference. The sizes of the squares reflect the weight given to each effect size. Letters in brackets indicate different SVD cohorts in a given study

Each has been associated with increased SVD risk, but trials of risk-lowering interventions have produced mixed results.[1] Additionally, a recent meta-analysis of early life risk factors for SVD found lower childhood socioeconomic status, lower childhood IQ, and fewer years of education to be associated with increased radiological burden of SVD,[45] although these risk factors are related to one another and may convey interdependent effects.

Due to their associations with an increased brain burden of SVD, each of these risk factors has the potential to impact cognitive ability. Therefore, it is important that these factors are accounted for statistically (where appropriate) and considered carefully when interpreting study results. Of the studies included in our meta-analysis, almost all reported data on the age, sex, and education of study cohorts, however, reporting of vascular risk data was less complete (see File S2 in supporting information). Approximately half of all studies reported history of hypertension or diabetes, and only one third of studies reported smoking status, despite its known association with SVD progression. Vascular risk data were least often reported for cohorts with a cognitive presentation of SVD, which could suggest that these factors are percieved as being less relevant to cohorts with MCI or dementia.

We carried out further meta-regression analyses to investigate whether differences in age, education, or the prevalence of hypertension or diabetes between SVD and control cohorts accounted for the cognitive effects we observed in our meta-analyses. The results of these analyses suggest that differences in years of education between SVD and control groups account for a proportion of the differences in cognitive test scores in the domains of memory, executive function, and visuospatial ability. All other cognitive domains showed a similar direction of effect (albeit non-significant) except processing speed, which could support the suggestion that processing speed might be less amenable to beneficial effects of education than other cognitive abilities.[46] These findings highlight education as a (potentially modifiable) risk factor for SVD-related cognitive impairment, emphasizing the importance of accounting for education in analyses of cognitive change over time, or comparisons of cognitive ability between groups. An additional factor for consideration that is closely related to educational level is peak (or premorbid) cognitive ability. In any analysis of cognitive decline, observed levels of cognitive ability will be relative to an individual's prior abilities.[47] Despite this, peak cognitive ability is seldom considered in clinical studies. Of the 69 studies included in our meta-analysis, only seven[52,56,57,64,66,92] estimated peak ability and only two of these studies included this score as a covariate in their analyses.[56,92]

1.5 | Summary of findings and recommendations for future work

Based on 3229 individuals with SVD and 3679 control participants from 69 studies, our meta-analyses demonstrated that SVD-related cognitive impairments affect all major domains of cognitive ability. To accurately assess the full extent of SVD-related cognitive impairments, we recommend the use of comprehensive test batteries that cover a range of cognitive domains, such as that proposed by the National Institute for Neurological Disorders and Stroke (NINDS) and the Canadian Stroke Network (CSN[48]). This test protocol is designed for use with participants with VCI and assesses a broad range of cognitive abilities. The full-length protocol takes 60 minutes to administer, but can be shortened to 30 or 5 minutes, while still capturing information from a fairly broad range of cognitive abilities. Widespread use of a standard cognitive testing protocol will also facilitate more accurate cross-comparison or meta-analysis of cognitive data from different studies.

The majority of studies in our meta-analysis had small sample sizes, and very few studies carried out power calculations. To make inferences about cognitive impairments in SVD, it is of vital importance that studies are adequately powered to detect cognitive effects. This meta-analysis summarizes 69 publications on a broad range of SVD presentations—references 52 to 120 provide a useful database of effect sizes, which can be consulted and used to estimate power calculations in future studies.

The results of our first meta-regression analysis suggested that cohorts with a cognitive presentation of SVD performed more poorly than cohorts with non-clinical presentations of the disease on tests of delayed memory, executive function, and visuospatial ability, and more poorly than cohorts with stroke presentations on tests of delayed memory. Our grouping of cohorts into their respective SVD presentation categories was based on cohort descriptions, recruitment settings, and diagnostic criteria, all of which varied considerably between studies. A more effective approach to characterizing SVD subtypes would be to recruit subjects with differing presentations of SVD into the same study, which would facilitate comparison of cognitive and other clinical outcomes.

As we have described, vascular disease and neurodegeneration are interrelated. Where possible, data should be collected that is relevant to both vascular and neurodegenerative disease processes. In terms of cognitive data, this would mean collecting data from a broad range of cognitive domains, as previously recommended. In terms of neuroradiological data, this would mean considering radiological markers of SVD (WMH, enlarged perivascular spaces, lacunes, microbleeds, microinfarcts, altered diffusion tensor imaging metrics), and those more commonly associated with neurodegeneration such as cerebral atrophy and hippocampal volume. The collection of vascular risk data is also important. History of hypertension, diabetes, and smoking status are quick to ascertain and should be collected for all individuals with suspected SVD in clinical and research settings. The collection of vascular biomarkers at different stages throughout the development of dementia may also provide an indication of the changing contributions of vascular dysfunction to neurodegenerative disease processes over time. Through a more complete exploration of the risk factors, brain changes, and cognitive consequences that are shared between stroke and dementia, more accurate characterization of SVD subtypes and their precipitating factors might be possible.

Finally, the results of our second set of meta-regression analyses indicated that level of education is associated with the severity of SVD-related cognitive impairments. We strongly recommend that future studies account for educational level or peak cognitive ability when

examining cognitive change over time, or comparing cognitive ability between groups. A range of methods can be used to estimate peak cognitive ability, some of which are free and have been validated in multiple languages.[49]

2 | APPENDIX

2.1 | Methods

We performed this systematic review and meta-analysis in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. The review protocol is registered on the PROSPERO database (ID: CRD42017080215).

2.1.1 | Search strategy and study selection criteria

We developed and tested a detailed search strategy (see File S3 in supporting information) to identify studies reporting the results of cognitive testing in a cohort with SVD (performed contemporaneous with identification of SVD), and a control cohort with no history of neurological or psychiatric conditions. We searched OVID MEDLINE, Embase, and PsycINFO, for human studies published in any language from January 1, 1985, when MRI became more widely available in clinical practice, to October 6, 2019. To identify additional studies, we checked the reference lists of relevant review articles and hand-searched the previous 7 years of *Stroke* and the *Journal of Cerebral Blood Flow and Metabolism*. Study inclusion and exclusion criteria are presented in File S4 in supporting information.

2.1.2 | Data extraction

Two authors (OH and EB) independently extracted key information, which included group-level demographic data for the SVD and control groups (age, sex, education), group-level data on vascular risk factors (% cohorts with hypertension, diabetes, hypercholesterolemia, and smoking status), group-level data on WMH burden, and group-level cognitive test scores for SVD and control groups. The vast majority of cognitive data were presented as mean and standard deviation. To avoid introducing additional heterogeneity into the meta-analysis dataset, we did not convert cognitive data presented as median and range to mean and standard deviation—instead these data are summarized in File S5 in supporting information. Where individual participant data were presented, we calculated the mean and standard deviation of the variables we extracted. Cognitive data were then categorized into seven domains of cognitive ability: information processing speed, executive function, delayed memory, attention, reasoning, visuospatial ability, and language. However, it is important to note that subdomains of cognitive ability are not discrete, and that individual cognitive tests often engage abilities from multiple cognitive domains. To ensure that tests were reliably categorized according to the cognitive domain that they are considered to primarily assess, two authors experienced in neuropsychological testing (OH and AJ) independently categorized cognitive data into the seven domains listed above and resolved disagreements by consensus (see File S6 in supporting information for further information). Studies reported a wide range of memory tests, including tests of long-term, short-term, and working memory. To reduce heterogeneity in the dataset, we included only tasks featuring a delayed recall/recognition component, as these were the most frequently reported memory tasks. We excluded data for which we could not identify the specific test score (eg, where authors reported results for a Trail Making task, but did not specify whether the score was for Trail Making A, Trail Making B, or Trail Making A-B). We also excluded data for which we could not discern whether a higher or lower score indicated better performance. Where studies reported multiple scores for one cognitive test (eg, for the Wisconsin Card Sorting Test: number of perseverative errors, total number of errors, number of categories, etc.), we included the score most commonly reported in the meta-analysis dataset. Due to the large number of included studies and the large number of variables used in our analyses (ie, sociodemographic, cognitive, and vascular risk variables), we did not contact the authors of original publications to obtain missing data.

2.1.3 | Statistical analysis

We calculated a standardized mean difference (SMD) to represent the difference between performance of the SVD and control cohorts on each cognitive test. We multiplied the SMD by −1 for tests on which a lower score indicated better performance. We excluded three studies due to reporting of implausibly large effect sizes, which upon examination appeared to be due to statistical or reporting errors in the original publications. While several larger effect sizes (SMD > 3) remain in our meta-analyses, these effect sizes come from small study samples so are unlikely to affect results if omitted.

2.1.4 | Meta-analysis models

We ran seven separate random effects meta-analyses to assess the differences in performance between SVD and control groups on cognitive tests in each cognitive domain. We conducted all meta-analyses using the robumeta package[50] in R version 3.6.1.[51] robumeta permits the meta-analysis of multiple effect sizes from one study using robust variance estimation (RVE) to account for their statistical dependency. This approach maximizes the amount of data included from a single study, increasing the statistical power of each meta-analysis. Dependency in our dataset arose from the inclusion of multiple effect sizes from the same study sample, and the inclusion of studies that used the same control group as a comparison for multiple SVD groups. Covariance matrices for multiple outcomes arising from a single study are rarely published; therefore, robumeta imputes a user-specified value

for the within-study effect size correlation. We were conservative in our choice of within-study effect size correlation—we specified rho as 0.8 and carried out sensitivity analyses in robumeta, which impute rho values at increments of 0.1 to test whether this alters the model results. For all analyses, we weighted effect sizes according to a correlated effects dependence structure within the robumeta package and used small sample size corrections. Small sample corrections, which correct both the residuals and degrees of freedom (df) used in the RVE, increase the accuracy of models including <40 studies.[50] After correction, if the Satterthwaite df for the model are less than four, the *P* value is considered unreliable due to the probability of type I error being greater than 0.05. In our analyses, results of models with Satterthwaite df < 4 were considered unreliable. We report I^2 and τ^2 as measures of heterogeneity.

2.1.5 | Meta-regression models

We carried out two secondary analyses to examine the following study-level and cohort-level variables:

1 SVD presentation

To test whether the pooled study effect size differed according to SVD presentation, we grouped each SVD cohort into one of three categories according to the characterization of the cohort and recruitment setting detailed in the original publication (see File S7 in supporting information).

a) Stroke presentations

Cohorts in this category most commonly presented to stroke or neurology services with symptoms of lacunar syndrome, with or without evidence of corresponding vascular lesions. Other cohorts in this category had radiologically identified SVD, or subcortical ischemic vascular disease.

b) Cognitive presentations

Cohorts in this category were identified on the basis of impaired cognitive ability ranging from MCI to vascular dementia. Typically, cohorts presented with cognitive impairment (according to clinical diagnosis, objective cognitive testing, or subjective concern) and either radiological evidence supporting a vascular etiology, or multiple risk factors for cerebrovascular disease.

c) Non-clinical presentations

Non-clinical cohorts had radiological evidence of SVD (WMH or lacunes of presumed vascular origin), but no clinical diagnosis. Typically, cohorts were community-dwelling older individuals recruited within a defined geographical region, or via community advertising. Several cohorts in this category presented to clinical services with non-specific symptoms such as dizziness or headache, but received no diagnosis upon examination.

We then entered SVD presentation as an ordinal predictor in the meta-regression model for each cognitive domain, with the cognitive presentation category as the reference group.

2 Differences in the prevalence of vascular risk between the SVD and control cohorts

All extracted cognitive data were unadjusted for demographic or vascular risk factors. Therefore, to test whether differences in age, education, hypertension, or diabetes between SVD and control cohorts accounted for study effect sizes, we calculated the difference in age, years of education, % sample with hypertension, and % sample with diabetes (eg, difference in age = mean age of control cohort – mean age of SVD cohort), and entered these variables as predictors in separate univariate meta-regression models for each cognitive domain.

2.1.6 | Quality assessment

Quality assessment criteria (see File S8 in supporting information) were devised according to STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines. Two authors (OH and EJ) independently assessed the quality of included publications on a scale ranging from 0 to 8 and resolved disagreements by consensus. To assess whether the inclusion of lower quality studies affected the results of the meta-analyses, we re-ran meta-analysis models excluding studies with quality scores lower than the median quality score of the meta-analysis sample.

2.2 | Results

We identified 69 studies for inclusion in the review[52-120] (see Table 1)), which reported data for 89 cohorts with SVD (n = 3229), and 71 control cohorts (n = 3679; demographic data for the SVD and control cohorts are presented in Table 2). We did not pre-select literature that focused on a certain lesion type, or clinical, cognitive, or behavioral presentation of SVD, therefore, our dataset included SVD cohorts recruited from specialized cerebrovascular clinics; memory clinics; hospital-based stroke, dementia, and general neurology services; non-specialist medical centers; a stroke research network; and also included several research cohorts of healthy community-dwelling individuals. Included studies were from 18 countries in six continents, published in four languages.

2.2.1 | Meta-analyses

The pooled estimated effect size for each meta-analysis demonstrated that on average, control cohorts outperformed SVD cohorts on cognitive tasks in every domain examined (see Table 3 and forest plots in

TABLE 1 Characteristics of all included studies

Study	SVD cohort described as	SVD n	Control n	SVD age mean (SD)	SVD % female	SVD years of Education mean (SD)	SVD % Hyperte-nsion	SVD % Diabetes	SVD % Ever smoking	Variables on which SVD & Controls are matched (blank cells = no matching, or data unavailable)	SVD Mean WMH/TIV (SD) *Mean Visual rating (SD)*
Anderson[52]	Lacunar syndrome	30	30	68.3 (16.8)	47%	9.7 (2.12)				1, 2	
Atwi, 2018[53]	Fazekas ≥ 2	18	28	72[5]	56%		22%	6%		1, 2, 3	9.2 ml (0.6)
Bella, 2016[54]	VCI-ND	25	20	67.5 (6.7)	60%	7.6 (3.9)	88%		28%	1, 3	
Boone, 1992[55]	1. WMH ≤ 1 cm^2 2. WMH > 1 cm^2 - 10 cm^2 3. Total WMH > 10 cm^2	27 21 6	46[a]	63.6 (9.9) 69.2 (6.8) 72.0 (4.9)		15.0 (1.9) 14.2 (3.1) 12.8 (1.3)				3 3 3	
Brookes, 2014[56]	SVD	45	80	69.7 (8.2)	44%	Highest formal qualification: None: 51% Secondary: 11% Further education.: 27% Degree: 9% Higher degree: 0% Unavailable: 2%	84%	21%	69%	1, 2	Modified Fazekas n (%): Fazekas 0: 6 (13%) Fazekas 1: 12 (27%) Fazekas 2: 12 (27%) Fazekas 3: 12[27] Unavailable: 3 (6%)
Brookes, 2015[57]	SVD	196	303	63.5 (9.9)	32%	13.7 (3.8)	75%	23%	44%	1, 2, 4	
DeCarli, 1995[58]	WMH volume > 0.5% TIV	5	17	74[14]			0%			1	WMH/TIV 0.80 (0.24)
Deguchi, 2013[59]	Lacunar infarction	76	105	73.4 (8.9)	34%	12.5 (2.3)	68%	30%	13%[a]	1, 2	
Fang, 2013[60]	1. Silent brain infarct 2. Microbleeds 3. Silent brain infarct + microbleeds	46 41 49	91[a]	70.9 (6.4) 70.6 (5.2) 72.1 (5.0)	57% 42% 47%	8.11 (2.3) 8.24 (1.9) 8.20 (2.3)	83% 81% 82%	22% 27% 25%	20% 22% 25%	1, 2, 5 1, 2, 5 1, 2, 5	
Fernández, 2011[61]	MCI with subcortical vascular damage	19	19	72.2 (7.6)	32%	3.6 (3.5)					
Gainotti, 2008[62]	MCI + multiple subcortical infarcts	41	65	71.7 (5.9)	41%	Reporting unclear				1, 3	

(Continues)

TABLE 1 (Continued)

Study	SVD cohort described as	SVD n	Control n	SVD age mean (SD)	SVD % female	SVD years of Education mean (SD)	SVD % Hyperte-nsion	SVD % Diabetes	SVD % Ever smoking	Variables on which SVD & Controls are matched (blank cells = no matching, or data unavailable)	SVD Mean WMH/TIV (SD) *Mean Visual rating (SD)*
Garrett, 2004[63]	VCI-ND	18	25	78.4 (6.4)	44%	13.6 (2.5)					
Gonçalves 2017[64]	Subcortical vascular dementia	16	40	74.94 (5.4)	38%	3.2 (1.8)				1,2	
Graham, 2004[65]	VaD	19	19	71.2 (7.8)	26%	11.6 (3.1)				1, 3	
Hassan, 2010[66]	Symptomatic lacunar infarction	30	12	59.1(9.5)	40%	Able to read and write: 53% Educated to between primary and university level: 46.7%	100%	47%	53%	1	
Hsu, 2016[67]	MCI due to SIVD	20	30	68.5 (10.8)	30%	7.6 (4.17)	40%	25%		1,2,3	*23.9 (9.9) Scheltens*
Ishii, 2007[68]	1. CDR 0, non-strategic CVD 2. CDR 0, strategic CVD 3. CDR 0.5, non-strategic CVD 4. CDR 0.5, strategic CVD	68 38 21 21	234[a]	74.9 (7.9) 73.0 (6.3) 79.1 (6.9) 80.7 (6.5)		8.3 (1.5) 8.4 (2.1) 7.3 (2.2) 7.6 (1.7)	84% 92% 76% 86%	10% 16% 14% 5%			
Jokinen, 2009[69]	SIVD	89	524	73.6 (4.9)	48%	8.8 (4.2)	80%	18%	15%[a]	1, 2	*WMH severity ratings: Mild: 0 Moderate: 10 Severe: 79*
Kim, 2018[70]	Subcortical VCI	61	19	78.7 (6.3)	72%	7.3 (5.1)				1,2,3	
Kramer, 2002[71]	SIVD	12	27	73.7 (6.2)		15.3 (2.6)				1, 3	
Kuriyama, 2018[72]	1. dWMH Fazekas grade 1 2. dWMH Fazekas grade 2 3. dWMH Fazekas grade 3	134 62 16	68[a]	69.3 (5.7) 71.5 (6.3) 73.8 (6.6)	31% 36% 38%	Reporting unclear	47% 57% 81%	12% 15% 6%	16%[b] 7%[b] 13%[b]	2	*PWMH ≥ grade 2 (de Groot classification), n (%):* *4 (3%)* *17 (27%)* *11 (69%)*

(Continues)

TABLE 1 (Continued)

Study	SVD cohort described as	SVD n	Control n	SVD age mean (SD)	SVD % female	SVD years of Education mean (SD)	SVD % Hypertension	SVD % Diabetes	SVD % Ever smoking	Variables on which SVD & Controls are matched (blank cells = no matching, or data unavailable)	SVD Mean WMH/TIV (SD) *Mean Visual rating (SD)*
Ledesma-Amaya, 2014[73]	Lacunar infarction	16	16	63 (9.4)	38%	7.1[4]	13%	8%		1,3	
Lee, 2014[74]	Subcortical vascular mild cognitive impairment	67	75	73.7 (6.7)	61%	9.0 (5.2)	75%	25%		2	34.9 mL (17.8)
Lewine, 1993[75]	1. Men with WMH 2. Women with WMH	4 6	4 6	35.2 (11.8) 43.3 (8.4)	0% 100%					1 1	
Li, 2001[76]	Leukoaraiosis	29	25	64.9 (6.8)		7.5 (6.8)				1, 2, 3	
Li, 2012[77]	Lacunar stroke with ischaemic leukoaraiosis	20	20	65.8 (8.4)	45%	Reporting unclear	60%		60%		
Li, 2015[78]	Symptomatic lacunar infarction	19	23	66 (12.0)	37%	8.5[3]	68%	37%	11%[a]	3	
Li, 2017[79]	Leukoaraiosis	13	13	63[6]	39%	10.3 (3.3)	69%			1, 2, 6	
Liu, 2008[80]	Subcortical small vessel infarction	60	52	73[8]	47%		27%	14%		1, 2, 3	
Liu, 2015[81]	WMH	30	30	78.2 (5.7)		8.4[2]	23%	11%		1, 3	
Liu 2019a[82]	1. Subcortical ischaemic vascular impairment impairment (pre-SVCI) 2. Subcortical ischaemic vascular disease with cognitive	25 29	27 [a]	70.5 (3.5) 70.5 (5.8)	36% 45%	10.6 (2.6) 9.4 (1.7)	56% 59%	40% 37%	20% 24%	1, 2, 3 1, 2, 3	12.6 ml (5.0) 19.8 ml (8.8)
Liu 2019b[83]	1. SVD without cognitive impairment 2. SVD with cognitive impairment	21 20	25 [a]	64.6 (10.9) 66.5 (7.9)	52% 50%	10.5 (3.6) 13.1 (3.8)				1, 2, 3 1, 2, 3	3.2 ml (3.0) 3.4 ml (4.1)

(Continues)

TABLE 1 (Continued)

