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SYSTEMATIC REVIEW

Gait and falls in cerebral small vessel disease: a systematic review and meta-analysis

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Abstract

Background: Gait impairment contributes to falls and frailty. Some studies suggest that cerebral small vessel disease (CSVD) is associated with gait impairment in the general population. We systematically reviewed and meta-analysed the literature on associations of CSVD with gait impairment and falls.
Methods: The protocol was published in PROSPERO (CRD42021246009). Searches of Medline, Cochrane and Embase databases were conducted on 30 March 2022. Cross-sectional and longitudinal studies of community-dwelling adults were included, reporting relationships between diagnosis or neuroimaging markers of CSVD and outcomes related to gait or falls. Partial correlation coefficients were calculated and pooled using a random-effects model for meta-analysis.
Results: The search retrieved 73 studies (53 cross-sectional; 20 longitudinal). Most studies reported an association between CSVD and gait impairments or falls risk: 7/7 studies on CSVD score or diagnosis, 53/67 studies on white matter hyperintensities (WMHs), 11/21 studies on lacunar infarcts, 6/15 studies on cerebral microbleeds and 1/5 studies on perivascular spaces. Meta-analysis of 13 studies found that higher WMH volume was mildly correlated with lower gait speed, in all studies ($r = -0.23$, 95% confidence interval: -0.33 to -0.14, $P < 0.0001$). However, there was significant heterogeneity between studies ($I^2 = 82.95\%$; $\text{tau}^2 = 0.02$; $Q = 79.37$, $P < 0.0001$), which was unexplained by variation in age, sex, study quality or if the study adjusted for age.
Conclusions: Findings suggest that CSVD severity is associated with gait impairment, history of falls and risk of future falls. Prevention of CSVD should be part of a comprehensive public health strategy to improve mobility and reduce risk of falls in later life.

Keywords: cerebral small vessel disease, gait, falls, neuroimaging, systematic review, older people

Key Points

- This systematic review and meta-analysis examines the literature on the associations of cerebral small vessel disease (CSVD) with gait impairment and falls.
- Neuroimaging markers of cerebral small vessel disease (CSVD) (i.e. white matter hyperintensities, lacunar infarcts, cerebral microbleeds and enlarged perivascular spaces) were found to be associated with gait impairment and falls risk.

- A meta-analysis found that higher white matter hyperintensity volume was significantly correlated with slower gait speed.
- Prevention of CSVD should be part of a comprehensive public health strategy to improve mobility and reduce risk of falls in later life.

Introduction

Cerebral small vessel diseases (CSVDs) are a group of pathologies that affect the small arteries and veins of the brain, of which arteriolosclerosis and cerebral amyloid angiopathy are the two most common forms. On neuroimaging, CSVD can manifest as white matter hyperintensities (WMHs) of presumed vascular origin, lacunar infarcts, cerebral microbleeds (CMBs), cortical superficial siderosis (cSS) and enlarged perivascular spaces (PVSs) [1, 2].

The function of complex brain networks is vulnerable to the effects of CSVD, as CSVD-related injury can affect white matter pathways, subcortical networks or the cortex itself to produce dysfunction. For example, CSVD is a major contributor to age-related cognitive decline [3]. Several studies also suggest that CSVD can impair gait and contribute to risk of falls [4]. Gait is a complex function that requires the coordinated interaction of distributed brain regions [5]. However, there have been no recent systematic reviews or meta-analyses of the association between diagnosis and neuroimaging markers of CSVD and gait impairment or falls.

This systematic review examines the associations between CSVD and gait impairment, future gait decline and risk of falls. Additionally, a meta-analysis was conducted to investigate the relationship between the most common radiological feature of CSVD, WMH volume, and the most commonly reported gait measurement, gait speed. We hypothesised that there would be an association between greater CSVD severity and impaired gait.

Methods

This review was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The protocol was published in PROSPERO (CRD42021246009). Ethics approval and informed consent were not required due to the nature of the study. Statistical code and data files are available by request to the corresponding author.

Search strategy and selection criteria

We searched Medline, Cochrane and Embase databases for relevant studies from inception to 29 March 2021 using search terms for gait (including gait metrics and assessment methods) and CSVD described in full in Supplementary Appendix A available in *Age and Ageing* online. The search was rerun on 30 March 2022, to include recent publications. Each study was reviewed by two independent reviewers for eligibility (EES and either BS or CRM). This included screening of titles, abstracts and full texts. Disagreements between reviewers were resolved via discussion.