Study	SVD cohort described as	SVD n	Control n	SVD age mean (SD)	SVD % female	SVD years of Education mean (SD)	SVD % Hyperte-nsion	SVD % Diabetes	SVD % Ever smoking	Variables on which SVD & Controls are matched (blank cells = no matching, or data unavailable)	SVD Mean WMH/TIV (SD) *Mean Visual rating (SD)*
Maeshima, 2002[84]	1. Silent brain infarct 2. pWMH	21 14	63 70	49.4 (5.6) 51.4 (6.6)	62% 57%	12.5 (2.1) 12.4 (2.1)	24% 21%	14% 29%		1, 2, 3 1, 2, 3	
Nebes, 2013[85]	WMH	26	40	75.1 (5.8)	65%	14.5 (2.7)				1, 2, 3	
Nordahl 2005[86]	MCI + severe WMH	11	20	77.6 (3.6)	55%	13.5 (1.5)	82%	27%		1, 3	WMH/TIV 3.9 (1.3)
Nordlund, 2007[87]	Vascular MCI	60	60	67.0 (7.3)	63%	11.2 (3.2)				1, 2, 3	
Oguro, 2000[88]	PWMH	18	9	73.6 (4.2)	61%	9.3 (3.2)			Scale unclear	1, 2, 3	
Pascual, 2010[89]	1. Vascular white matter disease without dementia 2. Vascular white matter disease with dementia	12 12	12 (cog-nitive data for 10 only)[a]	80.7 (5.2) 79.5 (4.6)	50% 50%					1, 2, 3 1, 2, 3	
Pinkhardt, 2014[90]	Small vessel cerebrovascular disease	25	19	75[58–91]	68%						*Fazekas pWMH 2.36; Fazekas dWMH 2.2 SD not reported*
Price, 2009[91]	Dementia with: mild leukoaraiosis moderate leukoaraiosis severe leukoaraiosis	73 44 27	24 [a]	78.5 (5.7) 81.0 (5.0) 79.4 (4.4)	82% 66% 81%	12.6 (2.8) 12.2 (2.8) 11.9 (2.1)				2, 3	*Junque score* *4.0 (2.8)* *12.0 (2.3)* *22.3 (4.4)*
Quinque, 2012[92]	Early cerebral microangiopathy	11	21	61.4 (6.3)	40%	13.8 (3.0)				1, 2, 3, 4	*8.3 (4.0) ARWMC*
Rao, 1989[93]	Leukoaraiosis	10	40	47.1 (7.8)	90%	14 (1.9)				1, 2, 3	
Schmidt, 1993[94]	WMH	74	76	61.3 (6.6)		11.4 (2.6)	4%			3	

(Continues)

TABLE 1 (Continued)

Study	SVD cohort described as	SVD n	Control n	SVD age mean (SD)	SVD % female	SVD years of Education mean (SD)	SVD % Hypertension	SVD % Diabetes	SVD % Ever smoking	Variables on which SVD & Controls are matched (blank cells = no matching, or data unavailable)	SVD Mean WMH/TIV (SD) *Mean Visual rating (SD)*
Seo, 2010[95]	1. Subcortical vascular MCI 2. Subcortical VaD	34 (cognitive data for between 30-34 only) 20 (cognitive data for between 15-18 only)	96 (cognitive data for 63 only)[a]	70.6 (6.4) 74.2 (6.1)	44% 55%	10.1 (4.8) 7.2 (5.5)	84% 100%	29% 30%		2, 3	
Sierra, 2004[96]	Hypertensive with WMH	23	37	55.2 (4.2)	39%	11.2 (3.7)	100%		22%	1, 2, 3	
Squarzoni, 2017[97]	Silent brain infarct	57	187	72.1 (3.4)	56%		68%	33%		1	
Sudo, 2013[98]	Vascular MCI	15	11	74.1 (8.1)	60%	8.9 (4.0)				1, 2, 3	*Fazekas rating, n (%)* *Fazekas 0: 0 (0%)* *Fazekas 1: 0 (0%)* *Fazekas 2: 7(47%)* *Fazekas 3: 8 (53%)*
Sun, 2014[99]	Mild WMH	51	49	65.3 (7.2)	55%	10.3 (3.4)	16%	10%	8%	1, 2, 3	
Tupler, 1992[100]	dWMH	48	18	69.9 (10.1)	69%	13.9 (4.2)					
van Swieten, 1991[101]	Hypertensive with confluent WMH	10	18	67.8 (5.3)	32%		100%	50%		1, 2	*Normal white matter = 20; focal lesions = 12; confluent lesions = 10*

(Continues)

TABLE 1 (Continued)

Study	SVD cohort described as	SVD n	Control n	SVD age mean (SD)	SVD % female	SVD years of Education mean (SD)	SVD % Hyperte-nsion	SVD % Diabetes	SVD % Ever smoking	Variables on which SVD & Controls are matched (blank cells = no matching, or data unavailable)	SVD Mean WMH/TIV (SD) *Mean Visual rating (SD)*
van Zandvoort, 2003[102]	Lacunar infarct in brainstem	17	17	60.1 (11.6)	29%	<6 years primary school: 0% 6 years of education (YoE): 6% 8 YoE: 0% 9 YoE: 47% 10-11 YoE: 23.5% 12-18 YoE: 23.5% > 18 YoE: 0%				1, 2, 3	
van Zandvoort, 2005[103]	Supratentorial lacunar infarct	26	14	60.5 (12.3)	38%	Scale unclear				1, 3	
Villeneuve, 2011[104]	MCI with confluent WMH	21	27	73.4 (5.1)	48%	12.4 (5.2)				1, 2, 3	*10.0 (3.1) Wahlund*
Wolfe, 1990[105]	Multiple lacunar infarcts	11	11	64.6 (6.0)	No information	10.1 (3.1)				1, 3	
Wong, 2007[106]	Stroke associated with SVD	32	42	72.8 (10.0)	44%	Scale unclear				1, 2, 3	56.9 ml (8.7)
Yamauchi, 2000[107]	Lacunar infarct	28	34	69.3 (6.3)	32%	8.9 (1.3)	21%	11%		1, 3	*Anterior WMH 3.6 (3.1) Posterior 3.6 (2.8) Scale – see publication*
Yang, 2015[108]	Vascular MCI	15	15	61.7 (6.2)	73%	9.3 (2.4)				1, 2, 3	
Yang, 2016[109]	Lacunar infarct	60	30	67.0 (7.0)	42%	7.2 (2.3)	58%	18%	38%[a]	1, 2, 3	
Yi, 2012[110]	Subcortical vascular MCI	26	28	66.7 (9.5)	58%	9.9 (4.4)				1, 2, 3	

(Continues)

TABLE 1 (Continued)

Study	SVD cohort described as	SVD n	Control n	SVD age mean (SD)	SVD % female	SVD years of Education mean (SD)	SVD % Hypertension	SVD % Diabetes	SVD % Ever smoking	Variables on which SVD & Controls are matched (blank cells = no matching, or data unavailable)	SVD Mean WMH/TIV (SD) *Mean Visual rating (SD)*
Yu, 2019[111]	Extensive SIVD	29	25	71.8 (11.0)	52%	14.4 (3.2)	75%	10%	58%	1, 2, 3	DWMH 2.55 (2.5) cm^3 PWMH 29.0 (21.6) cm^3
Yuan, 2012[112]	Leukoaraiosis	46	38	72.0 (6.0)	70%	8[4]	74%	61%		1, 2, 3	
Yuan, 2017[113]	Leukoaraiosis	50	50	71.7 (5.5)	58%	7.5 (4.3)	67%	50%	26%	1, 2, 3	
Yuspeh, 2002[114]	SVaD	29	38	74.1 (8.2)	35%	13.2 (4.4)				1, 2, 3	
Zhang 2019a[115]	SVD	77	39	70[11]	40%	Educational level: Low = 45% Medium = 35% High = 20%	64%	16%	25%	1, 2	WMH/TIV 0.014 (0.002)
Zhang, 2019b[116]	Amnestic MCI with Fazekas > 1	30	90	68.33 (5.3)	47%	12.30 (2.6)				1, 2	
Zhao, 2016[117]	1. Lacunar infarct 2. WMH 3. Lacunar infarct + WMH	62 60 61	55[a]	73.2 (4.7) 71.9 (4.2) 73.9 (3.8)	42% 38% 33%	10.7 (3.2) 10.9 (3.6) 10.5 (3.2)	76% 75% 78%	37% 33% 43%	31%[a] 23%[a] 34%[a]		
Zhou, 2009[118]	MCI due to SVD	56	80	67.3 (6.2)	36%	9.6 (3.1)				2, 3	
Zhou, 2014[119]	1. Subcortical vascular MCI 2. Subcortical vascular disease	79 82	77[a]	72.2 (7.1) 74.1 (7.1)	53% 51%	9.9 (3.3) 7.4 (3.3)	63% 73%	29% 22%	32%[b] 42%[b]	2	
Zi, 2014[120]	pWMH	16	16	62.0 (4.9)	56%	8 (6.3-10.3)	63%	19%	19%[a]	1, 2, 3	

Notes: Data are presented as mean (standard deviation) or median (range), unless otherwise stated. Controls matched for: 1 Age; 2 Sex; 3 Education; 4 Premorbid IQ; 5 Vascular risk factors; 6 history of hypertension. Where cells are blank, no data were available.

Abbreviations: CDR, Clinical Dementia Rating scale; CVD, cerebrovascular disease; dWMH, deep white matter hyperintensities; MCI, mild cognitive impairment; pWMH, periventricular white matter hyperintensities; SIVD, subcortical ischemic vascular disease; SVaD, subcortical ischemic vascular dementia; SVD, cerebral small vessel disease; TIV, total intracranial volume; VaD, vascular dementia; VCI, vascular cognitive impairment; VCI-ND, vascular cognitive impairment–no dementia; WMH, white matter hyperintensities.

[a]Same control group used as comparison for both/all SVD groups.

[b]Current smoker.

TABLE 2 Summary of sociodemographic and vascular risk data for SVD and control cohorts

	SVD cohorts		Control cohorts	
	Cohorts (n = 89)	Mean (SD or 95% CI)	Cohorts (n = 71)	Mean (SD or 95% CI)
Mean age[a]	88	69.3 (67.8, 70.9)	70	66.4 (64.6, 68.2)
% female	76	49.0 (15.9)	63	50.9 (15.0)
Mean years education[a]	67	10.3 (9.7, 10.9)	53	10.8 (10.1, 11.6)
% hypertension	48	66.7 (23.0)	34	37.8 (20.7)
% diabetes	45	25.5 (13.7)	31	17.1 (13.5)
% hypercholesterolemia	5	55.1 (20.0)	4	35.1 (12.3)
% history of smoking	28	28.3 (16.1)	16	25.6 (16.9)

[a]Mean age and mean years of education were calculated using random effects meta-analysis in the meta package in R version 3.6.1.[121] Only studies that presented group-level data for age and years of education as mean and standard deviation were included in these meta-analyses. We did not test for differences in age, sex, level of education, or vascular risk factors between the SVD and control groups as some studies only reported these data for the SVD group, therefore, comparisons would not include all participants contributing cognitive data to the meta-analyses.
Abbreviations: CI, confidence interval; SD, standard deviation; SVD, cerebral small vessel disease.

TABLE 3 Results of meta-analysis models for each cognitive domain

							Heterogeneity	
	Studies	Outcomes	Estimate (SE)	95% CI	Degrees of freedom	Uncorrected p value	τ^2	I^2
Processing speed	37	88	−0.885 (0.14)	−1.17, −0.60	35.8	2.3×10^{-7}	0.6	91.4
Executive function	58	188	−0.936 (0.08)	−1.09, −0.78	56.1	$<2 \times 10^{-16}$	0.4	87.6
Delayed memory	41	98	−0.898 (0.10)	−1.10, −0.69	39.6	7.2×10^{-11}	0.5	88.0
Attention	12	19	−0.622 (0.14)	−0.94, −0.31	10.6	0.001	0.2	80.8
Reasoning	16	25	−0.634 (0.14)	−0.93, −0.34	14.6	4.2×10^{-4}	0.2	76.5
Visuospatial ability	27	50	−0.720 (0.11)	−0.96, −0.48	25.3	1.3×10^{-6}	0.3	77.6
Language	24	42	−0.808 (0.10)	−1.01, −0.60	22.7	3.2×10^{-8}	0.3	81.2

Abbreviations: CI, confidence interval; SE, standard error.

Figure 2 and Figures S1–S6 in supporting information). I^2 values, which are an indicator of inconsistency between effect sizes in the meta-analyses, were high in each model.

2.2.2 | Meta-regression analyses

Our meta-analysis dataset included 26 cohorts with stroke presentations of SVD, 31 cohorts with cognitive impairment or dementia, and 32 cohorts with non-clinical presentations of SVD. There were no differences in years of education, or prevalence of hypertension or diabetes among the three SVD presentation categories, but cohorts with cognitive impairment/dementia were significantly older than those with non-clinical presentations of the disease ($P = .002$; see Table 4).

Meta-regression models investigating differences in cognitive effect sizes of the three SVD presentation groups indicated that the effect size for delayed memory was 0.83 standard deviations greater for the stroke cohorts (95% confidence interval [CI]: 0.44, 1.21; $P < .001$) and 0.85 standard deviations greater for non-clinical cohorts (95% CI: 0.40, 1.29; $P = .001$), than cohorts with cognitive impairment/dementia. We also found that the effect size was 0.49 standard deviations greater in the domain of executive function (95% CI: 0.10, 0.88; $P = .015$), and 0.68 standard deviations greater in the domain of visuospatial ability (95% CI: 0.30, 1.01; $P = .002$) for the non-clinical cohorts than the cohorts with cognitive impairment/dementia (see File S9 in supporting information for full results). Including SVD presentation as a predictor in meta-regression models had little effect on study heterogeneity.

Meta-regression models investigating the impact of differences in age, education, and the prevalence of vascular risk factors between SVD versus control groups on cognitive effect sizes, indicated that the difference in cognitive performance between SVD and control groups could be due to lower levels of education in SVD cohorts (see File S10 in supporting information for full results). For every 1 year of difference in education between SVD and control groups, the cognitive effect size decreased (indicating superior performance of the control groups) by an estimated 0.23 standard deviations in the domain of executive function (95% CI: −0.37, −0.09; $P = .004$), 0.28 standard deviations in the

TABLE 4 Demographics of SVD cohorts with non-clinical presentations of SVD, stroke, or cognitive impairment/dementia

	Non-clinical		Stroke		Cognitive impairment/dementia		
	% cohorts (n = 32)	Mean (SD or 95% CI)	% cohorts (n = 26)	Mean (SD or 95% CI)	% cohorts (n = 31)	Mean (SD or 95% CI)	Uncorrected *P* value[c]
Mean age[a]	100%	66.1 (62.8, 69.4)	96.2%	69.0 (67.0, 71.1)	100%	72.8 (70.9, 74.7)	.002[b]
% female	71.9%	53.2 (20.8)	92.3%	42.0 (8.5)	93.5%	51.6 (14.6)	.027
Mean years education[a]	68.8%	10.6 (9.5, 11.7)	61.5%	10.6 (9.4, 11.8)	93.5%	9.9 (8.8, 10.9)	.515
% hypertension	62.5%	60.3 (28.7)	65.4%	68.6 (17.6)	35.5%	75.1 (16.4)	.214
% diabetes	59.4%	23.4 (16.4)	61.5%	28.6 (12.7)	32.3%	24.4 (9.1)	.524

[a]Mean age and mean years of education were calculated using random effects meta-analysis in the meta: An R package for meta-analysis. R News 2007, 7(3), 40–45.[121] Only studies that presented group-level data for age and years of education as mean and standard deviation were included in these meta-analyses.
[b]Significant difference at $P < .01$ between non-clinical and cognitive impairment/dementia groups.
[c]P value refers to comparisons made by one-way analysis of variance.
Abbreviations: CI, confidence interval; SD, standard deviation; SVD, cerebral small vessel disease.

domain of visuospatial ability (95% CI: −0.46, −0.10; $P = .009$), and 0.31 standard deviations in the domain of language (95% CI: −0.46, −0.16; $P = .001$). Including education as a predictor in meta-regression models reduced I^2 values by ≈13% in the domain of visuospatial ability and language, suggesting that education may account for some of the variability in cognitive effect sizes in these domains. Overall, however, I^2 values remained high. This could be due to our use of group-level demographic and vascular risk data, which may limit power to detect interactions between individual-level covariates and cognitive effect sizes. Meta-analytic approaches using individual patient data are increasingly popular but rely upon the availability of patient-level datasets, which in our sample were rare.

The majority of the meta-regression models assessing the influence of age on cognitive effect size produced df < 4, suggesting that model results were unreliable. Therefore, we further investigated the potential influence of age by re-running meta-analysis models excluding studies in which SVD and control groups were not matched for age. In these analyses magnitudes of estimated effect sizes were similar to the initial meta-analysis models and all models remained significant. Meta-regression models investigating the impact of hypertension and diabetes on cognitive effects also produced df < 4 suggesting that model results were unreliable, likely due to the limited availability of vascular risk data.

2.2.3 | Study quality

The mean study quality score was 4.97 (median 5, range 2–8). The magnitudes of estimated effect sizes were comparable to those using the full meta-analysis dataset, and all models remained significant (see File S11 in supporting information). I^2 values reduced by a small amount in the domains of executive function, visuospatial ability, attention, and language, but increased in the other domains.

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AUTHOR CONTRIBUTIONS

The study was designed by OH and supervised by JMW and IJD. OH conducted the literature search and OH, EB, TR, AS, and CM screened papers for inclusion in the review. OH, EB, XL, and EJ extracted data from eligible papers. OH and AJ categorized cognitive test data into domains. OH analyzed and interpreted the data with contributions from JMW and IJD. OH wrote the first draft of the manuscript; all authors contributed to later versions.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Appendix B: Supplementary files for Chapter 4

Cognitive impairment in sporadic cerebral small vessel disease: a systematic review and meta-analysis

Supplementary Files

Supplementary File 1: Search Strategies used to conduct literature searches
Supplementary File 2: Systematic review inclusion and exclusion criteria
Supplementary File 3: Overview of studies excluded due to metrics of cognitive data
Supplementary File 4: Cognitive tests included in the meta-analysis dataset, organised by domain
Supplementary File 5: SVD cohort descriptions, diagnostic criteria, and inclusion and exclusion criteria of included studies
Supplementary File 6: Criteria used to assess the quality of studies included in the meta-analysis
Supplementary File 7: Results of meta-regression models comparing cognitive effect sizes between SVD presentation categories
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Supplementary Figures

Supplementary Figure S1: Forest plot of meta-analysis of tests of processing speed
Supplementary Figure S2: Forest plot of meta-analysis of tests of executive function
Supplementary Figure S3: Forest plot of meta-analysis of tests of attention
Supplementary Figure S4: Forest plot of meta-analysis of tests of reasoning
Supplementary Figure S5: Forest plot of meta-analysis of tests of visuospatial ability
Supplementary Figure S6: Forest plot of meta-analysis of tests of language

Supplementary File 1: Search Strategies used to conduct literature searches

Database: OVID MEDLINE

1 Cerebral Small Vessel Diseases/
2 (small vessel disease or small-vessel disease or CSVD or SVD).ti,ab.
3 microangiopathy.ti,ab.
4 Stroke, Lacunar/
5 ((lesion* or hyperinten*) adj3 white matter).ti,ab.
6 Leukoaraiosis/
7 (micro bleed* or micro-bleed* or microbleed*).ti,ab.
8 ((perivascular or peri-vascular or peri vascular) adj1 space*).ti,ab.
9 lacune*.ti,ab.
10 ((lacun* or subcort* or ischemi* or ischaemi* or silent or microscopic) adj3 infarct*).ti,ab.
11 ((lacun* or subcort* or ischemi* or ischaemi* or silent or microscopic) adj3 lesion*).ti,ab.
12 (cerebral atrophy or brain atrophy).ti,ab.
13 Cognitive Dysfunction/
14 neuropsychological tests/
15 cognition/ or executive function/ or learning/ or perception/ or thinking/ or memory/
16 ((executive function* or processing speed or memory or learning or visu*-spatial or visu* spatial or attention or intelligence or sensorimotor) adj3 (abilit* or disorder* or difficult* or decline or deficit* or problem* or dysfunction)).ti,ab.
17 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
18 13 or 14 or 15 or 16
19 17 and 18

Database: EMBASE

1 (small vessel disease or small-vessel disease or SVD or CSVD).ti,ab.
2 microangiopathy.ti,ab.
3 lacunar stroke/
4 white matter lesion/
5 (white matter adj3 hyperintens$).ti,ab.
6 leukoaraiosis/
7 (microbleed$ or micro-bleed$ or micro bleed$).ti,ab.
8 (perivascular space$ or peri-vascular space$ or peri vascular space$).ti,ab.
9 lacune*.ti,ab.
10 ((lacun* or subcort* or ischemi* or ischaemi* or silent or microscopic) adj3 infarct*).ti,ab.
11 ((lacun* or subcort* or ischemi* or ischaemi* or silent or microscopic) adj3 lesion*).ti,ab.
12 (cerebral atrophy or brain atrophy).ti,ab.
13 exp neuropsychological test/
14 cognition/ or attention/ or executive function/ or learning/ or memory/ or orientation/ or perception/ or thinking/

15 ((executive function* or processing speed or memory or learning or visu*-spatial or visu* spatial or attention or intelligence or sensorimotor) adj3 (abilit* or disorder* or difficult* or decline or deficit* or problem* or dysfunction)).ti,ab.
16 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
17 13 or 14 or 15
18 16 and 17

Database: PsycINFO

1 cerebral small vessel disease/ or cerebral ischemia/
2 (small vessel disease or small-vessel disease or SVD or CSVD).ti,ab.
3 microangiopathy.ti,ab.
4 lacunar stroke.ti,ab.
5 ((lesion* or hyperintens*) adj3 white matter).ti,ab.
6 leukoaraiosis/
7 (microbleed* or micro-bleed* or micro bleed*).ti,ab.
8 ((perivascular or peri vascular or peri-vascular) adj1 space*).ti,ab.
9 lacune*.ti,ab.
10 ((lacun* or subcort* or ischemi* or ischaemi* or silent or microscopic) adj3 infarct*).ti,ab.
11 ((lacun* or subcort* or ischemi* or ischaemi* or silent or microscopic) adj3 lesion*).ti,ab.
12 (cerebral atrophy or brain atrophy).ti,ab.
13 cognitive ability/ or cognitive impairment/ or cognitive processing speed/ or executive function/ or memory
14 cognitive processes/ or neuropsychology/
15 neuropsychological assessment/ or exp cognitive assessment/
16 ((executive function* or processing speed or memory or learning or visu*-spatial or visu* spatial or attention or intelligence or sensorimotor) adj3 (abilit* or disorder* or difficult* or decline or deficit* or problem* or dysfunction)).ti,ab.
17 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
18 13 or 14 or 15 or 16
19 17 and 18

Supplementary File 2: Systematic review inclusion and exclusion criteria

Study inclusion criteria

- Study cohort has radiological or clinical evidence of SVD (see characterisation of SVD, below)
- Study includes control cohort free from radiological or clinical evidence of SVD, stroke, dementia, or other major neurological or psychiatric conditions
- Study reports group-level results of domain-specific cognitive tests for both the SVD and control cohorts.

Study exclusion criteria

- Study cohorts with genetic SVDs (e.g. CADASIL)
- Study cohorts recruited on the basis of a non-vascular/non-neurodegenerative disease aetiology (e.g. traumatic brain injury)
- Case studies
- Studies not published in full (e.g. conference abstracts)
- Studies reporting cognitive data as an outcome measure following an intervention
- Studies reporting only total scores of cognitive screening tests such as the Mini Mental State Examination (MMSE) or the Montreal Cognitive Assessment (MoCA), or scores representing general cognitive ability.

Characterisation of SVD

We included cohorts with either clinical, or radiological evidence of SVD. We considered clinical evidence of SVD to be a clinical presentation typically associated with underlying SVD, such as lacunar stroke or lacunar stroke syndrome; subcortical ischaemic vascular disease plus radiological evidence of SVD; vascular cognitive impairment-no dementia plus radiological evidence of SVD; or subcortical vascular dementia plus radiological evidence of SVD. Cohorts recruited due to the presence of cortical infarcts, cohorts including patients with haemorrhagic stroke, and cohorts with syndromes of cardio-embolic aetiology were excluded. In the absence of any of the clinical syndromes described above, radiological evidence of SVD was considered and was defined as the presence of WMH, or lacunar infarcts according to STRIVE criteria (Wardlaw, Smith, Biessels, et al., 2013)(Wardlaw, Smith, Biessels, et al., 2013). Studies that provided insufficient information to establish the presence of SVD according to these criteria were excluded.

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Wardlaw JM, Smith EE, Biessels GJ, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *Lancet Neurol*. 2013;12(8):822-838.

Supplementary File 3: Overview of studies excluded due to metrics of cognitive data

Table 3.1: Characteristics studies excluded due to metrics of group-level cognitive data

Study	Cohort described as	SVD n	Control n	Age mean (SD)	Female %	Years of Education, mean (SD)	HTN %	DB %	Ever smoking %	Matched on	WMH/TIV or *Visual rating (italicised)* mean (SD) unless otherwise specified
Baune, 2009 [1]	Lacunar infarction	41	227	73.3 (no SD reported)	34%		61%	15%	10%*	Age, sex	
Dey, 2019 [2]	SVD	23	23	71 (5.5)	52%	16.45 (3.57)	57%	26%	44%	Age, sex, education, number of vascular risk factors	11.267cm^3 (9.232)
Han, 2019 [3]	Fazekas score ≥ 2	21	128	Median 70 (IQR: 65–74)	76%	Median 6 (IQR: 6–12)					Median (IQR) WMH/ICV: 4.065 (2.655–6.463)
Jokinen, 2006 [4]	Subcortical Ischemic vascular disease, but originally had ischemic stroke.	85	38	71.7 (6.9)	50%	8.3 (3.6)					Scale unclear
Kynast, 2018 [5]	1) Fazekas grade 1 2) Fazekas grade 2 3) Fazekas grade 3	372 93 16	368 † †	64.2 (10.5) 69.4 (7.9) 71 (7.7)	50% 52% 30%	% >=10 years n=70 n=58 n=44	60% 84% 87%	13% 16% 20%			
Lange, 2017 [6]	Vascular Dementia	33	18	83.9 (5.5)	55%	14.1 (3.7)				Age, sex, education	Mean (SD): 32.63ml (15.55); range: 13.74–74.37
Margraf, 2009 [7]	Subcortical ischaemic vascular disease + positive findings for cerebral microangiopathy	17	17	median 69 (min 46, max 79)	53%	9 years n=1; 10 years n=1; 12 years n=8; 13 years n=4; >13 years n=3				Age, premorbid IQ, sex	
O'Sullivan, 2004† [8]	Ischaemic leukoaraiosis	36	19	69.5 (8.8)	33%	10.8 (3.6)	11%	83%		Age, sex, education	

Papma, 2013 [9]	MCI with SVD	16	25	74.3 (4.4)	31%	5.6 (1.2) Scale ranging from 1 (less than 6 years elementary school) to 7 (academic degree)	88%		88%	Age, sex, education	Median (IQR) WMH: 30.8ml (23.9; 40.9) Median (IQR) WMH/TIV: 2.8 (2.6; 3.7) *Median (IQR) Fazekas: 2 (2; 2)*
Scherr, 2014 [10]	Subcortical ischaemic vascular disease	58	58	74.5 (11.4)	47%					Age, sex	*Fazekas 0 n=0; Fazekas 1 n=0; Fazekas 2 n=5; Fazekas 3 n=53*
Schroeter, 2007† [11]	Cerebral microangiopathy	12	12	61.2 (4.9)	17%		83%	42%		Age	
Söderlund, 2003† [12]	1) 1st tertile subcortical WMH volume 2) 2nd tertile subcortical WMH volume 3) 3rd tertile subcortical WMH volume	37 37 36	13	66.9 (3.1) 68.4 (3.2) 69.6 (4.0)	50% 57% 50%	9.7 (3.5) 8.1 (2.4) 9.7 (3.5)				Not reported	
Zhu, 2019 [13]	1) WMH without cognitive impairment 2) WMH with MCI	43 23	55 †	65.72 ± 5.94 65.17 ± 6.65	37% 35%	10.28 ± 3.60 9.34 ± 3.89				Age, sex, education Age, sex, education	13.53cm^3 ± 13.97 *4.47 ± 1.18 Fazekas* 18.19cm^3 ± 15.02 *5.13 ± 1.10 Fazekas*

Note: None of these studies presented data from cognitive tests in the domain of reasoning. Data from cognitive tests in the other six domains are presented in tables 3.2 to 3.7 below. MCI mild cognitive impairment; SVD sporadic cerebral small vessel disease; WMH white matter hyperintensities. *current smokers only; † Raw cognitive data for this paper were extracted from graphs using WebPlotDigitizer [14].

Table 3.2: Narrative summary of excluded cognitive data in the domain of processing speed

Study	Cognitive tests reported	Metric	Effect size	Statistical test	Variables adjusted for	Results
Baune, 2009 [1]	Stroop 1 Stroop 2 Letter Digit substitution	Mean (no SD reported)	SVD: 22.5 Control: 19.9 SVD: 30.8 Control: 27.2 SVD: 20.6 Control: 23.3	ANOVA	Age, sex, education	Controls performed significantly better on all tests (p<0.01)
Dey, 2019 [2]	Composite score	Mean (95% CI) of composite score calculated via principal components analysis	SVD: -0.168 (-0.588, 0.252) Control: 0.168 (-0.252, 0.588) Partial eta squared = 0.03	MANCOVA	Age, education	No significant difference between controls and SVD group (p=0.263)
Han, 2019 [3]	TMT A (black and white)	Median and range	SVD: 89.77 (70.69–155.69) Control: 60.91 (42.76–84.77)	Student's t or Mann Whitney U		Controls performed significantly better than SVD group (p=0.001)
Jokinen, 2006 [4]	Composite score	z-score mean (SD)	SVD: -0.15 (0.86) Control: 0.44 (0.32) Partial eta squared=0	ANCOVA	Age, education	Controls performed significantly better than SVD group (p=0.001
Lange, 2017 [6]	CERAD-Plus TMT A	z-score mean (SD)	SVD: −2.41 (2.98) Control: 0.20 ± 0.80	One way ANOVA with Scheffe's or Tamhane's post hoc test	Z-scores adjusted for age, sex and education	Controls performed significantly better than SVD group (p=0.004)
Margraf, 2009 [7]	Zahlenverbindungs-Test (similar to TMT A)	Median and range	SVD: 49 (16.5-220) Control: 23 (14.0-86.5)	Mann Whitney U		Controls performed significantly better than SVD group (p>0.002)
O'Sullivan, 2004 [8]	WAIS-R Digit Symbol	Mean group difference in z-score	Mean difference: 2.861	Student's t test	Motor speed	Control group performed significantly better than SVD group (p=0.007)
Papma, 2013 [9]	Composite score	z-score mean (SD)	SVD: -0.68 (1.07) Control: 0 (0.87)	ANCOVA	Age, sex, education	No significant difference between controls and SVD group (p>0.05)
Scherr, 2014 [10]	CERAD-Plus TMT A	z-score mean (SD)	SVD: -0.88 Control: 1.36	Mann-Whitney U	z-scores adjusted for age, sex, and education	Control group performed significantly better than SVD group (p=0.009)
Schroeter, 2007 [11]	Stroop 3	Mean (SEM)	SVD: 1910.1 (210.7) Control: 1216.3 (78.7)	Student's t test		Control group performed significantly better than SVD group (p=0.01)

Söderlund, 2003 [12]	Letter Digit Substitution	z-score mean (no SD reported)	1st tertile WMH: 0.026 2nd tertile WMH: -0.131 3rd tertile WMH: 0.037 Control: 0.159	ANCOVA	Age	No significant difference between performance of the control and any of the SVD groups.
Zhu, 2019 [13]	Composite score	z-score mean (SD)	WMH no CI: 0.04 (0.82) WMH + MCI: –1.53 (0.95) Control: 0.00 (0.91)	One way ANOVA		Controls performed significantly better than the WMH+MCI group (<0.001), but there was no difference between the control and WMH no CI group

Note: Table 3.2 presents the results of 17 comparisons (Zhu [13] and Söderlund [12] include multiple SVD groups). In 11 of these comparisons, the control group performed significantly better on cognitive tests than their respective SVD groups. The remaining 6 comparisons found no significant differences between SVD and control groups.

Table 3.3: Narrative summary of excluded cognitive data in the domain of executive function

Study	Cognitive tests reported	Metric	Effect size	Statistical test	Variables adjusted for	Results
Baune, 2009 [1]	Stroop 3 Animal naming	Mean (no SD)	SVD: 67.4 Control: 61 SVD: 19.7 Control: 21.1	ANOVA	Age, sex, education	Controls performed significantly better than SVD group on both tests ($p<0.05$)
Dey, 2019 [2]	Composite score	Mean (95% CI) of composite score calculated via principal components analysis	SVD: -0.090 (-0.522, 0.342) Control: 0.090 (-0.342, 0.522) Partial eta squared: 0.008	MANCOVA	Age, education	No significant difference between controls and SVD group ($p=0.557$)
Han, 2019 [3]	TMT B (black and white)	Median and range	SVD: 176.47 (145.47–285.27) Control: 129.64 (95.55–180.29)	Student's t or Mann Whitney U		Controls performed significantly better than SVD group ($p=0.005$)
Jokinen, 2006 [4]	Composite score	z-score mean (SD)	SVD: -0.33 (0.7) Control: 0.45 (0.42) Partial eta squared=0.022	MANCOVA	Age, education	Controls performed significantly better than SVD group ($p=0.001$)
Kynast, 2018 [5]	Composite score Verbal fluency	z-score mean (SD)	Fazekas 1: 0.021 (0.692) Fazekas 2: -0.175 (0.683) Fazekas 3: -0.137 (0.715) Control: 0.316 (0.755) Fazekas 1: -0.056 (0.896) Fazekas 2: -0.111 (0.873) Fazekas 3: -0.147 (0.964) Control: 0.097 (0.619)	Nonparametric rank sum	Age, sex, education	Controls performed significantly better than Fazekas 2 group on the composite score ($p<0.05$), but there was no difference in scores on the verbal fluency test
Lange, 2017 [6]	CERAD-Plus Animal naming CERAD-Plus TMTB	z-score mean (SD)	SVD: −1.23 (0.82) Control: −0.25 (0.61) SVD: −2.38 (1.59) Control: −0.18 (0.84)	One way ANOVA with Scheffe's or Tamhane's post hoc test	Z-scores adjusted for age, sex and education	Controls performed significantly better than SVD group on both tasks ($p<0.001$)
Margraf, 2009 [7]	CLOX 1	Median and range	SVD: 10 (4-14) Control: 13 (12-15)	Mann Whitney U		Controls performed significantly better than SVD group on all tasks ($p<0.05$)

	Tower of London time Phonemic fluency Five Point test productivity		SVD: 10.3 (3.1-57.4) Control: 4.3 (2.2-14.3) SVD: 17 (2-29) Control: 29 (17-45) SVD: 18.5 (6-28) Control: 21 (15-37)			
O'Sullivan, 2004 [8]	Phonemic Fluency WCST total errors Reitan TMT B-A	Mean group difference in z-score	Mean difference: 0.923 Mean difference: 0.795 Mean difference: 2.186	Student's t test	Reitan TMTB-A: comparison controlled for motor speed	Phonemic fluency and WCST: Authors report that performance of the SVD group was "more severely affected" than the control group, but numeric results of comparisons are not reported. Reitan TMT B-A: control group performed significantly better than SVD group (p=0.021)
Papma, 2013 [9]	TMTB + Stroop 3	z-score mean (SD)	SVD: -0.94 (1.4) Control: 0 (0.9)	ANCOVA	Age, sex, education	Controls performed significantly better than SVD group (p<0.05)
Scherr, 2014 [10]	CERAD-Plus TMT B	z-score mean (SD)	SVD: -0.50 (1.23) Control: 0.11 (1.1)	Mann-Whitney U	z-scores adjusted for age, sex, and education	Control group performed significantly better than SVD group (p=0.03)
Schroeter, 2007 [11]	Stroop 3	Mean (SEM)	SVD: 2559.7 (280.0) Control: 1536.9 (100.7)	Student's t test		Control group performed significantly better than SVD group (p<0.005)
Söderlund, 2003 [12]	Stroop 3 Animal naming	z-score mean (no SD reported)	1st tertile WMH: 0.116 2nd tertile WMH: 0.030 3rd tertile WMH: -0.235 Control: 0.210 1st tertile WMH: 0.166 2nd tertile WMH: 0.070 3rd tertile WMH: -0.183 Control: -0.198	ANCOVA	Age	No significant differences between performance of the control and any of the SVD groups on either task
Zhu, 2019 [13]	Composite score	z-score	WMH no CI: –0.26 (0.57) WMH + MCI: –1.52 (0.68) Control: 0.00 (0.72)	One way ANOVA		Controls performed significantly better than the WMH+CI group (<0.001), but there was no difference between the control and WMH+no MCI group

Note: Table 3.3 presents the results of 31 comparisons (Kynast [5], Söderlund [12] and Zhu [13] include multiple SVD groups). In 16 of these comparisons, the control group performed significantly better on cognitive tests than their respective SVD groups. Thirteen comparisons found no significant differences between SVD and control groups. O'Sullivan [8] did not report the results of statistical comparisons for the phonemic fluency and WCST, so these comparisons cannot be evaluated.

Table 3.4: Narrative summary of excluded cognitive data in the domain of delayed memory

Study	Cognitive tests reported	Metric	Effect size	Statistical test	Variables adjusted for	Results
Dey, 2019 [2]	Hopkins Verbal Learning Test –delayed recall Hopkins Verbal Learning Test – delayed recognition	Mean (95% CI) of composite score calculated via principal components analysis	SVD: 9.540 (8.768, 10.311) Control: 10.373 (9.602, 11.145) Partial eta squared=0.131 SVD: 11.027 (10.576, 11.478) Control: 11.103 (10.653, 11.554) Partial eta squared=0.828	MANCOVA	Age, education	No significant difference between controls and SVD group on either task (p>0.05)
Jokinen, 2006 [4]	Composite score	z-score mean (SD)	SVD: -0.32 (0.87) Control: 0.74 (0.56) Partial eta squared=0.014	ANCOVA	Age, education	Controls performed significantly better than SVD group (p=0.001)
Kynast, 2018 [5]	Composite score	z-score mean (SD)	Fazekas 1: 0.028 (0.586) Fazekas 2: -0.138 (0.72) Fazekas 3: -0.355 (0.748) Control: 0.074 (0.619)	Nonparametric rank sum	Age, sex, education	Controls performed significantly better than the Fazekas 2 group and the Fazekas 3 group (p<0.01)
Margraf, 2009 [7]	NAI word list delayed recognition	Median and range	SVD: 5 (0-7) Control: 5 (0-8)	Mann Whitney U		No significant difference between performance of the control and SVD group (p=0.419)
Scherr, 2014 [10]	CERAD-Plus Wordlist – DR CERAD-Plus Wordlist – recog.	z-score mean (SD)	SVD: -1.30 (1.34) Control: -0.82 (1.13) SVD: -0.79 (1.76) Control: -0.48 (1.6)	Mann Whitney U	z-scores adjusted for age, sex, and education	No significant difference between performance of the control and SVD group on either test (p>0.05)

Note: Table 3.4 presents the results of 9 comparisons (Kynast [5] includes multiple SVD groups). In 3 of these comparisons, the control group performed significantly better on cognitive tests than their respective control groups. The remaining 6 comparisons found no significant differences between SVD and control groups.

Table 3.5: Narrative summary excluded cognitive data in the domain of attention

Study	Cognitive tests reported	Metric	Effect size	Statistical test	Variables adjusted for	Key results
Kynast, 2018 [5]	Composite score	z-score mean (SD)	Fazekas 1: -0.023 (0.832) Fazekas 2: -0.146 (0.873) Fazekas 3: -0.675 (1.82) Control: 0.753 (0.804)	Nonparametric rank sum	Age, sex, education	Controls performed significantly better than the Fazekas 2 group and the Fazekas 3 group ($p<0.05$)

Note: Table 3.5 presents the results of 3 comparisons from a single study. In 2 of these comparisons, the control group performed significantly better on cognitive tests than the SVDs groups. The remaining comparison found no significant differences between SVD and control group.

Table 3.6: Narrative summary excluded cognitive data in the domain of visuospatial ability (note overleaf)

Study	Cognitive tests reported	Metric	Effect size	Statistical test	Variables adjusted for	Key results
Jokinen, 2006 [4]	WAIS-R Block design	z-score mean (SD)	SVD: -0.32 (0.95) Control: 0.84 (0.74) Partial eta squared=0.004	ANCOVA	Age, education	Controls performed significantly better than SVD group ($p=0.001$)
Kynast, 2018 [5]	CERAD-Plus Figure copy	z-score mean (SD)	Fazekas 1: 0.167 (0.864) Fazekas 2: -0.094 (1.14) Fazekas 3: 0.045 (0.952) Control: 0.009 (0.993)	Nonparametric rank sum	Age, sex, education	Controls performed significantly better than the Fazekas 2 group and the Fazekas 3 group ($p<0.01$)
Margraf, 2009 [7]	CLOX 2	Median and range	SVD: 13 (8-15) Control: 15 (14-15)	Mann Whitney U		Controls performed significantly better than SVD group ($p=0.001$)
O'Sullivan, 2004 [8]	Benton Facial Recognition	Mean group difference in z-score	Mean difference: 1.022	Student's t test		Does not report whether a significant difference was found.
Papma 2013 [9]	WAIS Block design Clock drawing	z-score mean (SD)	SVD: -0.35 (1.32) Control: 0 (1.0) SVD: -0.73 (1.1) Control: 0 (1.0)	ANCOVA	Age, sex, education	No significant difference between control and SVD group on either task ($p>0.05$)
Scherr, 2014 [10]	CERAD-Plus figure copy	z-score mean (SD)	SVD: 0.01 (1.91) Control: -0.19 (1.61)	Mann-Whitney U	z-scores adjusted for age, sex, and education	No significant difference between performance of the control and SVD group ($p>0.05$)

Note: Table 3.6 presents the results of 9 comparisons (Kynast [5] includes multiple SVD groups). In 4 of these comparisons, the control group performed significantly better on cognitive tests than their respective SVD groups. The remaining 4 comparisons found no significant differences between SVD and control groups. O'Sullivan [8] did not report the results of statistical comparisons for the Benton Facial Recognition test, so this comparison cannot be evaluated.

Table 3.7: Narrative summary of excluded cognitive data in the domain of language

Study	Cognitive tests reported	Metric	Effect size	Statistical test	Variables adjusted for	Results
Kynast, 2018 [5]	Boston Naming Test	z-score mean (SD)	Fazekas 1: 0.035 (1.047) Fazekas 2: -0.169 (1.045) Fazekas 3: -0.095 (0.651) Control: 0.074 (0.803)	Nonparametric rank sum	Sex, education	No significant difference between performance of the control and SVD groups (p>0.05)
Lange, 2017 [6]	CERAD-Plus Boston Naming Test	z-score mean (SD)	SVD: −2.15 (1.61) Control: −0.34 (0.78)	One way ANOVA with Scheffe's or Tamhane's post hoc test	Z-scores adjusted for age, sex and education	Controls performed significantly better than SVD group (p<0.001)
Papma 2013 [9]	Composite score	z-score mean (SD)	SVD: -0.63 (0.83) Control: 0 (0.71)	ANCOVA	Age, sex, education	No significant difference between performance of the control and SVD group (p>0.05)
Scherr, 2014 [10]	CERAD-Plus Semantic fluency CERAD-Plus Phonemic fluency CERAD-Plus Boston Naming Test	z-score		Mann Whitney U	Z-scores adjusted for age, sex and education	Controls performed significantly better than SVD group on semantic fluency (p=0.033) and phonemic fluency tasks (p=0.045) No significant difference between control and SVD group on Boston Naming Test (p>0.05)

Note: Table 3.7 presents the results of 8 comparisons (Kynast [5] includes multiple SVD groups). In 3 of these comparisons, the control group performed significantly better on cognitive tests than their respective SVD groups. The remaining 5 comparisons found no significant differences between SVD and control groups.