We included studies that recruited adults (age >18 years) from the general population, or cases with the CSVD subtypes cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) or cerebral amyloid angiopathy (CAA), and reported an association between CSVD (based on radiological evidence of WMH, lacunar infarcts, CMBs, cSS or enlarged PVSs; a CSVD summary score; or a diagnosis of CADASIL or CAA) and one or more of these outcomes: quantitative gait measures (such as gait speed), gait scales (such as the Short Physical Performance Battery [SPPB]), self-report questionnaires, number of falls and risk of future falls. Included studies had to be journal articles published in the English language. We included cross-sectional studies and longitudinal studies of any duration. Clinic-based studies of patients with stroke, Alzheimer's disease, mild cognitive impairment and other central nervous system diseases such as Parkinson's disease or multiple sclerosis were excluded.

Data extraction

A predefined data extraction template was used to collect study information. This included general study characteristics (author, title, publication year, source study name, study design type [i.e. longitudinal or cross-sectional] and study duration for longitudinal studies), participant characteristics (sample size, age, female percent and inclusion/exclusion criteria), methods (CSVD definitions, neuroimaging modality used, gait analysis tools used, and gait variables measured, effect estimate and covariates), gait outcomes and falls outcomes. Because most covert brain infarcts in the general population are lacunes, we grouped infarcts not otherwise specified along with lacunar infarcts. Two reviewers (E.E.S. and either B.S. or C.R.M.) extracted data independently from articles, and any differences were resolved by consensus among the three reviewers.

Risk of bias assessment

Risk of bias was assessed by two reviewers (E.E.S. and either B.S. or C.R.M.) using modified versions of the Newcastle–Ottawa Quality Assessment Scale, adapted for cross-sectional studies (see Supplementary Appendix B available in *Age and Ageing* online) and longitudinal cohort studies (see Supplementary Appendix C available in *Age and Ageing* online), as appropriate. Discrepancies were resolved by consensus among the three reviewers.

Statistical analysis

After assessing possible ways to meta-analyse CSVD and gait measures, only the combination of WMH volume and gait

speed produced a reasonable number of studies to meta-analyse. As such, a meta-analysis of 13 studies was conducted based on a random-effects model wherein partial correlation coefficients were used to describe the linear relationship between WMH volume and gait speed while controlling for the effects of additional variables [6]. This was calculated based on correlation coefficients as previously described [6] and pooled to obtain a summary score. If odds ratios, Spearman's correlation coefficients or linear regression coefficients were reported, these were converted to correlation coefficients, with standardised regression coefficients first being reverted to unstandardised regression coefficients, if necessary [7–9]. For those studies that reported log-transformed WMH volumes, values were converted to raw WMH volumes [10]. The authors were contacted for missing information [11, 12].

Heterogeneity of the included studies was reported using Q-statistic, tau^2 and I^2. To investigate possible sources of heterogeneity, the following were conducted: the leave-one-out method, a meta-regression of select study-level characteristics and study quality and a subgroup analysis considering differences between studies that did and did not adjust for age. Publication bias was assessed using funnel plots and Egger's linear regression test. In cases where multiple studies from the same source data were available, recent studies with larger sample sizes and results most relevant to the research questions were used. Statistical analyses were conducted using R (version 4.1.2) and the metafor package (version 3.0.2).

Results

Search yield

A flowchart of the inclusion of studies is shown in Figure 1. The search on 30 March 2022 included publications from June 1967 onwards and yielded a total of 1716 studies. After excluding duplicates (281) and irrelevant studies from title and abstract screening (1,234), 202 underwent full-text review, yielding 73 eligible studies. An overview of the eligible studies, broken down by sub-analyses of individual CSVD markers is displayed in Table 1. Study quality was generally good (see Appendices D–E); the most common shortcomings were sample size not being justified (cross-sectional studies), proportion of study non-respondents either being high (>20%) or insufficiently explained (cross-sectional studies) and no demonstration that study outcome was not present at the start of the study (longitudinal studies).

Methodological comparisons

Of the studies reviewed, 53 were cross-sectional [3, 11–62] (see Table 2) and 20 were longitudinal [63–82] (see Table 3). Study participants in cross-sectional studies had mean ages ranging from 45 to 83.1 years (see Table 2) and mean ages ranging from 62.5 to 85.1 years in longitudinal studies (see Table 3).

CSVD measurements

Imaging modalities used in the studies were magnetic resonance imaging (MRI), with the exception of one that used computed tomography (CT) [64]. Strengths of MRI scanners were 0.35T (n = 3) [39, 40, 70], 0.5T (n = 3) [16, 27, 67], 1.0T (n = 1) [49], 1.5T (n = 42) [12–16, 18–23, 27, 29, 30, 33, 39, 40, 43, 44, 47, 48, 53, 56–58, 62, 63, 65–67, 69–74, 76–79, 81, 82] or 3.0T (n = 31) [3, 11, 17, 24–26, 28, 31, 32, 34–38, 41, 42, 46–48, 50–52, 54, 55, 59–61, 68, 71, 75, 80]. One study [45] did not report scanner strength (see Tables 2 and 3).