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Supplementary File 4: Cognitive tests included in the meta-analysis dataset, organised by domain

Cognitive domain	Cognitive test	Abbreviated test name used in forest plots
Information Processing Speed	• Brief Memory and Executive Test (BMET) Digit-Symbol Coding	• BMET Digit-Symbol Coding
	• BMET Letter-Number Matching	• BMET Letter-Number Match
	• BMET Letter Sequencing	• BMET Letter Sequencing
	• BMET Motor Sequencing	• BMET Motor Sequencing
	• Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Trail Making Test A	• CERAD TMT A
	• Conceptual comparison task	
	• Digit Symbol test	
	• Flanker task congruent condition	• Flanker task congruent
	• Farbworttest (German adaptation of Stroop Test)	
	• Letter Number sequencing	
	• Line Cancellation	
	• Paced Auditory Serial Addition Test	
	• Perceptual comparison task	
	• Reaction time task	
	• Sternberg High Speed Scanning Test	• Sternberg High Speed Scan
	• Stroop dots	
	• Stroop Test I (colour condition)	• Stroop 1
	• Stroop Test II (word condition)	• Stroop 2
	• Symbol Digit Modalities	
	• Symbol Substitution Coding	
	• Trail Making Test A	• TMT A
	• Vascular Dementia Assessment Scale-cognition (VDAS-cog) Digit Cancellation	• VDAS-cog Symbol Digit
	• VDAS-cog Symbol Digit Modalities	
	• Wechsler Adult Intelligence Scale (WAIS)/Wechsler Adult Intelligence Scale – Revised (WAIS-R) Digit Symbol Coding	• WAIS/WAIS-R Digit Symbol
	• Wechsler Adult Intelligence Scale – Revised Chinese version (WAIS-RC) Digit Symbol Coding	• WAIS-RC Digit Symbol
	• WAIS III Coding	• WAIS III Digit Symbol
	• WAIS III Digit Symbol Coding	
	• WAIS III Symbol Search	
Executive Function	• 5-point Figural Fluency	
	• Brief Memory and Executive Test (BMET) number-letter sequencing	• BMET number-letter seq.
	• BMET Trail Making Test B-A	• BMET TMT B-A
	• California Card Sorting Test – number of sorts	• California Card Sorting # sorts
	• California Verbal Learning Test – semantic clusters	• CVLT semantic clusters
	• Cambridge Cognition (CAMCOG) Chinese version executive function subscore	• CAMCOG-C executive subscore
	• Cognitive abilities screening instrument (CASI) – semantic fluency	• CASI semantic fluency
	• Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Figure copy	• CERAD figure copy
	• CERAD Phonemic Fluency	
	• CERAD Semantic Fluency	
	• CERAD Trail Making Test B	• CERAD TMT B
	• Clock drawing test/CLOX 1	
	• Continuous Performance Test - errors	
	• Farbworttest 1 minus 3 (German adaptation of Stroop Test 1 minus 3)	• Farbworttest 1-3
	• Flanker task executive trial	
	• Frontal Assessment Battery	• FAB
	• Frontal Assessment Battery - semantic fluency	• FAB semantic fluency
	• Mattis Dementia Rating Scale - Initiation Perseveration	• DRS Initiation Persev.
	• Parallel Serial Mental Operations	• Parallel Serial Mental Ops.
	• Phonemic Fluency / Controlled Oral Word Association Test (e.g. letters F, A, S)	
	• Stroop Colour Word test III – colour-word condition	• Stroop 3
	• Stroop Colour Word test III - interference time (e.g. Stroop 3 minus Stroop 1 or 2)	• Stroop 3 interference time
	• Taiwanese Frontal Assessment Battery – orthographic fluency	• T-FAB orthographic fluency

	• Tower of Hanoi/Tower of London – number of movements • Trail Making Test B • Trail Making Test B-A • Vascular Dementia Assessment Scale-cognition (VDAS-cog) Semantic Fluency • Semantic Fluency/Categorical Fluency (e.g. animal naming, naming supermarket items, naming professions) • Wisconsin Card Sorting Test - categories/perseverations N.B. Where studies do not clarify whether verbal fluency tasks were semantic or phonemic, they are described as 'verbal fluency'	 • TMT B • TMT B-A • VDAS-cog Semantic Fluency • Semantic Fluency (1 or 2 indicates different semantic categories) • WCST categories/perseverations
Delayed Memory	• 7/24 Spatial Recall Test - delayed recall • Auditory verbal learning test – delayed recall • Auditory verbal learning test – recognition • Biber Visual Memory – delayed recall • Brief Memory and Executive Test 5-item recall • BMET 5-item recognition • Buschke Selective Reminding Test - consistent long-term retrieval • Chinese Auditory Verbal Learning Test – delayed recall • Chinese Auditory Verbal Learning Test – recognition • Consortium to Establish a Registry for Alzheimer's Disease (CERAD) figure recall • CERAD List Learning – delayed recall • CERAD Constructional praxis – delayed recall • California Verbal Learning test – delayed recall • California Verbal Learning test – recognition • Chinese Verbal Learning test – delayed recall • Doors and People – verbal delayed recall • Doors and People – visual delayed recall • Face recognition • Free and Cued Selective Reminding test- delayed recall • Hopkins Verbal Learning Test-Revised – delayed recall • Memory Assessment Scale list learning - delayed recall • Memory Assessment Scale list learning - recognition • MoCA delayed recall subscore • (Modified) Rey Osterrieth Complex Figure Test – delayed recall • Rey Osterrieth Complex Figure Test – delayed reproduction • Philadelphia Verbal Learning Test – delayed recall • Philadelphia Verbal Learning Test – recognition • Rey Auditory Verbal Learning Test - delayed recall • Rey Auditory Verbal Learning Test – recognition • RL/RI verbal learning - delayed recall • Spoken language delayed recognition • Seoul Verbal Learning Test – delayed recall • Seoul Verbal Learning Test – recognition • Story recall/Logical memory – delayed recall • Text Memory of the BEM-144 - delayed recall • Vascular Dementia Assessment Scale-cognition (VDAS-cog) word list learning – delayed recall • VDAS-cog word list learning – recognition • Wechsler Adult Intelligence Scale (WAIS) Verbal Memory – delayed recall • WAIS Visual Memory - delayed recall • World Health Organization-University of California-Los Angeles Auditory Verbal Learning Test – delayed recall • World Health Organization-University of California-Los Angeles Auditory Verbal Learning Test – recognition • Wechsler Memory Scale (WMS)/Wechsler Memory Scale – Revised (WMS-R) Logical Memory - delayed recall • WMS Logical Memory (Russell revision) – delayed recall • WMS Visual Reproduction (Russell revision) – delayed recall • WMS III Auditory memory • WMS III Auditory recognition • WMS III Visual memory	• 7/24 Spatial Recall Test - DR • AVLT – DR • AVLT - recog. • Biber Visual Memory – DR • BMET 5-item recall • BMET 5-item recog. • Buschke Selective Reminding • AVLT-C – DR • AVLT-C – recog. • CERAD figure recall • CERAD List Learning – DR • CERAD constructional praxis - DR • CVLT – DR • CVLT – recog. • CHVLT - DR • Doors and People – verbal DR • Doors and People – visual DR • FCSRT - DR • HVLT-R - DR • MAS List Learning – DR • MAS List Learning – recog. • (m)ROCFT – DR • ROCFT – delayed reproduction • PVLT – DR • PVLT – recog. • RAVLT – DR • RAVLT recog. • RL/RI verbal learning – DR • Spoken lang. recog. – delayed • SVLT – DR • SVLT – recog. • BEM text memory - DR • VDAS-cog verbal learn – DR • VDAS-cog verbal learn – recog. • WAIS verbal memory – DR • WAIS visual memory – DR • WHO CVLT – DR • WHO CVLT – recog. • WMS/WMS-R Logical Memory – DR • WMS Logical Mem. (RR) – DR • WMS Visual Repro. (RR) - DR
Attention	• Alters-konzentrations test	

	• Cambridge Cognition (CAMCOG) attention subscore • CAMCOG Chinese version attention subscore • Continuous Performance Test – omissions • Kana-Hiroi task • MoCA attention subscore • Multiple Features Targets Cancellation • Paced Auditory Serial Addition Test • Short Cognitive Performance Test attention subscore • Test of Everyday Attention (TEA) – lottery • TEA – map search • TEA – visual elevator • TEA – elevator counting with distraction	• CAMCOG-C attention subscore • Continuous Performance • SKT attention subscore • TEA Lottery • TEA Map Search • TEA Visual Elevator • TEA Elevator distraction
Reasoning	• Barcelona Abstraction • Booklet Category Test - errors • Cambridge Cognition (CAMCOG) Abstraction subscore • Camel and Cactus test • Frontal Assessment Battery – conceptualisation subscore • MoCA Reasoning subscore • Raven's Coloured Progressive Matrices • Raven's Standard Progressive Matrices • Similarities task • Synonym task • TFAB Similarities subscore • WAIS/WAIS-R/WAIS-RC Similarities • WAIS-R Picture Completion • WAIS-RC Picture Arrangement	• Booklet Category errors • FAB conceptualisation • Raven's CPM • Raven's SPM
Visuospatial Ability	• Benton Visual Form Discrimination • Benton Judgment of Line Orientation Test • Cambridge Cognition (CAMCOG) Perception subscore • CLOX 2 • Hooper Visual Organisation Test • Kohs IQ Block Design • Modified Rey-Osterreith Complex Figure – copy • Rey Complex Figure - copy • Rey Osterrieth Complex Figure – copy • Visual Object and Space Perception Battery (VOSP) Cube Analysis • VOSP Dot Counting • VOSP Incomplete Letters • VOSP Number Location • VOSP Object Decision • VOSP Silhouette naming • Wechsler Adult Intelligence Scale – Revised (WAIS-R)/ Wechsler Adult Intelligence Scale - Revised Chinese version (WAIS-RC) Block Design • WAIS-R modified block design	• Benton Visual Form • Benton Line Judgement • CAMCOG perception subscore • mROCFT copy • RCFT copy • ROCFT copy • VOSP cube analysis • WAIS-R/WAIS-RC mBlock Design
Language	• Assessment of Subtle Language Deficits Logical Grammar and Repetition • Abbreviated Boston Naming Test • Boston Naming Test • Cambridge Cognition (CAMCOG) Language subscore • Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Boston Naming Test • Graded Naming Test • Korean Boston Naming Test • MoCA naming subscore • MoCA language subscore • Naming actions/objects • NART Full Scale IQ • Token Test • Vocabulary task • Wechsler Adult Intelligence Scale – Revised (WAIS-R) Vocabulary • Word-Picture Matching	• ASLD Logical Grammar • BNT short version • BNT • CAMCOG language subscore • CERAD BNT • WAIS-R vocabulary

Supplementary File 5: SVD cohort descriptions, diagnostic criteria, and inclusion and exclusion criteria of included studies

Study	Characterisation of SVD cohort	Recruitment setting	SVD cohort description, diagnostic criteria, and inclusion and exclusion criteria (where available)	Category of SVD presentation
Anderson 2008	Lacunar syndrome	Research cohort: geographical recruitment	Ischemic stroke diagnosis based on the clinical Oxfordshire Community Stroke Project classification system [1], which incorporates well-established lacunar syndromes: pure motor stroke; pure sensory stroke; ataxic hemiparesis; and sensorimotor stroke.	Stroke
Atwi 2018	Healthy adults Fazekas ≥2	Community based recruitment	Exclusion criteria: <21 on MoCA, stroke, dementia, cardiopulmonary illness, type 2 diabetes requiring insulin.	Non-clinical
Bella 2016	Vascular cognitive impairment – no dementia	Cerebrovascular disease centre	Patients fulfilled the neuroradiological criteria for subcortical vascular disease with predominant white matter lesions (DSM-IV-TR), but did not meet the (DSM-IV-TR) criteria for dementia	Cognitive impairment/dementia
Boone 1992	Elderly with WMH	Research study: public advertisement in local newspaper	Inclusion criteria: free of current or past psychotic, major affective, and alcohol and other drug dependence disorders; score 24 or greater on the Mini-Mental State Examination; and fluent in English. Subjects were excluded if there was a history or physical findings of neurologic disease, such as stroke, Parkinson's disease, or seizure disorder. Also excluded were individuals with laboratory findings showing serious metabolic abnormalities (e.g. low sodium level, elevated glucose level, or thyroid or liver function abnormalities).	Non-clinical
Brookes 2014	SVD	Specialised cerebrovascular services in hospitals in London	Clinical lacunar stroke syndrome (i.e. pure motor hemiparesis, pure sensory syndrome, sensorimotor stroke, ataxic hemiparesis, or dysarthria-clumsy hand) [1], and radiological confirmation of lacunar infarction in an anatomical location corresponding to the clinical deficit.	Stroke
Brookes 2015	SVD	19 sites across the English Stroke Research network	Clinical lacunar syndrome (e.g. hemiparesis, hemisensory deficit, sensorimotor deficit, ataxic hemiparesis, or clumsy hand dysarthria) or partial lacunar syndrome (e.g. pure motor stroke affecting face and arm or arm and leg) with an MRI confirmed lacunar infarct in an anatomically corresponding location.	Stroke

DeCarli 1995	Healthy with WMH volume > 0.5%TIV	Research cohort	Exclusion: chronic medical illnesses including hypertension, heart or cerebrovascular disease, psychiatric disorders, history of head trauma, or substance abuse were excluded.	Non-clinical
Deguchi 2013	Lacunar infarction	Stroke outpatient clinic	TOAST stroke subtype classification system [2]	Stroke
Fang 2013	1) Silent brain infarcts 2) Microbleeds 3) Silent brain infarcts + microbleeds	Neurology dept. complaints of non-specific symptoms such as headache, dizziness, vertigo, and dysmnesia	Inclusion criteria: 1) three years or longer education, with basic reading ability and will to give consent to this study; 2) no history of stroke, simple Alzheimer's Disease, dementia with Lewy bodies, schizophrenia, or other diseases that might cause the decline in cognitive function and behaviour competence; or new diagnosis of above mentioned diseases during this study; 3) no claustrophobia or metallic implants; 4) periventricular leukoaraiosis of grades 2 to 3 identified through magnetic resonance imaging (MRI) according to Fazekas scale. Silent brain infarctions were counted on T1- and T2-weighted images and fluid-attenuated- inversion-recovery (FLAIR) images. Susceptibility weighted images (SWI) were further obtained to evaluate the presence and number of microbleeds. Microbleeds were defined as homogenous round areas of signal loss with diameters less than 10mm on SWI images [3]. Hypointense lesions within the subarachnoid space, basal ganglia mineralization, and other lesions or structures with similar signals were excluded during the microbleeds' evaluation. Silent brain infarction was defined as a focal cavitated lesion 3mm to 15 mm in diameter, with hypointensity on T1-weighted images, hyperintensity on T2-weighted images, without corresponding stroke history [4].	1) Non-clinical 2) Non-clinical 3) Non-clinical
Fernández 2011	Mild cognitive impairment with subcortical vascular damage	Hospital: dementia unit	MCI according to Petersen criteria [5], then applied criteria of Frisoni [6] criteria to identify MCI with subcortical vascular damage.	Cognitive impairment/dementia
Gainotti 2008	MCI with multiple subcortical infarcts	Neuropsychology clinic. Patients presented with "onset of a mental deterioration"	Patients had amnestic MCI according to Petersen criteria [7] and three or more small subcortical infarcts <2mm in size, or two small infarcts and periventricular white matter hyperintensities. Patients with both hippocampal atrophy and subcortical infarcts were excluded from the study.	Cognitive impairment/dementia

Garrett 2004	Vascular cognitive impairment – no dementia	Data obtained from archival study records.	The vascular cognitive impairment – no dementia (VCI-ND) group was selected from a larger group of patients that met research criteria for MCI. A mild decline in cognitive functioning, as assessed by the Clinical Dementia Rating Scale, neuroimaging, neurologic exam, were used as the criterion for MCI. All individuals in the VCI-ND group received a score of 0.5 on the Clinical Dementia Rating Scale, indicating cognitive disturbance of mild severity that did not interfere with daily function. While mild functional memory decline can alone yield a CDR score of 0.5, functional memory decline was not the exclusive factor in selecting the VCI-ND participants. All individuals in the VCI-ND group exhibited evidence of CVD either on neuroimaging (n = 13) or upon neurologic examination (n = 5), and reported significant risk factors for CVD, including hypertension and diabetes (n = 4). The cognitive symptoms reported on the CDR were determined to be associated with a vascular etiology. This determination was made by consensus following review of clinical history. Individuals were excluded if they had a major medical illness not directly related to VCI-ND, neurologic condition (including traumatic brain injury, seizures), or history of chronic substance abuse or psychiatric disturbance (including depression or significant depressive features).	Cognitive impairment/dementia
Gonçalves 2017	Subcortical vascular dementia	Hospital: Neurology dept.	Patients with subcortical vascular dementia fulfilled NINDS-AIREN criteria [8]. The brain imaging criteria for SVD of Erkinjuntti [9] were used to select the subcortical type. These criteria include the presence of extensive periventricular and deep white matter lesions and lacunar infarcts on brain imaging. Specifically with respect to the SVD patients, CT and MRI showed the typical imaging findings of microvascular leukoencephalopathy with diffuse periventricular and/or subcortical white matter lesions.	Cognitive impairment/dementia
Graham 2004	Vascular dementia	Memory clinic	Included patients had substantial subcortical white matter pathology on T2 weighted magnetic resonance imaging (MRI), together with vascular risk factors plus a history of transient ischaemic attacks (TIA) or focal neurological signs on examination. Focal signs included mild facial paresis, clumsiness of fine finger movements, reflex asymmetry, extensor plantar responses, and cortical sensory signs. None of the patients had visual field defects on clinical testing. Authors did not apply the NINDS-AIREN criteria for probable vascular dementia as these require	Cognitive impairment/dementia

			a chronological relation between a major vascular event and cognitive impairment, and the presence of focal neurological signs. Excluded patients who had major cortical strokes or strategic thalamic infarcts.	
Hassan 2010	Symptomatic lacunar infarction	Hospital: neurology department	Exclusion criteria: clinically demented and aphasic patients, stroke onset less than one month from the study; patients with history of head trauma; patients with systemic disorders as renal or hepatic impairment; patients on psychoactive drugs and subjects older than 75 years.	Stroke
Hsu 2016	MCI due to subcortical ischemic vascular disease	Hospital: neurology department	MCI criteria [10]: (1) not cognitively normal, not dementia; (2) self and/or informant report and impairment on objective cognitive tasks of at least 1.5 standard deviations below normative values; and (3) preserved basic activities of daily living/minimal impairment in complex instrumental functions. Among the patients with MCI, those with MCI due to subcortical ischaemic vascular disease fulfilled the following criteria: (1) appearance of subcortical ischemic pathology in brain magnetic resonance imaging (MRI) studies [9]; and (2) Hachinski Ischemic Scale ≥ 7.	Cognitive impairment/dementia
Ishii 2007	5) CDR 0, non-strategic CVD 6) CDR 0, strategic CVD 7) CDR 0.5, non-strategic CVD 8) CDR 0.5, strategic CVD	Research study: geographical recruitment	CVD was radiologically defined: The lesion of T2 high and T1 (TR/TE ¼ 400/14) low intensities at the same area was regarded as état criblé when it was under 4mm at the maximum size, and as CVD when the size was over 4mm. Exclusion: CDR>1, other neurological conditions (depression, brain tumour, CO intoxication, hypoxemic encephalopathy, Parkinson's, impaired visual acuity). The following areas were defined as strategic, since even minor cerebrovascular disease in these regions can cause cognitive dysfunction: thalamus, caudate head, anterior limb of the internal capsule, hippocampus, amygdala, basal forebrain, dorsolateral frontal area, and the association cortices of the frontal, temporal, and parietal lobes. The putamen, globus pallidus and deep white matter were defined as nonstrategic areas, since damages to these areas are not likely to cause cognitive dysfunction. This discrimination between strategic and non-strategic was made blindly to the CDR and neuropsychological information by neurologists independent of this study on mutual agreement.	1) Non-clinical 2) Non-clinical 3) Cognitive impairment/dementia 4) Cognitive impairment/dementia
Jokinen 2009	Subcortical ischaemic vascular disease	Stroke unit or stroke department or cerebrovascular disease clinic,	Subcortical ischaemic vascular disease defined according to Erkinjuntti criteria [11-13] e.g. (a) cases with predominantly WML, i.e., extending periventricular and deep WML (extending caps or irregular halo and diffusely confluent hyperintensities or extensive white matter change) and lacune(s), and (b) cases with predominantly	Stroke

		memory or dementia clinic, neurological or geriatric wards/clinic, and population studies on aging	lacunar infarcts, i.e., >5 lacunes and at least moderate WML (extending caps or irregular halo or diffusely confluent hyperintensities or extensive white matter change). Inclusion criteria: age 65–84 years, changes in cerebral white matter of any degree (classified as mild, moderate or severe according to a revised version of the Fazekas scale), no or mild impairment in instrumental activities of daily living (none or one item compromised in the instrumental activities of daily living scale), and presence of a contactable informant. Exclusion criteria: presence of severe illness likely leading to drop out, severe unrelated neurological disease, leukoencephalopathy of nonvascular origin, severe psychiatric disorders, and inability or refusal to undergo brain MRI.	
Kim 2018	Subcortical vascular cognitive impairment	Medical centre	Clinical diagnosis was established by consensus among a multidisciplinary team. Inclusion: (1) subjective cognitive complaint by the patient or caregiver; (2) objective cognitive impairment less than the 16th percentile of the norm in any domain including language, visuospatial, memory, or frontal function on neuro psychological tests; (3) significant ischemia on brain magnetic resonance imaging (MRI), defined as periventricular WMH at least 10mm and deep WMH at least 25mm; and (4) focal neurologic symptoms or signs. Exclusion: participants who showed structural lesions including territorial cerebral infarction, cortical stroke, brain tumour, hippocampal sclerosis, or vascular malformation on brain MRI	Cognitive impairment/dementia
Kramer 2002	Subcortical ischaemic vascular disease	Clinic: dementia; and Veterans' Association neurology and radiology services	Participants were SIVD if they had lacunes on MRI: defined as small (>3 mm) areas of the brain with increased signal relative to CSF on proton density MRI in subcortical grey and white matter. Lacunes were differentiated from perivascular spaces (PVS) because only lacunes are hyperintense relative to CSF on proton density images. Isointense lesions on PD MRI at the level of the anterior commissure or inferior putamen were termed perivascular spaces; outside that region they were defined as cavitated lacunes if they were 3mm at maximum width. None of the patients had sought out evaluations because of concerns about cognitive changes.	Stroke
Kuriyama 2018	1) dWMH Fazekas 1 2) dWMH Fazekas 2	Community based recruitment	Individuals with dementia and a past medical history of stroke and symptomatic brain haemorrhage were excluded. The absence of a large symptomatic brain haemorrhage or other findings suggesting an infectious disease or neurodegenerative condition was established in all subjects.	1) Non-clinical 2) Non-clinical 3) Non-clinical

	3) dWMH Fazekas 3			
Ledesma-Amaya 2014*	Lacunar infarction	Institute of Neurology and Neurosurgery (Mexico)	The lacunar infarction was established clinically by a vascular neurologist, based on the TOAST classification criteria [2]. The lacunar infarction is defined as an event that occurred in patients without a history of vascular event. The clinical history associated with the vascular event was confirmed by a vascular neurologist through review of records and neuroimaging studies by computer of each patient.	Stroke
Lee 2014	Subcortical vascular mild cognitive impairment	Hospital	Subcortical vascular mild cognitive impairment was defined according to modified Petersen criteria [7]. Modifications included: (1) subjective report of cognitive difficulty by the patient or caregiver; (2) normal activities of daily living (ADL), with the score determined clinically and by the Seoul Instrumental Activities of Daily Living scale; (3) an objective cognitive decline below the 16th percentile on the Seoul Neuropsychological Screening Battery; (4) no dementia; (5) a subcortical vascular feature defined as a focal neurologic symptom or sign including corticobulbar signs, pyramidal signs, or parkinsonism; and (6) significant ischemia shown on MRI.	Cognitive impairment/dementia
Lewine 1993	1) Men with WMH 2) Women with WMH	Healthy controls from previous research study	Inclusion: never mentally ill, negative toxicology screen, no first degree relative with a major psychiatric disorder.	1) Non-clinical 2) Non-clinical
Li 2001*	Leukoaraiosis	Presented to hospital with general headache, dizziness and some physical health examinations	Cohort described as “neurologically healthy elderly” and had no history of neuropsychiatric disease/disorder.	Non-clinical
Li 2012	Lacunar stroke with ischaemic leukoaraiosis	Clinic: cerebrovascular neurology	Patients had evidence of radiological leukoaraiosis and a history of at least one clinical lacunar stroke.	Stroke
Li 2015*	Symptomatic lacunar infarction	Hospital: neurology department	Clinical manifestations were mild hemiparesis, dizziness, mild facial paralysis, and the NIHSS SCORE <3. Inclusion criteria: patients with symptomatic lacunar infarction within 72 hours of acute onset, FLAIR & DWI suggesting a T2 weighted high signal, a	Stroke

			T1 weighted imaging low signal, a DWI high signal, lesion diameter <20mm and a degree of white matter lesions (Fazekas) graded 0-1; transcranial doppler ultrasound head and neck, CT angiography, or MR angiography confirmed the lack of pre-intra and extra-vascular stenosis; no embolic source. There was no cognitive decline before enrolment; scores well on activities of daily living (90-100 points); no history of mental illness. Exclusion: pre-existing cognitive impairment, history of drugs or alcohol; psychiatric disease, Alzheimer's disease, severe leukoencephalopathy and other neurological diseases, speech or consciousness barrier.	
Li 2017*	Leukoaraiosis	Hospital	Inclusion: Diagnosis of leukoaraiosis [15], 50-75 years of age, right handed, head MRI and related medical history. Exclusion: Aphasia, hearing impairments, disturbance of consciousness, congenital mental retardation, mental symptoms and diseases, mental and psychological diseases such as non-vascular induced white matter lesions, stroke, multiple sclerosis, epilepsy, Parkinson's disease, etc., severe systematic diseases such as severe heart disease, liver disease, lung disease, kidney failure etc., depression.	Non-clinical
Liu 2008*	Subcortical small vessel infarction	Hospital: neurology department	MRI and Diagnostic criteria for the Fourth Cerebrovascular Conference (no further information provided). Inclusion criteria: first onset duration <2 weeks; head MRI T2 weighted image showing localised high signal or T1 weighted image low signal, or head CT showing low density shadow. Lesions with diameters of about 0.2-2cm in each layer located in the subcortical white or grey matter, cerebellum white matter, brain stem can explain the clinical manifestations of neurological deficits, with or without white matter damage. Further inclusion criteria: Glasgow coma score >8; no cognitive rehabilitation within 12 weeks of onset. Exclusion criteria: small infarction caused by intracranial aortic disease, extracranial stenosis of the internal carotid artery, cardiogenic embolism, or other causes; cortical or >2cm subcortical infarction; subarachnoid haemorrhage; haemorrhage; TIA; clinical signs cannot be explained by imaging findings of small infarcts; non-ischaemic lesions, such as tumours, demyelination; pre-existing dementia; or suspected cognitive impairment; DSM major depression; communication barriers affecting evaluation of cognitive function; heart, lung, liver kidney or other important organ dysfunction or failure; previously cerebral infarction.	Stroke

Liu 2015*	WMH	Medical University: geriatric department. Patients presented with self-report dizziness and memory impairment.	Inclusion criteria: Over 60 years old with or without cerebral infarction (except for the acute phase, where the infarct site is located in the white matter region). Participants met diagnostic criteria of white matter lesions (WML; i.e. evidence of WML in periventricular or subcortical regions, and spotted/speckle-like or patchy lesions of the white matter in the centrum semiovale region; T1 weighted images showing equal or low signals; T2 weighted images and FLAIR images showing high signals).	Non-clinical
Liu 2019a	3) Pre-subcortical vascular cognitive impairment vascular disease (pre-SVCI) 4) Subcortical vascular cognitive impairment (SVCI)	Day hospital	All participants met criteria for subcortical ischaemic vascular disease (SIVD) [11]: 1) white matter lesions: hyperintensities extending into periventricular and deep white matter; extending caps (>10mms measured parallel to ventricle), or irregular halo (>10mm with broad, irregular margins and extending into deep white matter); and diffusely confluent hyperintensities (>25mm, irregular shape), or extensive white-matter change (diffuse hyperintensity without focal lesions); 2) lacunar cases: multiple lacunes (>2) in the deep grey matter and at least moderate white-matter lesions; 3) absence of haemorrhages, cortical and/or territorial infarcts and watershed infarcts; signs of normal pressure hydrocephalus; and specific causes of white matter lesions. The diagnosis of SVCI was made according to the criteria [15] as follows: 1) in accordance with the criteria of SIVD; 2) subjective cognitive complaints reported by the participant or his/her caregiver; 3) objective cognitive impairments, although not meeting the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-V) criteria for dementia; 4) a Clinical Dementia Rating Scale (CDR) score=0.5; 5) a Mini Mental State Examination (MMSE) score:24–26. The pre-SVCI group met the following criteria: 1) in accordance with the criteria of SIVD; 2) normal daily life activities and cognitive assessments; 3) a Clinical Dementia Rating Scale (CDR) score=0; 4) a Mini Mental State Examination (MMSE) score≥27.	1) Cognitive impairment/dementia 2) Stroke
Liu 2019b	1) SVD without cognitive impairment	Hospital	Inclusion criteria: (1) age >50 years, (2) possible subjective complaints such as dizziness, postural instability, depression, or memory impairment, and (3) presence of lacunes or/and WMH on MRI images. The definitions and imaging standards for	1) Stroke 2) Cognitive impairment/dementia

	2) SVD with cognitive impairment		lacunes and WMH were according to STRIVE criteria [16,17]. The exclusion criteria were as follows: (1) intracranial haemorrhage, (2) history of ischemic stroke with infarct >15 mm in diameter or cardiogenic cerebral infarction, (3) coronary atherosclerosis, heart disease, or carotid artery stenosis (>75%), (4) other neurological disorders, such as parkinsonism/Parkinson disease, Alzheimer disease, multiple sclerosis, and epilepsy, (5) systemic disease, such as shock, cancer, thyroid dysfunction, and anaemia, (6) prominent decline of vision or audition, and (7) MRI contraindications. SVD subjects with MoCA scores lower than education-adjusted norms (the cutoff was < 26 for > 12 years of education, ≤24 for 7–12 years of education, and ≤19 for 1–6 years of education) were defined as the SVD with cognitive impairment group, and the other SVD subjects were defined as the SVD without cognitive impairment group.	
Maeshima 2002	1) Silent brain infarcts 2) pWMH	Volunteers for brain health check-up, who had incidental findings	Inclusion: neurologically normal with no history of cerebrovascular disease. Silent cerebral infarcts (SCI) were defined as focal lesions >5 mm in diameter that showed prolongation on both T2-weighted and proton density images. As defined, SCI was synonymous with “asymptomatic lacune”. Periventricular hyperintense lesions were considered separately, and subcortical patchy or confluent hyperintense lesions were not included.	1) Non-clinical 2) Non-clinical
Nebes 2013	WMH	Research study: Community advertising and direct mailings to individuals who expressed interest in aging studies	Exclusion: history of major psychiatric or central nervous system disease, use of psychoactive medications (i.e., narcotics, benzodiazepines, sedatives), depression, MCI, dementia.	Non-clinical
Nordahl 2005	MCI with severe WMH	Dementia clinic Patients presented initially with memory complaints	MCI participants received a clinical diagnosis through the Alzheimer's Disease Center of MCI based on neurological exams and neuropsychological evaluations. The diagnosis of MCI was adjudicated at a multidisciplinary case conference, based upon all available clinical information. Subjects with MCI all met criteria for an amnestic form of MCI [7] as all had memory complaints (usually verified by an informant), performed poorly on neuropsychological tests of verbal memory	Cognitive impairment/dementia

			(Memory Assessment Scales (MAS) List Learning, Logical Memory I and II), had normal general cognitive function, and intact activities of daily living. Exclusion criteria were limited to clinical depression, history of cortical strokes, and red–green colour blindness	
Nordlund 2007	Vascular MCI	Research study – community based recruitment	Diagnosis of MCI: subjective and objective (as verified by an informant) evidence of progressive cognitive impairment for more than 6 months. Both cognitive symptoms (memory impairment, disorientation, reduced abstract thinking, visuospatial impairment, language impairment, frontal lobe symptoms) at neuropsychiatric examination and absence of dementia, in accordance with DSM–IV, were required. MCI subjects with vascular disease were identified as follows: occurrence of (a) symptoms of MCI; two (or more) expressions of vascular disease (arterial hypertension, cardiac insufficiency, angina pectoris, cardiac rhythm disturbance, cardiac infarction, transient ischemic attack, stroke, hyperlipidemia, diabetes mellitus, or peripheral vessel disease); and findings on MRI that were due to vascular disease. These findings included moderate white matter changes, in accordance with a four-grade scale [18], and/or several lacunae (more than two) and/or signs of infarctions on MRI; and (b) symptoms of MCI, transient ischemic attack, and/or stroke and moderate white matter changes/lacunae formations, and/or signs of infarction on MR.	Cognitive impairment/dementia
Oguro 2000*	pWMH	Hospital: presented as healthy elderly with incidental imaging findings	No history of cerebral disease including cerebral infarction and Alzheimer's disease.	Non-clinical
Pascual 2010	1) Vascular white matter disease without dementia 2) Vascular white matter disease with dementia	Recruitment setting unclear	Authors did not classify the study groups through an a priori definition of vascular dementia. Rather, they compared the metabolic findings in Alzheimer's disease with the findings in 2 groups of patients with a similar amount of vascular disease on MRI but different cognitive status: non-demented in one group and demented in the other group. The 2 groups with vascular disease included 24 patients whose T2-weighted MRI scans revealed confluent hyperintensities in the periventricular and subcortical white matter (graded as severe or score 3 according to the modified Fazekas scale) These 24 patients were selected from among 1099 patients with "leukoaraiosis" or white matter changes on the official radiological report. From	1) Stroke 2) Cognitive impairment/dementia

			these 123 patients with vascular disease, authors first detected a group of 12 patients with mild to moderate dementia who gave informed consent for the full study. Then, from the same group of 123 patients with vascular disease on MRI, authors selected 12 patients without dementia matched to the white matter lesions with dementia group.	
Pinkhardt 2014	Small vessel cerebrovascular disease	No information	Diagnoses were made by a certified neurologist based on the clinical presentation excluding cases of acute cerebral ischemia as well as Parkinsonism other than small vessel cerebrovascular disease (SVCD) related. Patients were included in the present study if at least two of the following three scores indicated a pathology: mini-mental state examination, Tinetti score of fall risk and classification of white matter lesions in terms of periventricular and deep white matter hyperintensity by grades 0–3 as suggested by Fazekas.	Stroke
Price 2009	Dementia with: 1) Mild leukoaraiosis (Junque score 0-8) 2) Moderate leukoaraiosis (Junque score 9-17) 3) Severe leukoaraiosis (Junque score 18 and higher)	Memory clinic	A team consisting of a neurologist, neuropsychologist, and social worker diagnosed the presence of dementia based on (1) a decline in activities of daily living (ADLs) and/or instrumental activities of daily living (IADLs), (2) medical and neurological evaluations including an MRI study of the brain and laboratory studies to assess for reversible causes of dementia, (3) a comprehensive neuropsychological evaluation that included the Philadelphia (repeatable) Verbal Learning Test (PrVLT), and (4) a social work assessment. A brain MRI was obtained on all dementia patients within 2 weeks of the neuropsychological assessment. The sample consisted of 83 patients who met criteria for probable AD [19] and 61 patients who met criteria for the diagnosis of probable/possible ischemic vascular dementia (also known as subcortical vessel vascular dementia [20]). Due to growing evidence of pathology overlap and validity concerns for several subcortical vessel vascular dementia diagnostic criteria, authors did not base analyses on these dementia diagnoses. No dementia outpatient presented with a Hachinski ischemic score <4, no patient presented with either a sudden onset of cognitive decline or a stepwise course with respect to their dementing illness, and findings on the neurological examination were non-focal for all patients. Exclusion: endorsement of current depression via interview and subjective measurement (Geriatric Depression Scale, GDS), history of stroke (excluding evidence of incidental small vessel lacunes on dementia MRIs, which were coded as	1) Cognitive impairment/dementia 2) Cognitive impairment/dementia 3) Cognitive impairment/dementia

			either present or absent), major medical/CNS disease, seizure disorder, thyroid disease, closed head injury, substance abuse, major depression, or other serious psychiatric disorders	
Quinque 2012	Early cerebral microangiopathy	Neurology clinic Patients presented initially with cognitive complaints	Twelve patients with early CMA were recruited among former patients of the Clinic for Cognitive Neurology of the University Hospital Leipzig who had initially presented with cognitive complaints. Diagnosed with cerebral microangiopathy (CMA) after thorough clinical examination and structural MRI and all had a total age-related white matter change (ARWMC) score of >2. Exclusion criteria: history of psychiatric or neurologic disorders including stroke, craniocerebral injury or neurodegenerative disease and dementia.	Cognitive impairment/dementia
Rao 1989	Leukoaraiosis	Public advertisement	Exclusion: history of hypertension, cardiac or cerebrovascular disease, neurologic illness or injury, substance abuse, or psychiatric illness, subjects taking psychoactive medications.	Non-clinical
Schmidt 1993	Healthy with WMH	Research study: participants randomly selected from official register of city of Graz, Austria.	Definition of WMH: Caps around the anterior horns of the lateral ventricles and periventricular lining were disregarded since they probably represented normal anatomic variants.	Non-clinical
Seo 2010	1) Subcortical vascular mild cognitive impairment (svMCI) 2) Subcortical Vascular Dementia (VaD)	Medical centre	VaD met criteria for VaD (DSM-IV) and also fulfilled the imaging criteria for SVaD [14]. VaD patients showed at least two focal neurological signs that included corticobulbar signs (facial palsy, dysarthria, dysphagia, or pathologic laughing or crying), pyramidal signs (hemiparesis, hyperactive deep tendon reflexes, or extensor plantar responses), or parkinsonism (short step gait, festination gait, shuffling gait, decreased arm swing while walking, rigidity, bradykinesia, or postural instability). svMCI based on the following criteria: modified from those proposed by Petersen [7]: (1) subjective cognitive complaints by the patient or his/her caregiver, (2) normal general cognitive function as measured by a score on the Korean version of the Mini-Mental State Examination (MMSE) above the 16th percentile of age- and sex-matched norms, (3) normal activities of daily living (ADL) as judged by both an interview with a clinician and the standardized ADL scale, (4) objective cognitive decline below the 16th percentile of norms on standardized neuropsychological	1) Cognitive impairment/dementia 2) Cognitive impairment/dementia

			tests, (5) presence of focal neurological signs suggestive of stroke described earlier, (6) significant small-vessel ischemic changes without territory infarction on brain MRI as described below, and (7) not demented. The presence of significant ischemic changes associated with small-vessel disease was defined as WMH on T2-weighted or FLAIR images that fulfilled the following criteria: (1) periventricular WMH (caps or rim) longer than 10 mm, and (2) deep WMH consistent with extensive white matter lesion or diffusely confluent lesion ≥25 mm in maximum diameter. When defining deep white matter, hyperintensities evident in the axial slice just above the top of lateral ventricles was considered to be a periventricular white matter lesion, while hyperintensities evident in the second or more axial slices above the top of the lateral ventricles were considered to be deep white matter lesions. These imaging criteria indicate that patients had ischemia significant enough to meet at least grade 3 of Fazekas ischemia criteria.	
Sierra 2004	Hypertensive with WMH	Hospital: hypertension unit	The diagnosis of essential hypertension was considered on the basis that no known cause of high BP could be detected after complete clinical, biochemical, and radiologic examination. All patients had a systolic BP greater than or equal to 140 mm Hg or a diastolic BP greater than or equal to 90 mm Hg in at least three different measurements at 1-week intervals. The final diagnosis of WML was made by consensus. Authors distinguished between white matter hyperintensities directly adjacent to the ventricles (periventricular lesions) and punctate or confluent white matter hyperintensities at some distance from the ventricles (focal lesions). Small caps on the horns of the lateral ventricles and pencil-thin lining around the ventricles were considered normal as other investigators have previously reported. Lesions appearing as lacunar infarctions were not included in this study.	Non-clinical
Squarzoni 2017	Silent brain infarcts	Research study – community based recruitment	Infarcts were detected as low-signal-intensity lesions on the spoiled gradient echo sequence and hyperintense lesions on the T2-weighted images. Vascular lesions that were 3 to 15mm in diameter were classified as lacunae. Exclusion: dementia, depression and history of major neurological disorders (such as epilepsy and Parkinson's disease).	Non-clinical
Sudo 2013	Vascular MCI	Centre for Alzheimer Disease	Criteria for probable Vascular MCI: 1) Evidence, based on cognitive testing, of impairment of 1.5 SD below the mean on one or more cognitive tests in relation to normative values for age and schooling (AHA/ASA criteria [21]); 2) Preserved or	Cognitive impairment/dementia

		and Related Disorders	mildly impaired functional activities, as established with functional activities questionnaire <5; 3) Evidence of small-vessel disease, indicated by modified Fazekas scale ≥2; 4) Absence of hippocampal atrophy suggestive of neurodegenerative disease, as defined by de Leon score ≤1.	
Sun 2014	Mild WMH	Research Study - community based recruitment	Exclusion: structural abnormalities, e.g. tumours, subdural hematomas, or contusions due to previous head trauma; had no history of addiction, neurologic or psychiatric diseases; had no conditions known to influence cerebral function, including alcoholism, current depression, Parkinson's disease, or epilepsy; and had no large vessel disease such as cortical or subcortical infarcts and watershed infarcts.	Non-clinical
Tupler 1992	dWMH	Research Study - community based recruitment	Exclusion: history of any cerebral or psychiatric illness (including substance abuse), and all denied use of psychotropic medications	Non-clinical
van Swieten 1991	Hypertensive with confluent WMH	Hospital: outpatient dept.	Inclusion: diagnosis of hypertension. Exclusion: history suggesting a transient ischemic attack (TIA) or stroke, patients with alcoholism or drug abuse.	Non-clinical
van Zandvoort 2003	Lacunar infarct in brainstem	Hospital: stroke unit	Presence of the clinical symptoms of a non-disabling brainstem stroke (Rankin score = 3) was diagnosed by a senior neurologist. A lacunar infarct in the brainstem area (pons and medulla oblongata) had to be visible on a CT scan or MR image. Patients with other relevant brain abnormalities, such as disproportionate white matter abnormalities or prior ischemic lesions, were excluded.	Stroke
van Zandvoort, 2005	Supratentorial lacunar infarct	Recruitment setting unclear Patients presented with "one of the classical lacunar syndromes"	Patients presented with one of the classical lacunar syndrome. Lacunar infarcts were identified on magnetic resonance imaging (MRI) by a senior neurologist, blind for the neuropsychological and neurometabolic evaluations, and lesions ranged from 3 to 20 mm in diameter.	Stroke
Villeneuve 2011	MCI with confluent WMH	No information	MCI met the following criteria: (a) subjective complaint, preferably corroborated by an informant; (b) performance 1.5 standard deviations (SD) below the mean adjusted for age and education on at least one cognitive domain based on the neuropsychological assessment described above; (c) essentially preserved activities of daily living as measured with the functional autonomy measurement system and	Cognitive impairment/dementia