Measurements of CSVD included WMH volume (n = 48) [3, 11, 15, 17–19, 21–24, 26, 27, 29, 31–33, 35–38, 41, 42, 44, 46–48, 50, 53, 55–57, 59, 62, 63, 65, 66, 68, 69, 72–79, 81, 82] or WMH grade (using visual rating scales such as Fazekas scale [83]; n = 21) [13, 14, 16, 20, 27, 28, 30, 39, 40, 43–45, 49, 52, 60, 63, 64, 67, 70, 71, 80]; infarct presence or count (n = 27) [12, 16, 19, 21–23, 30, 32, 34, 39, 40, 46, 47, 50–52, 54, 56, 64, 70, 73, 75–78, 81, 82]; CMB presence or count (n = 15) [12, 19, 22, 30, 32, 34, 46, 47, 50, 52, 54, 55, 75–77] and enlarged PVSs (n = 5) [12, 34, 52, 55, 81]. Six studies used a composite score to measure total CSVD burden [12, 34, 51, 54, 58, 61] and one study defined CSVD cases based on imaging markers and compared them to controls [51]. One study identified CSVD based on a diagnosis of CADASIL by genetic analysis or skin biopsy [25]. No relevant studies examining cSS were found (see Tables 2 and 3).

Gait modalities

Gait analyses were conducted using the following tools: timed walk of a set length (n = 23) [3, 11, 12, 18, 20, 24, 26, 28, 30, 31, 48, 50, 52, 55, 57, 60, 69, 70, 72, 73, 75, 78, 81], GAITRite electronic walkway (n = 14) [19, 21–23, 25, 36, 38, 53, 58, 65, 66, 74, 76, 77], SPPB (n = 17) [11, 12, 16, 27–29, 35, 46, 48, 51, 54, 56, 61, 67–69, 79], Tinetti test (n = 13) [13–15, 22, 23, 33, 49, 61, 63, 68, 72, 73, 80], GaitMat II electronic walkway (n = 6) [17, 37, 39–42], Timed Up and Go (TUG) test (n = 7) [11, 22, 23, 30, 47, 61, 80], calculation of dual task cost (n = 5) [20, 25, 26, 30, 45], timed chair stands (including Five Times Sit to Stand; n = 4) [18, 24, 50, 52], self-report questionnaires inquiring about subjective gait difficulties (n = 5) [11, 36, 57, 70, 71], other automated walkways (n = 4) [44, 59, 61, 62], motor examination (n = 2) [36, 43]; wearable gait-tracking device (n = 2) [34, 60], Dynamic Gait Index (n = 1) [24], Four Square Step Test (n = 1) [24], EquiTest (n = 1) [29], pyramidal and extrapyramidal scale (n = 1) [32] and RehaGait sensor system (n = 1) [45]. Falls were assessed via self-reported history of falls (n = 6; see Tables 2 and 3) [11, 63–65, 74, 82].

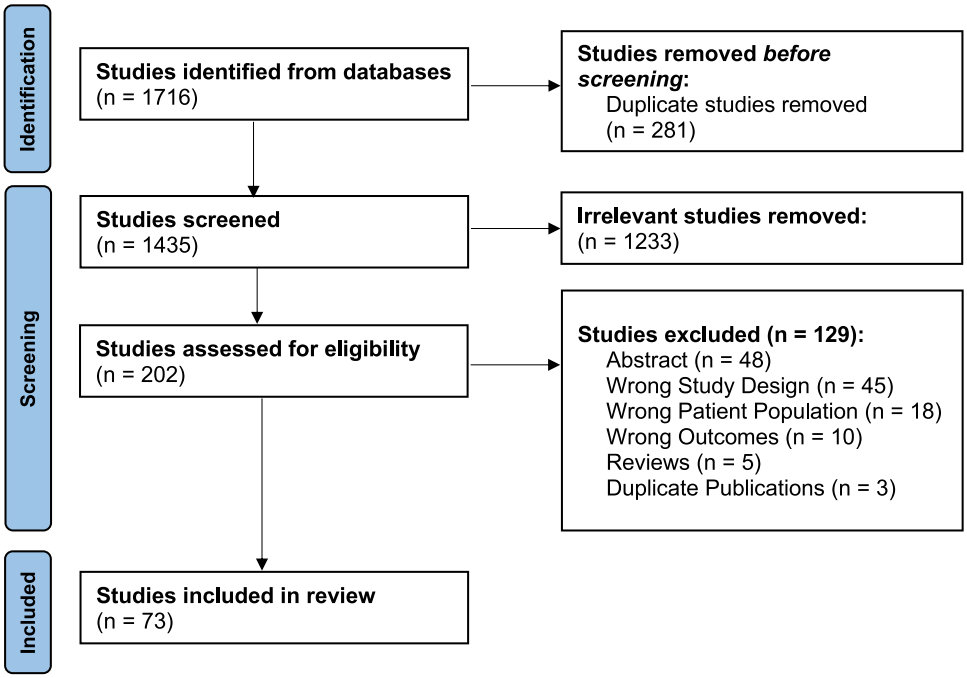

Figure 1. Selection of studies for inclusion in the systematic review.