			by means of a clinical interview with patients and proxies; and (d) no dementia. Significant WMH was defined as the presence of confluence on the MR image.	
Wolfe 1990	Multiple lacunar infarcts	Hospital: neurovascular department	Selected patients with clinical presentation suggesting multiple lacunar strokes (with or without a diagnosis of dementia). Those with cortical infarction were excluded.	Stroke
Wong 2007	Stroke associated with SVD	Hospital: stroke unit	All patients had one or more small subcortical infarcts relevant to the clinical stroke symptom(s) as determined by a board-certified neurologist. Small subcortical infarct was defined as a well-circumscribed hyperintense lesion on T2- weighted signal with a corresponding hypointense signal on T1-weighted sequence of size between 0.2 and 2cm in all dimensions that was located in the subcortical white and grey matter and the cerebellar white matter. We excluded patients with relevant small infarcts that were associated with relevant intracranial large artery disease as detected by Transcranial Doppler (TCD) or Magnetic Resonance Angiography (MRA), extracranial carotid artery stenosis by Carotid Duplex (CD), cardiac embolic sources, and other miscellaneous causes. Patients were presumed to have cardiac embolic sources if they had concurrent presence or past history of atrial fibrillation (AF), sick sinus syndrome, metallic heart valves, acute congestive failure, recent (≤6 weeks before stroke) myocardial infarction, atrial myxoma, or patent foramen ovale. Patients were considered to have miscellaneous causes if they had the following diseases: inflammatory disorders (for example, systemic lupus erythematosus), carotid or vertebral artery dissection as suggested by history and vascular neuroimaging, recreational drug misuse (for example, cocaine), or haematological disorders (for example, thrombocytosis). Other exclusion criteria were: (a) cortical or large subcortical (>2 cm) infarcts; (b) intracerebral haemorrhage; (c) clinical signs that could not be explained by the small infarct; (d) normal imaging; (e) non-ischaemic lesions, for example, tumour or demyelination; (f) presence of relevant small infarcts but with unknown vascular aetiology because of absence of MRA, transcranial sonographic temporal window, or default imaging appointment; (g) known pre-existing dementing illnesses that were not due to Alzheimer's disease or vascular dementia, for example, chronic alcoholism; (h) major depression according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition; 18 and (i) communication	Stroke

			problems hindering participation in cognitive assessment, such as a language barrier, or severe visual or hearing loss. Patients with post-stroke aphasia were not excluded from the study. A qualified psychiatrist excluded major depression 3 months after stroke.	
Yamauchi 2000	Lacunar infarct	Hospital – undergoing MRI to rule out CVD due to presenting with neurological symptoms	Inclusion criteria were as follows: (1) patients with a history of lacunar stroke, a clinical presentation consistent with one of the classic lacunar syndromes described by Fisher, and MRI evidence of lacunar infarcts that appeared responsible for symptoms; or (2) patients who underwent MRI because of headache or dizziness and showed normal neurological findings and no specific neurological diseases other than tension-type headache, irrespective of MRI evidence of lacunar infarcts or any degree of WMLs. Exclusion criteria were as follows: (3) cortical infarct on MRI; (4) strategically located lacunar infarcts causing dementia: infarcts in the genu of the internal capsule, thalamus, and caudate nucleus; (5) significant stenosis of the cervical or intracranial arteries on MR angiography; and (6) complications of other neurological or psychiatric disorders, including alcohol abuse and depression. A lacunar infarct was identified as an increased signal intensity on both proton-weighted and T2-weighted images with decreased signal intensity on T1-weighted images. No patients showed lesions with a diameter of >1.5 cm	Stroke
Yang 2015*	Vascular MCI	MCI clinic	Inclusion: Complaints about acquired cognitive impairment; neuropsychological tests suggest mild impairment of overall cognitive function, failing to meet diagnostic criteria for dementia; MRI suggesting white matter ischemic lesions; Fazekas: 1-4; Exclusion: Lacunar infarct or obvious brain atrophy; cortical or subcortical mixed lesions, cognitive impairment caused by other causes; severe organ disease, systemic disease or mental illness without drug control	Cognitive impairment/dementia
Yang 2016*	Lacunar infarct	Hospital: neurology department outpatients and hospitalised patients	Lacunar infarct according to TOAST criteria [2] - lesion diameter ≤1.5mm. Inclusion: Corresponding symptoms of ischemic stroke with 24 hours, MRI: Exclusion: Carotid and intracranial stenosis was confirmed by cervical vascular ultrasound, TCD, CTA, MRA, DSA, etc. > 50%, Severe one or more visceral insufficiency, other reasons for cognitive impairment, taking medicine that impairs cognition, severe mental illness.	Stroke
Yi 2012	Subcortical vascular MCI	Hospital: neurology department	The diagnosis of subcortical vascular MCI (svMCI) was performed by two experienced neurologists in consensus according to criteria [9,11,22,23] that included the following: 1) subjective cognitive complaints reported by the	Cognitive impairment/dementia

			participant or his/her caregiver; 2) objective cognitive impairments, although not meeting the DSM-IV criteria for dementia; 3) normal or near-normal performance of general cognitive functioning and no or minimum impairments of daily life activities; 4) a Clinical Dementia Rating Scale (CDR) score = 0.5; 5) a Mini-Mental State Examination (MMSE) score ≥24; and 6) subcortical vascular causes of the cognitive impairments according to a) moderate to severe white matter hyperintensity in at least one region with a Wahlund rating scale score >2. and/or multiple lacunar infarcts in the periventricular and deep WM structures (Wahlund rating scale score ≥ 2; diameter, 15 mm) on T2-weighted or FLAIR images, and b) evident neurological signs of hemiparesis, lower facial weakness, Babinski sign, dysarthria, sensory deficit, gait disorder, urgent urination or motor slowness that were assessed by general and neurological examination or reported by the participant or his/her caregiver.	
Yu 2019	Extensive subcortical ischaemic vascular disease	Stroke prevention clinic	Inclusion criteria: at least moderate WMH, defined as periventricular WMH extending at least 5 mm from the ventricular border consistent with Fazekas Periventricular score ≥2, or ≥4 focal lesions ≥5mm in diameter, was recruited within 3 months of a transient ischemic attack without residual physical symptoms. Participants who had other neurological disorders, cortical infarcts, or cortical hyperintensities (i.e. > 3 cortical hyperintense foci, or any cortical lesion >3mm in diameter) visible on 3.0 T MRI were excluded from each group. Participants with Alzheimer's disease or cortical stroke were excluded. Possible participants with any unstable medical condition or history of neurological or psychiatric disorder, beyond mild depressive symptoms, were excluded.	Stroke
Yuan 2012*	Leukoaraiosis	Hospital: neurology department	Inclusion: ≥60 years; head MRI confirmed the presence of varying degrees of white matter lesions; no disability according to instrumental activities of daily living scale; Exclusion: Severe medical diseases such as heart, liver, renal failure, tumour, or other systemic diseases of the whole body; severe neurological diseases such as non-vascular diseases induced by white matter lesions (immunization, demyelinations, metabolism, poisoning, infection etc.; tumour, stroke, Parkinson's disease, brain trauma etc.; severe neuropsychological diseases mental illness and uncontrolled administration of drugs within 24hours affecting cognition; MRI contraindications.	Non-clinical

Yuan 2017	Leukoaraiosis	Hospital: neurology department	Leukoaraiosis was defined as diffuse or confluent white matter hyperintensity (WMHs) in the periventricular or subcortical white matter observed on T2-weighted MRI or FLAIR. Inclusion: (1) age ≥ 60; (2) changes of cerebral subcortical white matter on MRI of any degree; (3) no disability as assessed by the Instrumental Activities of Daily Living scale. Exclusion: (1) severe illnesses (e.g., cardiac, hepatic or renal failure, cancer, or other relevant systemic diseases); (2) severe unrelated neurological diseases (e.g., any cause of stroke, former history of stroke, cerebral vascular malformations, intracranial space-occupying lesion, former brain injury, Parkinson's disease, epilepsy, dementia, or substance dependency); (3) leukoencephalopathy of nonvascular origin (immunological demyelinating, metabolic, toxic, infectious, other); (4) severe psychiatric disorders and subjects who had taken any drugs that might influence cognitive function; (5) conventional contraindications to undergo MRI scanning; and (6) inability or refusal to undergo brain MRI.	Non-clinical
Yuspeh 2002	Subcortical ischaemic VaD	Memory clinic	NINDS/AIREN criteria for Subcortical ischaemic vascular dementia (SVAD) [8]. Inclusion: Diagnosis of SVaD. SVaD subjects had neuroimaging data that revealed extensive WMLs, with no indication of cortical lesions.	Cognitive impairment/dementia
Zhang 2019a	SVD - made up of 44 lacunar stroke patients and 36 mild vascular cognitive impairment (mVCI) patients	Hospital: stroke unit	We defined lacunar stroke as an acute stroke syndrome with a compatible recent small subcortical infarct on clinical brain MRI. In cases in which no lesion was detected on MRI, we used established clinical criteria for lacunar syndrome [16,24]. Patients with mVCI due to presumed SVD we recruited from the outpatient clinic of the Department of Neurology and from the Memory Clinic of the Maastricht University Medical Centre, and Zuyderland Medical Centre. Criteria of mVCI consisted of (1) subjective complaints of cognitive functioning, (2) objective cognitive impairment in at least one cognitive domain at neuropsychological testing, (3) a Clinical Dementia Rating of ≤1 and a Mini Mental State Examination score of ≥20, and (4) vascular lesions on clinical brain MRI that suggest a link between the cognitive deficit and SVD [21]: moderate to severe WMH (Fazekas score deep WMH >1 and/ or periventricular WMH>2), or mild WMH (Fazekas scoredeep WMH =1 and/or periventricular WMH =1–2) with lacunes and/or microbleeds [25,26].	Stroke
Zhang 2019b	Amnestic MCI with Fazekas >1	Memory clinic	aMCI according to criteria of Petersen [5].All participants had at least an elementary education and no medical treatments that might affect cognitive function, such as cholinesterase inhibitors or memantine. Exclusion criteria: (1) significant visual	Cognitive impairment/dementia

			and/or auditory impairment; (2) presence of significant medical, neurological, or psychiatric illness (e.g., severe depression based on a Beck Depression Inventory (BDI) (Zheng & Lin, 1991) score ≥16) likely to impact cognitive ability; and (3) history of alcohol or substance abuse.	
Zhao 2016*	1) Lacunar infarct 2) WMH 3) Lacunar infarct + WMH	Hospital: neurology department	Diagnosed with SVD according to reference criteria for the diagnosis of cerebral small vessel disease [14]: MRI confirmed lacunar infarction, high white matter signal, MRA and carotid colour ultrasonography to exclude intracranial macrovascular disease. Exclusion criteria: large area of cerebral infarction, cerebral haemorrhage or craniocerebral trauma, severe stenosis or occlusion in intracranial large vessels, brain atrophy or cerebellar lesions, other non-vascular factors, high white matter signal, severe disease or other cognitive dysfunction disease.	1) Stroke 2) Stroke 3) Stroke
Zhou 2009	MCI due to SVD	Cognitive impairment/stroke clinic	MCI-SVD patients were recruited according to the following criteria [10,11,27,28] (1) Subjects had cognitive impairment that did not meet the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) criteria for dementia, and they obtained a score of 0.5 on CDR with preserved ADL skills. (2) The cognitive impairment was attributed to SVD as suggested by the following criteria: (a) one or more of the following neurological signs commonly seen in SVD, such as hemiparesis, lower facial weakness, Babinski sign, sensory deficit, dysarthria, gait disorder, urine urgency, or motor slowness; and (b) moderate to severe white matter changes (at least one region scored ≥ 2 according to the Wahlund rating scale) and/or multiple lacunar infarcts (≥ 2) on brain imaging, in the absence of large subcortical infarcts (greater than 15 mm diameter) or infarcts involving in the cerebral cortex. Exclusion criteria were as follows: (1) Early onset of memory deficits and progressive worsening of memory and other cognitive functions in the absence of corresponding focal lesions on brain imaging; (2) Cognitive impairments caused by other reasons, such as Parkinson's disease, Huntington's disease, multiple sclerosis, tumor, epilepsy, psychiatric disease, systemic disease, alcohol or drug abuse, and any other neurological disease that may result in cognitive impairment; and (3) Subjects with visual abnormalities, severe aphasia or palsy as a significant limiting factor for assessment. The diagnosis was made by consensus of two neurologists.	Cognitive impairment/dementia
Zhou 2014*	1) Subcortical vascular MCI	Hospital: neurology	Diagnosed according to the criteria proposed by Román [11] and the expert consensus on Vascular Cognitive Impairment in China [29]. Of the 161 patients with	1) Cognitive impairment/dementia

	2) Subcortical vascular disease	department inpatients and outpatients	SIVD, 79 patients had subcortical vascular mild cognitive impairment identified according to the MCI diagnostic criteria of Petersen [7]: subjective cognitive impairment confirmed by informant, objective cognitive impairment, does not meet DSM for vascular dementia, CDR of 0.5, basic daily living abilities, presence of neurological symptoms, signs and neurological changes of subcortical small vessel disease. 82 patients had subcortical vascular disease, which was according to the criteria of Román [11] and Vascular dementia in the DSM-V. They had symptoms and signs of the nervous system associated with subcortical small vessel disease, such as hemiparesis, central facial paralysis, positive Babinsky sign, sensory disturbance, dysarthria, gait disorder, pharyngeal disorders and other external traits, skull MRI suggests multiple lacunar infarcts (subcortical >5) and extensive demyelination of the periventricular and deep white matter. Exclusion: cardiogenic or aortic infarction, any cortical infarction or acute lesion, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL).	2) Cognitive impairment/dementia
Zi 2014	pWMH	Health Centre – regular check up	Inclusion: age range of 50–75 years. Exclusion: No participants had the disorders that might have confounded their current cognitive state, such as metabolic encephalopathy, thyroid disease, or syphilis. No participants had current or past somatic, psychiatric, or neurological disorders that might have caused the cognitive impairment, such as stroke, schizophrenia, epilepsy, severe head trauma, encephalitis, brain tumours, alcohol abuse, severe depression, or neurodegenerative diseases such as Parkinson's disease. pWMH were evaluated with conventional structural MRI techniques, including T1-weighted, T2- weighted, and FLAIR images. Periventricular regions were defined as regions between 3 and 13 mm from the ventricular surface.	Non-clinical

Note: CDR: Clinical Dementia Rating scale; CVD: cerebrovascular disease; dWMH: deep white matter hyperintensities; pWMH: periventricular white matter hyperintensities; SVD: small vessel disease; TIA: transient ischaemic attack; TIV: total intercranial volume; WMH: white matter hyperintensities. *Non-English language publication

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Supplementary File 6: Criteria used to assess the quality of studies included in the meta-analysis

Quality assessment criteria	Points awarded	
	Yes	No
Is the recruitment setting clearly described?	1	0
Are population characteristics provided (age and sex are the minimum requirements)?	1	0
Are the inclusion/exclusion criteria clearly described?	1	0
Are the outcome measures clearly defined (e.g. are the cognitive tests named, does the paper describe what tests make up general factors)?	1	0
Are the statistical methods clearly described and appropriate?	1	0
Does the paper correct for repeated statistical testing?	1*	0
Does the paper describe how missing data were dealt with?	1	0
Did the authors conduct a power calculation?	1†	0

Note: *0.5 points awarded if the publication corrects for multiple testing in a different portion of the study

†0.5 points awarded if the publication conducts power calculations for a different portion of the study.

Supplementary File 7: Results of meta-regression models comparing cognitive effect sizes between SVD presentation categories

			Non-clinical SVD cohorts*				Stroke cohorts*				Intercept					
	Studies	Outcomes	estimate (SE)	95% CI	Degrees of freedom	Uncorrected p value	estimate (SE)	95% CI	Degrees of freedom	Uncorrected p value	estimate (SE)	95% CI	Degrees of freedom	Uncorrected p value	τ^2	I^2
Processing Speed	37	88	-0.158 (0.39)	-0.94, 0.63	22.0	0.681	-0.117 (0.34)	-0.81, 0.58	22.1	0.731	-0.791 (0.28)	-1.40, -0.18	11.0	0.016	0.7	91.7
Executive function	58	188	0.491 (0.19)	0.10, 0.88	34	0.015	0.191 (0.16)	-0.13, 0.51	34	0.229	-1.151 (0.10)	-1.36, -0.94	18.8	7.8×10^{-10}	0.4	86.3
Delayed memory	41	98	0.847 (0.21)	0.40, 1.29	12.7	0.001	0.826 (0.19)	0.44, 1.21	28.3	1.5×10^{-4}	-1.345 (0.14)	-1.64, -1.05	18.2	1.4×10^{-8}	0.3	82.1
Attention	12	19	0.717 (0.32)	-0.07, 1.51	5.7	0.068	0.558 (0.35)	-0.31, 1.43	5.71	0.166	-1.053 (0.31)	-2.08, 0.02	2.83	0.0474	0.2	75.2
Reasoning	16	25	0.260 (0.25)	-0.46, 0.98	3.81	0.366	-0.661 (0.38)	-0.92, 0.78	10.3	0.866	-0.667 (0.14)	-1.01, -0.32	5.87	0.003	0.3	78.7
Visuospatial ability	27	50	0.676 (0.17)	0.30, 1.01	10.7	0.002	0.487 (0.31)	-0.61, 0.71	15.8	0.877	-0.883 (0.11)	-1.12, -0.64	11.2	5.2×10^{-6}	0.3	75.3
Language	24	42	0.967 (0.16)	0.45, 1.48	2.93	0.010	0.372 (0.18)	-0.03, 1.48	11.9	0.067	-1.042 (0.11)	-1.29, -0.80	12.9	4.4×10^{-7}	0.2	70.0

Note: *Cohorts with a cognitive impairment/dementia are the reference group

Results in grey are from analyses which produced degrees of freedom <4, so are considered unreliable.

Supplementary File 8: Results of univariate meta-regression models testing the impact of demographic and vascular risk factors on cognitive effect sizes (continues overleaf)

	Difference in mean age between SVD and control cohorts								Difference in mean years of education between SVD and control cohorts							
	Studies	Outcomes	Estimate (SE)	95% CI	Uncorrected p value	Degrees of freedom	τ^2	I^2	Studies	Outcomes	Estimate (SE)	95% CI	Uncorrected p value	Degrees of freedom	τ^2	I^2
Processing Speed	37	88	-0.060 (0.06)	-0.21, 0.09	0.363	7.3	0.57	90.65	25	63	0.042 (0.31)	-0.72, 1.80	0.896	5.8	0.87	93.39
Executive function	58	188	0.022 (0.02)	-0.03, 0.07	0.297	9.3	0.42	87.46	38	127	-0.228 (0.07)	-0.37, -0.09	0.004	13.5	0.43	87.45
Delayed memory	41	98	0.075 (0.03)	-0.00, 0.15	0.061	6.2	0.42	87.11	31	77	-0.159 (0.11)	-0.41, 0.09	0.191	9.5	0.65	90.21
Attention	12	19	0.043 (0.08)	-0.14, 0.23	0.590	6.2	0.25	81.14	8	13	-0.152 (0.21)	-0.79, 0.49	0.513	3.2	0.25	78.13
Reasoning	16	25	0.033 (0.06)	-0.11, 0.18	0.618	8.2	0.24	77.82	11	20	-0.092 (0.10)	-0.52, 0.33	0.455	2.1	0.14	69.57
Visuospatial ability	27	50	0.013 (0.03)	-0.06, 0.09	0.706	6.8	0.30	77.99	19	40	-0.279 (0.08)	-0.46, -0.10	0.009	7.3	0.14	64.43
Language	24	42	0.075 (0.02)	0.00, 0.15	0.044	3.3	0.27	78.59	17	30	-0.310 (0.07)	-0.46, -0.16	0.001	8.6	0.15	68.09

Note: Results in grey are from analyses which produced degrees of freedom <4, so are considered unreliable.

Continued: Supplementary File

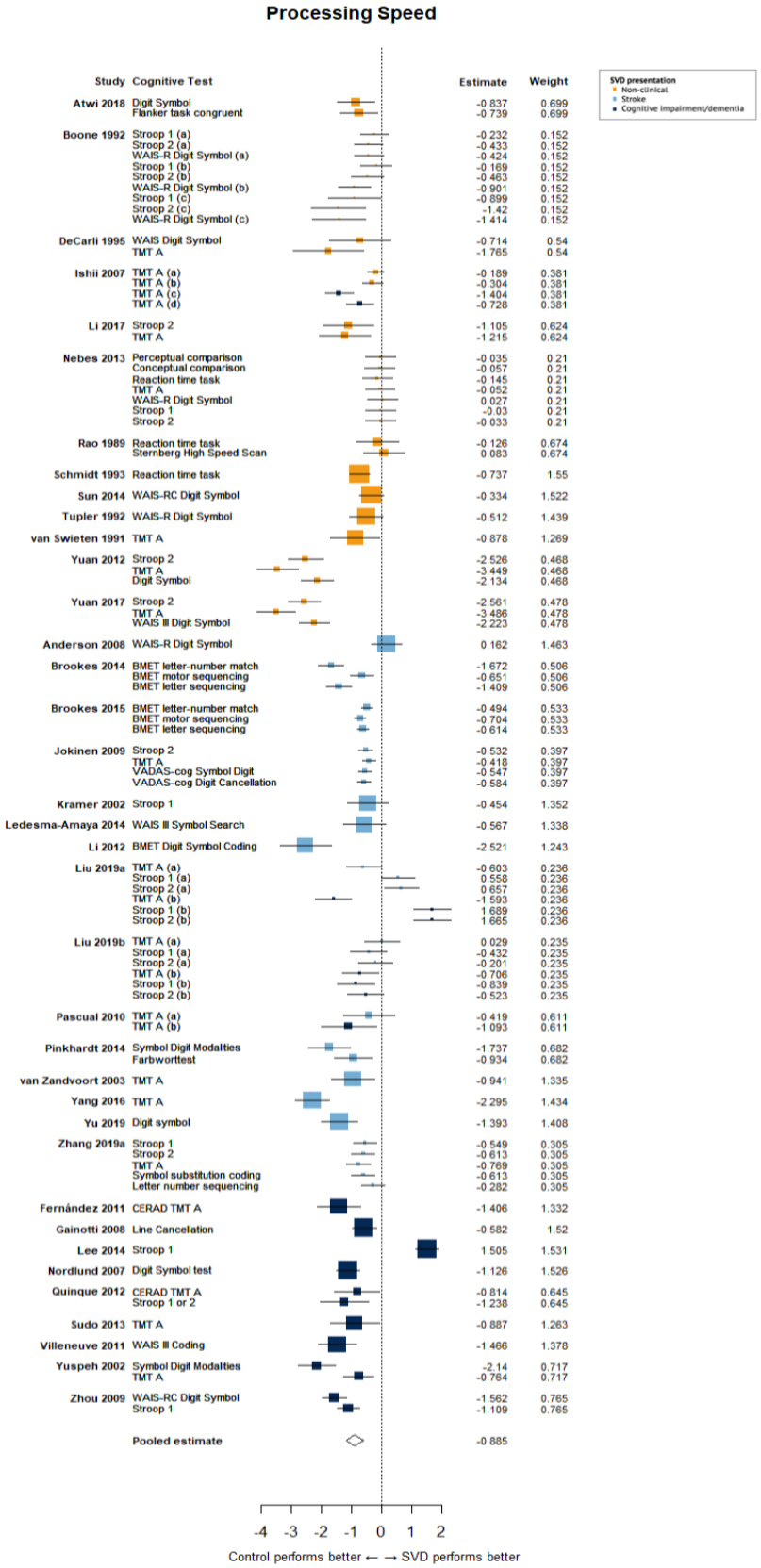
	Difference in % hypertension between SVD and control cohorts								Difference in % diabetes between SVD and control cohorts							
	Studies	Outcomes	Estimate (SE)	95% CI	Uncorrected p value	Degrees of freedom	τ^2	I^2	Studies	Outcomes	Estimate (SE)	95% CI	Uncorrected p value	Degrees of freedom	τ^2	I^2
Processing Speed	17	43	-0.012 (0.01)	-0.04, 0.01	0.246	4.7	0.93	94.97	15	39	0.005 (0.02)	-0.05, 0.06	0.082	3.2	0.86	95.58
Executive function	31	95	0.003 (0.004)	-0.01, 0.01	0.530	7.4	0.51	91.16	28	87	-0.003 (0.01)	4.84	-0.02, 0.01	0.564	0.45	91.32
Delayed memory	18	39	0.005 (0.01)	-0.01, 0.02	0.492	6.6	0.39	88.61	15	33	-0.004 (0.01)	-0.02, 0.02	0.638	3.1	0.41	90.58
Attention	4	8	0.008 (0.03)	-0.11, 0.13	0.819	2.1	0.57	93.19	5	9	-0.021 (0.03)	-0.15, 0.11	0.526	1.8	0.29	89.17
Reasoning	4	7	0.008 (0.01)	-0.07, 0.08	0.441	1.0	0.33	81.61	4	7	0.016 (0.00)	-0.00, 0.03	0.054	1.8	0.25	77.96
Visuospatial ability	7	11	0.004 (0.01)	-0.03, 0.04	0.711	3.1	0.44	85.04	6	10	0.004 (0.01)	-0.02, 0.03	0.559	1.7	0.45	87.98
Language	8	16	0.018 (0.01)	-0.01, 0.04	0.093	1.9	0.53	91.30	8	16	-0.005 (0.02)	-0.07, 0.06	0.816	2.9	0.70	93.21

Note: Results in grey are from analyses which produced degrees of freedom <4, so are considered unreliable.

Supplementary File 9: Results of meta-analyses for each cognitive domain excluding studies with quality score <5

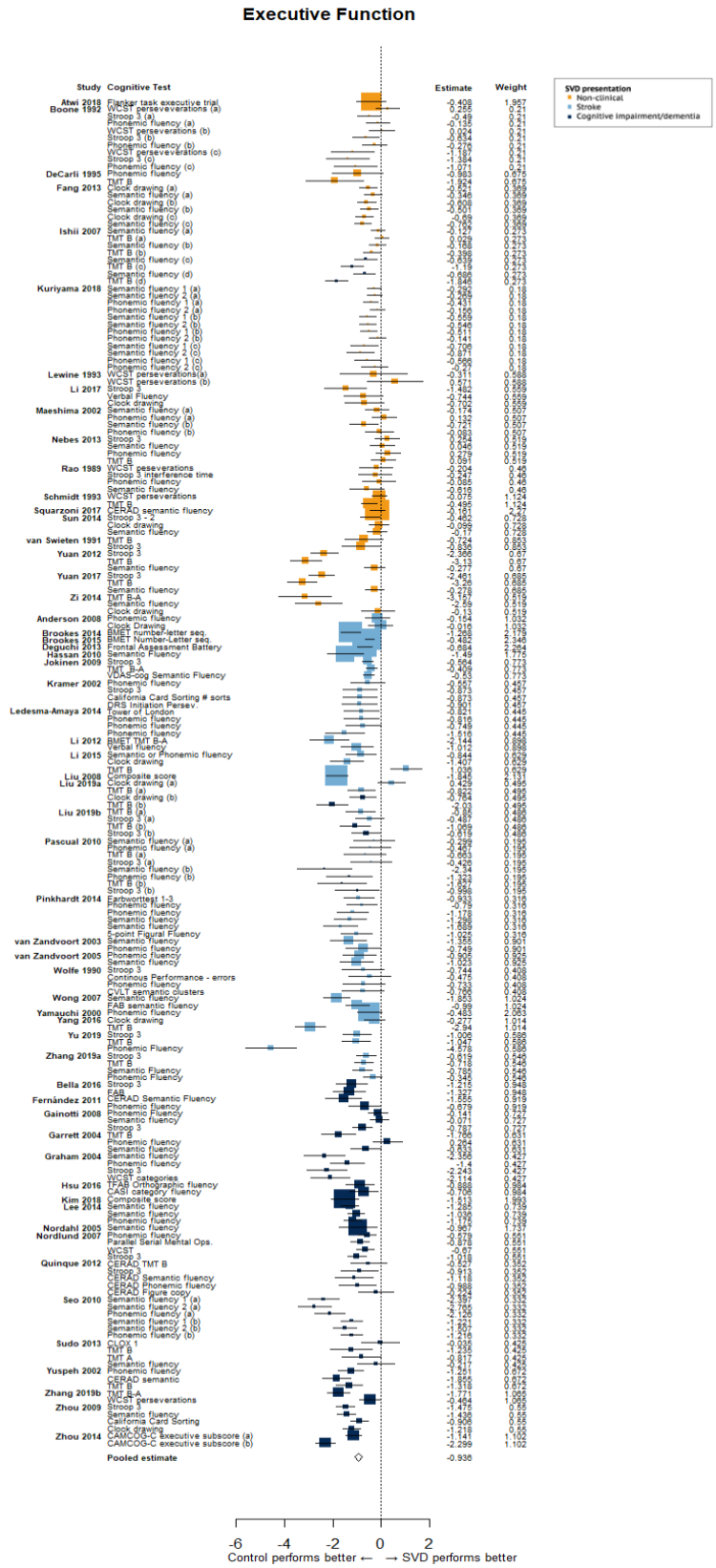
							Heterogeneity	
	Studies	Outcomes	Estimate (SE)	95% CI	Degrees of Freedom	Uncorrected p value	τ^2	I^2
Processing Speed	25	53	-0.860 (0.19)	-1.25, -0.47	23.9	$1.4x10^{-4}$	0.75	93.21
Executive function	40	122	-0.955 (0.09)	-1.14, -0.77	38.4	$1.8x10^{-12}$	0.38	87.26
Delayed memory	31	79	-0.941 (0.13)	-1.20, -0.68	29.8	$2.7x10^{-8}$	0.53	90.23
Attention	7	12	-0.637 (0.19)	-1.10, -0.17	5.75	0.016	0.19	75.70
Reasoning	12	20	-0.657 (0.18)	-1.06, -0.25	10.8	0.005	0.27	80.83
Visuospatial ability	20	36	-0.662 (0.13)	-0.94, -0.39	18.5	$8.3x10^{-5}$	0.27	77.07
Language	18	32	-0.828 (0.10)	-1.05, -0.61	16.7	$3.7x10^{-7}$	0.21	75.04

Supplementary Figure S1: Meta-analysis forest plot of tests of processing speed



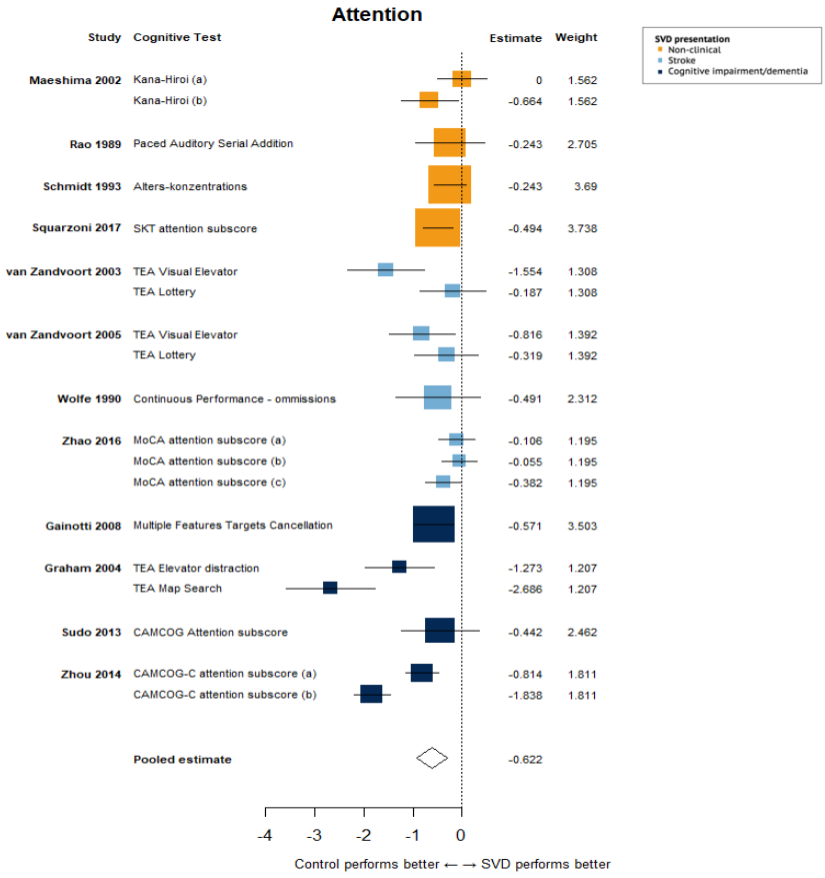
Note: The size of the squares reflects the weight given to the effect sizes. Letters in brackets indicate different SVD cohorts in a given study.

Supplementary Figure S2: Meta-analysis forest plot of tests of executive function



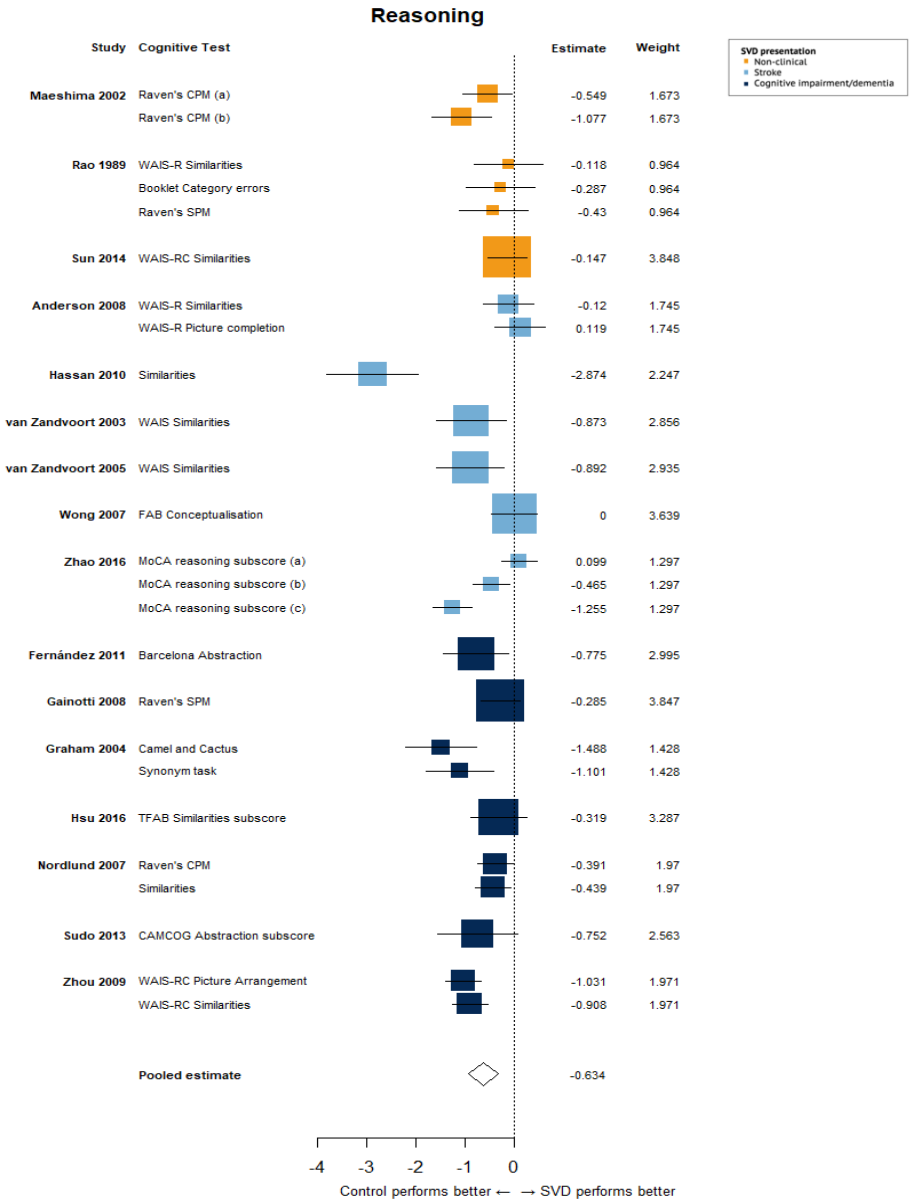
Note: The size of the squares reflects the weight given to the effect sizes. Letters in brackets indicate different SVD cohorts in a given study.

Supplementary Figure S3: Meta-analysis forest plot of tests of attention



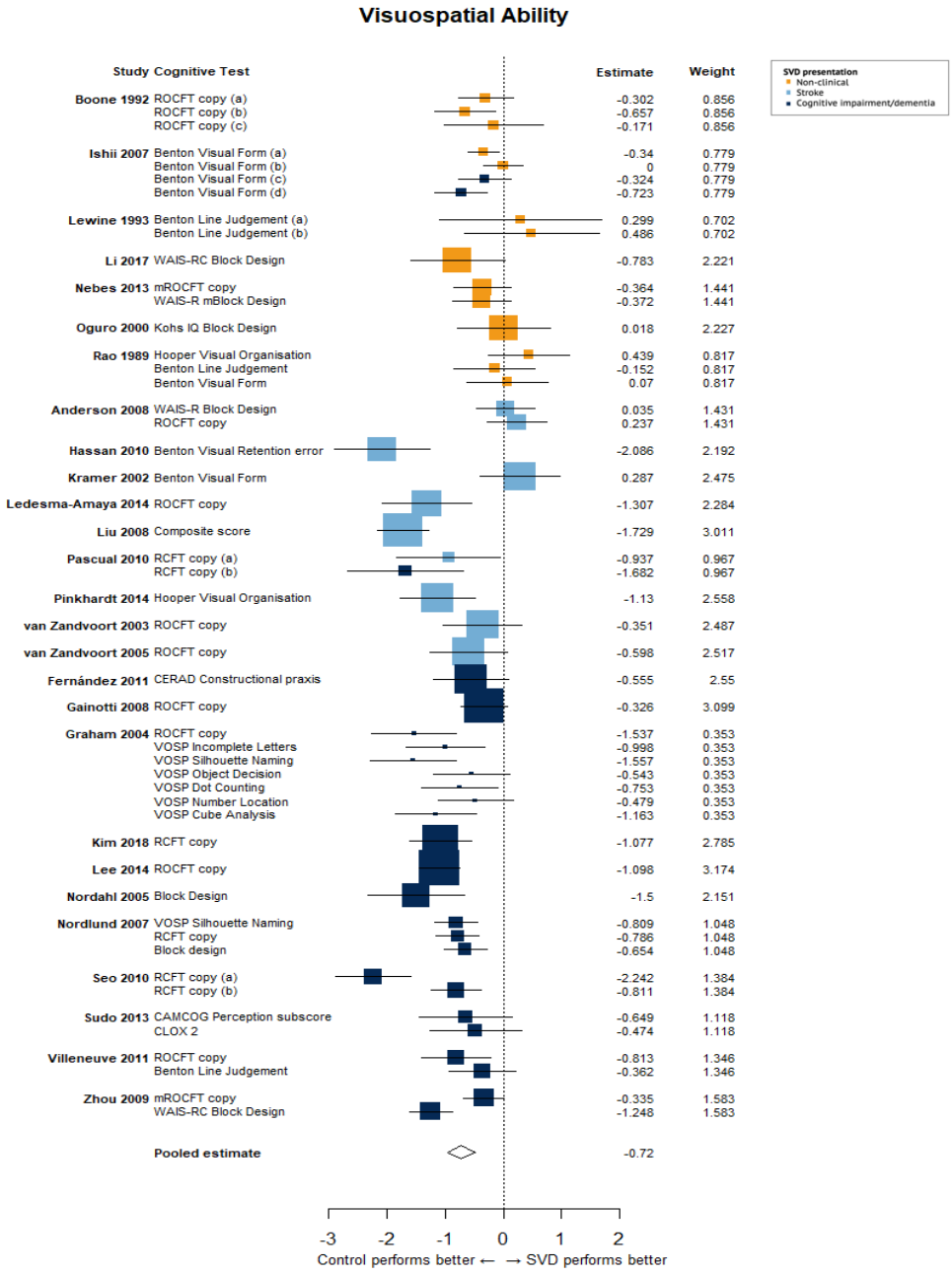
Note: The size of the squares reflects the weight given to the effect sizes. Letters in brackets indicate different SVD cohorts in a given study.

Supplementary Figure S4: Meta-analysis forest plot of tests of reasoning



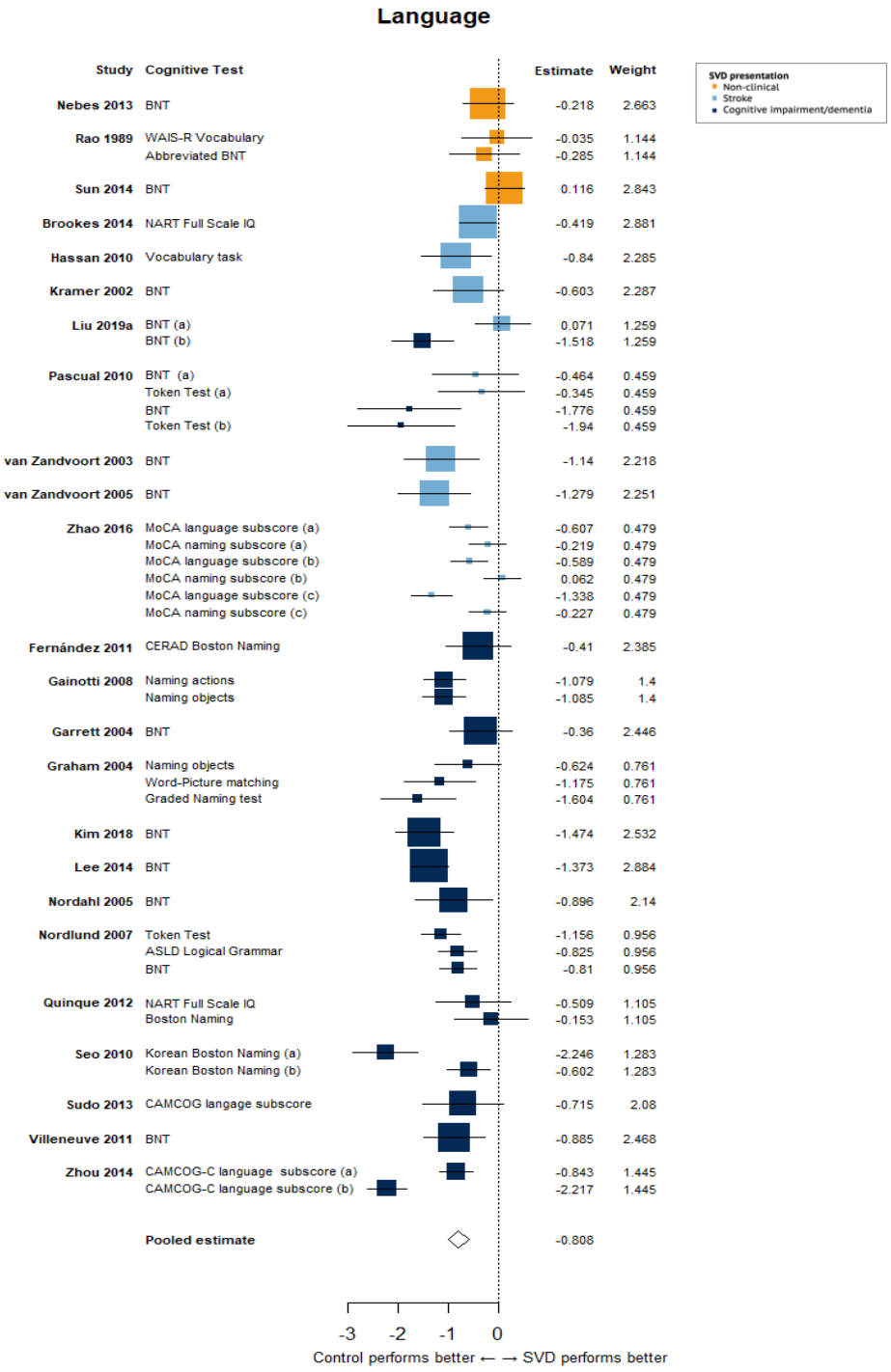
Note: The size of the squares reflects the weight given to the effect sizes. Letters in brackets indicate different SVD cohorts in a given study.

Supplementary Figure S5: Meta-analysis forest plot of tests of visuospatial ability



Note: The size of the squares reflects the weight given to the effect sizes. Letters in brackets indicate different SVD cohorts in a given study.

Supplementary Figure S6: Meta-analysis forest plot of tests of language



Note: The size of the squares reflects the weight given to the effect sizes. Letters in brackets indicate different SVD cohorts in a given study.

Appendix C: Supplementary files for Chapter 5

Associations between total MRI-visible small vessel disease burden and domain-specific cognitive abilities in a community-dwelling older-age cohort

Supplementary Tables:

Table S1: Correlation matrix (Pearson coefficients) of MRI variables contributing to the computationally-derived total SVD burden variable

Table S2: Correlation matrix (Pearson coefficients) of cognitive variables measured in older age

Table S3: Associations between the total WMH volume/TIV and cognitive factors

Table S1: Correlation matrix (Pearson coefficients) of MRI variables contributing to the computationally-derived total SVD burden variable

	WMH/TIV	Computational PVS count	Lacunes (present/absent)	Microbleeds (present/absent)
WMH/TIV	-			
Computational PVS count	0.16	-		
Lacunes (present/absent)	0.21	0.06	-	
Microbleeds (present/absent)	0.16	0.10	0.09	-

Table S2: Correlation matrix (Pearson coefficients) of cognitive variables measured in older age

	Symbol Search	Digit Symbol	Choice Reaction Time	Inspection Time	Verbal Paired Associates	Logical Memory	Backwards Digit Span	Matrix Reasoning	Block Design	Spatial Span
Symbol Search	-									
Digit Symbol	0.64	-								
Choice Reaction Time	0.49	0.52	-							
Inspection Time	0.35	0.42	0.40	-						
Verbal Paired Associates	0.25	0.29	0.20	0.22	-					
Logical Memory	0.29	0.33	0.23	0.18	0.53	-				
Backwards Digit Span	0.32	0.34	0.21	0.22	0.27	0.31	-			
Matrix Reasoning	0.37	0.35	0.22	0.28	0.34	0.34	0.32	-		
Block Design	0.46	0.41	0.26	0.29	0.28	0.27	0.26	0.53	-	
Spatial Span	0.37	0.30	0.29	0.28	0.21	0.23	0.34	0.39	0.47	-

Table S3: Associations between the total WMH volume/TIV and cognitive factors (note for Table S3 is overleaf)

	Standardised β (SE)	95% CI	Uncorrected p value	FDR corrected p value	X^2	RMSEA	CFI	TLI	SRMR
General cognitive ability	-0.272 (0.05)	-0.334, -0.154	<0.001	<0.001	0.000	0.06	0.953	0.933	0.038
+ age	-0.224 (0.05)	-0.315, -0.133	<0.001	<0.001	0.000	0.053	0.955	0.938	0.036
+ age + sex	-0.229 (0.05)	-0.320, -0.139	<0.001	<0.001	0.000	0.077	0.890	0.858	0.053
+ age + sex + vascular risk	-0.222 (0.05)	-0.313, -0.132	<0.001	<0.001	0.000	0.076	0.873	0.841	0.055
+ age + sex + vascular risk + depression	-0.220 (0.05)	-0.309, -0.131	<0.001	<0.001	0.000	0.071	0.875	0.848	0.053
+ age + sex + vascular risk + depression + age-11 IQ	-0.190 (0.04)	-0.265, -0.114	<0.001	<0.001	0.000	0.074	0.865	0.839	0.055
Processing speed	-0.239 (0.05)	-0.328, -0.150	<0.001	<0.001	0.010	0.061	0.985	0.969	0.027
+ age	-0.221 (0.05)	-0.310, -0.131	<0.001	<0.001	0.057	0.041	0.989	0.981	0.022
+ age + sex	-0.232 (0.05)	-0.319, -0.144	<0.001	<0.001	0.000	0.074	0.944	0.923	0.044
+ age + sex + vascular risk	-0.225 (0.05)	-0.313, -0.137	<0.001	<0.001	0.000	0.087	0.899	0.869	0.053
+ age + sex + vascular risk + depression	-0.221 (0.04)	-0.307, -0.135	<0.001	<0.001	0.000	0.076	0.907	0.885	0.048
+ age + sex + vascular risk + depression + age-11 IQ	-0.201 (0.04)	-0.280, -0.123	<0.001	<0.001	0.000	0.078	0.901	0.882	0.048
Verbal memory	-0.158 (0.05)	-0.257, -0.058	0.002	0.003	0.497	0.000	1.000	1.000	0.011
+ age	-0.152 (0.05)	-0.254, -0.051	0.003	0.004	0.211	0.029	0.992	0.983	0.017
+ age + sex	-0.176 (0.05)	-0.274, -0.077	<0.001	<0.001	0.011	0.052	0.954	0.931	0.032
+ age + sex + vascular risk	-0.175 (0.05)	-0.274, -0.076	0.001	0.002	0.000	0.088	0.823	0.758	0.052
+ age + sex + vascular risk + depression	-0.174 (0.05)	-0.272, -0.076	0.001	0.002	0.000	0.078	0.825	0.775	0.048
+ age + sex + vascular risk + depression + age-11 IQ	-0.141 (0.05)	-0.230, -0.052	0.002	0.003	0.000	0.086	0.835	0.796	0.049
Visuospatial ability	-0.159 (0.05)	-0.256, -0.063	0.001	0.002	0.400	0.000	1.000	1.000	0.012
+ age	-0.142 (0.05)	-0.239, -0.045	0.004	0.005	0.599	0.000	1.000	1.000	0.012
+ age + sex	-0.126 (0.05)	-0.223, -0.029	0.011	0.013	0.342	0.015	0.997	0.996	0.025
+ age + sex + vascular risk	-0.121 (0.05)	-0.218, -0.024	0.015	0.016	0.000	0.076	0.902	0.866	0.049
+ age + sex + vascular risk + depression	-0.117 (0.05)	-0.213, -0.022	0.016	0.017	0.000	0.067	0.905	0.878	0.044
+ age + sex + vascular risk + depression + age-11 IQ	-0.099 (0.04)	-0.183, -0.014	0.022	0.022	0.000	0.065	0.922	0.904	0.044

Note for table S3. N=536 for all analyses. CFI: Comparative Fit Index; RMSEA: Root Mean Square Approximation; SRMR: Standardized Root Mean Square Residual; TIV: total intracranial index; TLI: Tucker Lewis Index; WMH: white matter hyperintensities. After the inclusion of sex as a covariate in the models for general cognitive ability, processing speed and verbal memory, the TLI and/or CFI fell below conventional thresholds (both >0.95). Off-diagonal values of the residual correlation matrix indicated that there were correlations between sex and the residuals of several manifest cognitive variables, which were unaccounted for in our model. When we specified regressions between sex and these residuals, the TLI and CFI reached acceptable levels. Combined with the good fit of our initial measurement models, this indicates that the lower CFI and TLI values of these models are due to unspecified correlations between sex and cognitive variables and are not due to model mis-specification. Model estimator was Maximum Likelihood, therefore X^2 is also included as a measure of model fit.

Appendix D: Supplementary files for Chapter 6

Cerebral Small Vessel Disease Burden and Longitudinal Cognitive Decline from age 73 to 82: the Lothian Birth Cohort 1936

Supplementary Tables

Table S1: Baseline characteristics of study completers vs. participants lost to follow-up

Table S2: Unstandardised means and variances for the intercept and slope of each cognitive

Table S3: Results of factor-of-curves models of associations between total SVD burden and intercepts of latent cognitive variables

Table S4: Results of bifactor models of associations between total SVD burden and intercepts of latent cognitive variables

Table S5: Results of FoC models of associations between WMH volume/TIV and intercepts and slopes of latent cognitive variables between the ages of 73 and 82

Table S6: Fit indices for models presented in Table S5.

Table S1: Baseline characteristics of study completers vs. participants lost to follow-up

	n	Completers	n	Non-completers	*p*-value
Sociodemographic					
Age, years	300	72.5 (0.7)	240	72.5 (0.7)	0.538
Female, n (%)	300	147 (49.0%)	240	105 (43.8%)	0.224
Education, years	300	11.0 (1.2)	240	10.7 (1.1)	0.014
Vascular risk					
Hypertension history, n (%)	300	135 (45.0%)	240	124 (51.7%)	0.123
Systolic blood pressure	297	145.6 (18.0)	237	147.5 (18.1)	0.229
Diastolic blood pressure	297	79.4 (9.2)	237	80.1 (9.5)	0.373
Diabetes history, n (%)	300	20 (6.7%)	240	34 (14.2%)	0.004
HbA1c mmol/mol	290	38.8 (5.8)	228	39.3 (7.1)	0.403
Cholesterol, mmol/l	291	5.3 (1.1)	230	5.1 (1.2)	0.043
Cardiovascular disease history, n (%)	300	83 (27.7%)	240	71 (29.6%)	0.624
Smoking status, n (%)	300	Ever=141 (47.0%) Never=159 (55.0%)	240	Ever=133 (55.4%) Never=107 (44.6%)	0.052
Cognitive					
Moray House Test age 11 (max 76)	283	51.2 (11.5)	228	49.1 (12.3)	0.046
Neuroimaging					
Total WMH volume cm^3	298	10.47 (11.3)	239	14.40 (14.3)	0.004
Total brain volume cm^3	300	991.9 (87.2)	236	995.9 (90.1)	0.612
Lacunes, n (%)	300	Present=13 (4.3%) Absent=287 (95.7%)	240	Present=15 (6.25%) Absent=225 (93.75%)	0.318
Microbleeds, n (%)	300	Present=33 (11.0%) Absent=267 (89.0%)	240	Present=32 (13.3%) Absent=208 (86.7%)	0.408

Note for Table S1: Values are mean (standard deviation) unless otherwise specified. WMH: white matter hyperintensities of presumed vascular origin. Statistical comparisons performed using t-test for continuous variables and chi-squared test for binary variables. Total WMH volume was log transformed prior to statistical comparison due to right-sided skew.

Table S2: Unstandardised means and variances for the intercept and slope of each cognitive domain[a]

	Intercepts		Slopes			Fit indices				
	Mean (SE)	Variance (SE)	Mean (SE)	Variance (SE)	SD change/year	X^2	RMSEA	CFI	TLI	SRMR
General cognitive ability	28.60 (0.26)***	18.91 (1.99)***	-0.558 (0.03)***	0.140 (0.02)***	-0.128	0.000	0.039	0.950	0.948	0.065
Processing speed	55.959 (0.25)***	7.990 (1.32)***	-0.452 (0.04)***	0.140 (0.03)***	-0.160	0.000	0.051	0.968	0.966	0.065
Memory	27.188 (0.41)***	42.821 (6.33)***	-0.035 (0.05)***	0.540 (0.08)***	-0.005	0.001	0.035	0.988	0.987	0.029
Visuospatial ability	17.365 (0.21)***	13.754 (1.47)***	-0.303 (0.020)***	0.028 (0.013)*	-0.082	0.245	0.015	0.998	0.997	0.036

Note for Table S2: Slopes represent change from age 73 to age 82. SD: standard deviation; SE: standard error. SD change per year calculated by dividing the slope mean by the intercept standard deviation. All p-values are uncorrected. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

[a] Note that the cognitive domains will contain any variance due to general cognitive ability.

Table S3: Results of factor-of-curves models of associations between total SVD burden and intercepts of latent cognitive variables[a]

	Intercept			
	Standardised β (SE)	95% CI	Uncorrected p value	FDR-corrected p value[b]
General cognitive ability	-0.377 (0.08)	-0.531, -0.224	<0.001	<0.001
+ age + sex	-0.346 (0.08)	-0.511, -0.182	<0.001	<0.001
+ age + sex + vascular risk	-0.334 (0.08)	-0.495, -0.174	<0.001	<0.001
+ age + sex + vascular risk + age-11 IQ	-0.299 (0.08)	-0.447, -0.151	<0.001	<0.001
Processing speed	-0.402 (0.08)	-0.562, -0.243	<0.001	<0.001
+ age + sex	-0.364 (0.09)	-0.534, -0.193	<0.001	<0.001
+ age + sex + vascular risk	-0.351 (0.09)	-0.518, -0.183	<0.001	<0.001
+ age + sex + vascular risk + age-11 IQ	-0.322 (0.08)	-0.481, -0.164	<0.001	<0.001
Verbal memory	-0.280 (0.09)	-0.447, -0.113	0.001	0.003
+ age + sex	-0.280 (0.08)	-0.441, -0.118	0.001	0.003
+ age + sex + vascular risk	-0.278 (0.08)	-0.440, -0.117	0.001	0.003
+ age + sex + vascular risk + age-11 IQ	-0.225 (0.08)	-0.383, -0.068	0.005	0.012
Visuospatial ability	-0.240 (0.08)	-0.393, -0.086	0.002	0.005
+ age + sex	-0.220 (0.08)	-0.379, -0.062	0.007	0.016
+ age + sex + vascular risk	-0.209 (0.08)	-0.364, -0.055	0.008	0.017
+ age + sex + vascular risk + age-11 IQ	-0.173 (0.07)	-0.311, -0.036	0.014	0.022

Note for Table S3: Four separate models were run for each cognitive factor, including covariates in a stepwise manner. Likelihood ratio test statistic (LR) and degrees of freedom (DF) for each of the unadjusted models were as follows: General cognitive ability (LR=6.79; DF=30), processing speed (LR=0.22; DF=2), verbal memory (LR=2.95; DF=1), visuospatial ability (LR=1.54; DF=2). CI: confidence interval; FDR: false discovery rate; SE: standard error. [a] Note that the cognitive domains will contain any variance due to general cognitive ability. [b]FDR correction was conducted across results presented in this table and in Table 3.

Table S4: Results of bifactor models of associations between total SVD burden and intercepts of latent cognitive variables

	Intercept			
	Standardised β (SE)	95% CI	Uncorrected p value	FDR-corrected p value[a]
General cognitive ability	-0.277 (0.13)	-0.528, -0.026	0.030	0.178
+ age + sex	-0.230 (0.11)	-0.452, -0.009	0.042	0.178
+ age + sex + vascular risk	-0.225 (0.12)	-0.450, 0.000	0.050	0.178
+ age + sex + vascular risk + age-11 IQ	-0.185 (0.11)	-0.408, 0.038	0.103	0.275
Processing speed	-0.304 (0.15)	-0.603, -0.006	0.045	0.178
+ age + sex	-0.250 (0.13)	-0.498, -0.001	0.049	0.178
+ age + sex + vascular risk	-0.239 (0.13)	-0.489, 0.011	0.061	0.195
+ age + sex + vascular risk + age-11 IQ	-0.241 (0.13)	-0.501, 0.020	0.070	0.204
Verbal memory	-0.115 (0.12)	-0.341, 0.111	0.318	0.678
+ age + sex	-0.111 (0.10)	-0.303, 0.081	0.258	0.590
+ age + sex + vascular risk	-0.119 (0.10)	-0.313, 0.075	0.231	0.569
+ age + sex + vascular risk + age-11 IQ	-0.093 (0.10)	-0.294, 0.108	0.366	0.732
Visuospatial ability	0.008 (0.14)	-0.256, 0.272	0.954	0.982
+ age + sex	-0.017 (0.16)	-0.320, 0.286	0.912	0.982
+ age + sex + vascular risk	-0.004 (0.16)	-0.306, 0.299	0.982	0.982
+ age + sex + vascular risk + age-11 IQ	0.015 (0.16)	-0.293, 0.322	0.926	0.982

Note for Table S4: Each bifactor model estimates associations between SVD burden and the four cognitive variables simultaneously. Four bifactor models, one without covariates and three further models, including covariates in a stepwise manner. Likelihood ratio test statistic (LR) and degrees of freedom (DF) for the unadjusted model was as follows: LR=55.3; DF=9. CI: confidence interval; FDR: false discovery rate; SE: standard error. [a]FDR correction was conducted across results presented in this table and in Table 4.

Table S5: Results of FoC models of associations between WMH volume/TIV and intercepts and slopes of latent cognitive variables between the ages of 73 and 82[a]

	Intercept				Slope			
	Standardised β (SE)	95% CI	Uncorrected p value	FDR-corrected p value	Standardised β (SE)	95% CI	Uncorrected p value	FDR-corrected p value
General cognitive ability	-0.226 (0.05)	-0.323, -0.129	<0.001	<0.001	-0.127 (0.06)	-0.244, -0.009	0.035	0.047
+ age + sex	-0.222 (0.05)	-0.312, -0.133	<0.001	<0.001	-0.149 (0.06)	-0.257, -0.040	0.007	0.012
+ age + sex + vascular risk	-0.216 (0.04)	-0.303, -0.130	<0.001	<0.001	-0.148 (0.06)	-0.256, -0.039	0.008	0.012
+ age + sex + vascular risk + age-11 IQ	-0.194 (0.04)	-0.273, -0.115	<0.001	<0.001	-0.149 (0.06)	-0.259, -0.039	0.008	0.012
Processing speed	-0.231 (0.05)	-0.334, -0.128	<0.001	<0.001	-0.148 (0.07)	-0.277, -0.018	0.026	0.036
+ age + sex	-0.230 (0.05)	-0.320, -0.140	<0.001	<0.001	-0.177 (0.07)	-0.303, -0.050	0.006	0.012
+ age + sex + vascular risk	-0.224 (0.05)	-0.312, -0.136	<0.001	<0.001	-0.176 (0.06)	-0.301, -0.050	0.006	0.012
+ age + sex + vascular risk + age-11 IQ	-0.205 (0.04)	-0.287, -0.123	<0.001	<0.001	-0.176 (0.07)	-0.303, -0.049	0.007	0.012
Verbal memory	-0.140 (0.05)	-0.235, -0.045	0.004	0.010	-0.088 (0.08)	-0.236, 0.061	0.247	0.263
+ age + sex	-0.163 (0.05)	-0.251, -0.074	<0.001	<0.001	-0.079 (0.07)	-0.220, 0.063	0.277	0.277
+ age + sex + vascular risk	-0.162 (0.05)	-0.251, -0.073	<0.001	<0.001	-0.080 (0.07)	-0.220, 0.061	0.268	0.277
+ age + sex + vascular risk + age-11 IQ	-0.130 (0.04)	-0.216, -0.045	0.003	0.008	-0.084 (0.07)	-0.226, 0.058	0.245	0.263
Visuospatial ability	-0.161 (0.05)	-0.257, -0.066	0.001	0.003	-0.178 (0.10)	-0.366, 0.011	0.064	0.073
+ age + sex	-0.136 (0.05)	-0.232, -0.039	0.006	0.012	-0.197 (0.10)	-0.384, -0.010	0.039	0.048
+ age + sex + vascular risk	-0.130 (0.05)	-0.227, -0.033	0.008	0.012	-0.198 (0.10)	-0.386, -0.011	0.038	0.048
+ age + sex + vascular risk + age-11 IQ	-0.111 (0.05)	-0.203, -0.020	0.017	0.025	-0.190 (0.10)	-0.376, -0.004	0.046	0.055

Note for Table S5: CI: confidence interval; FDR: false discovery rate; FoC: factor-of-curves; SE: standard error; TIV: total intracranial volume; WMH: white matter hyperintensities. [a] Note that the cognitive domains will contain any variance due to general cognitive ability.

Table S6: Fit indices for models presented in Table S5

	X^2	RMSEA	CFI	TLI	SRMR
General cognitive ability	0.000	0.039	0.944	0.942	0.063
+ age + sex	0.000	0.037	0.941	0.937	0.068
+ age + sex + vascular risk	0.000	0.036	0.941	0.937	0.067
+ age + sex + vascular risk + age-11 IQ	0.000	0.037	0.938	0.933	0.066
Processing speed	0.000	0.045	0.967	0.964	0.064
+ age + sex	0.000	0.034	0.972	0.969	0.060
+ age + sex + vascular risk	0.000	0.033	0.972	0.969	0.060
+ age + sex + vascular risk + age-11 IQ	0.000	0.034	0.969	0.966	0.059
Verbal memory	0.003	0.031	0.988	0.986	0.031
+ age + sex	0.008	0.025	0.987	0.985	0.045
+ age + sex + vascular risk	0.004	0.026	0.985	0.983	0.046
+ age + sex + vascular risk + age-11 IQ	0.0017	0.026	0.983	0.981	0.047
Visuospatial ability	0.276	0.013	0.998	0.997	0.040
+ age + sex	0.119	0.017	0.994	0.993	0.081
+ age + sex + vascular risk	0.101	0.017	0.993	0.992	0.083
+ age + sex + vascular risk + age-11 IQ	0.042	0.020	0.989	0.988	0.081

Note for Table S6: CFI: comparative fit index; RMSEA: root mean square error of approximation; SRMR: standardized root mean square residual; TLI: Tucker Lewis index.