Table 1. Overview of sub-analyses within studies included in systematic review

CSVD marker	Study design	Number of studies	Number of participants
CSVD burden score	Cross-sectional	6	2,527
	Longitudinal	0	-
WMH	Cross-sectional	47	15,819
	Longitudinal	20	13,343
Lacunar infarct	Cross-sectional	14	5,188
	Longitudinal	7	7,582
CMB	Cross-sectional	12	4,940
	Longitudinal	3	2,444
Enlarged PVS	Cross-sectional	4	2,341
	Longitudinal	1	331
CADASIL	Cross-sectional	1	39
	Longitudinal	0	0

Note: Longitudinal is defined here as studies where gait or falls were assessed at one or more time points after the baseline MRI.

Associations of sporadic, age-related CSVD with gait and falls in sporadic CSVD

CSVD summary scores

Cross-sectional studies Six studies reported associations between a CSVD summary score and gait abnormalities (see Supplementary Appendix F available in *Age and Ageing* online). One study found that individuals with CSVD (defined by WMH severity and presence of one or more lacunes) performed worse than healthy controls on single task walks (as measured by gait speed and chair stands scale) [51]. Five studies found associations between greater CSVD burden (as indicated by a score out of 3 or 4, composed of presence or severity of select markers of CSVD) and gait impairment, namely on select gait measures (gait speed, cadence, stride length, stride width, swing velocity and double support time variability) and gait scales (SPPB, Tinetti test, TUG test and chair stands) [12, 34, 54, 58, 61].

No associations between CSVD and falls were reported.

Longitudinal studies

None of the studies reported longitudinal associations between CSVD summary scores and either gait or falls.

WMH

Cross-sectional studies

WMH was measured using either volumetric analysis [3, 11, 15, 17, 18, 21, 23, 24, 26–29, 31–33, 36–38, 41, 42, 44, 46–48, 50, 53, 55–57, 59, 62, 68, 82] or using visual rating scales (Brant-Zawadzki scale [43, 84], Fazekas scale [14, 16, 20, 27, 28, 30, 45, 49, 52, 60, 83], Rosano scale

Table 2. Study characteristics of cross-sectional studies

First author, year	Sample size	Age, mean (SD)	Female, number (%)	Neuroimaging modality	CSVD markers	Gait and falls measures	Quality score
Baloh, 1995 [13]	54	*Patients*: 82.0 (3.9); *Controls*: 81.2 (2.7)	30 (56%)	1.5T MRI	WMH grade (Rotterdam scale)	GAIT: Tinetti score	5
Ben Salem, 2008 [14]	80	75.8, (4.1)	47 (58.8%)	1.5T MRI	WMH grade (Fazekas score)	GAIT: Tinetti score	9
Bhadelia, 2009 [15]	173	72.83 (7.7)	129 (74.57%)	1.5T MRI	WMH volume; infarcts (presence/absence)	GAIT: Tinetti score	9
Blahak, 2009 [16]	639	74.13 (5.0)	351 (54.9%)	0.5T and 1.5T MRI	ARWMC grade (Fazekas score); Lacunes (presence/absence)	GAIT: SPPB FALLS: Number of falls over the previous year	8
Bolandzadeh, 2014 [17]	253	82.74 (2.7	147 (58%)	3.0T MRI	WMH volume, adjusted for total brain volume	GAIT: Speed, 4 m	8
Carmelli, 2000 [18]	390	72.3 (2.9)	0 (0%; study of males only)	1.5T MRI	WMH volume	GAIT: Time to walk 8 feet, time to rise from chair, balance score	8
Choi, 2012 [19]	377	*CMB*: 73.7 (7.7); *No CMB*: 72.0 (6.9); *SI*: 75.9 (6.0); *No SI*: 71.2 (6.8)	168 (44.6%)	1.5T MRI	WMH volume; silent infarcts: infarct (>3 mm) with no stroke; presence/absence; number, location; volume; CMB: presence/absence; number, location	GAIT: Speed, cadence, step length, step width and double support phase; single gait factor, 4.6 m FALLS: Standardised falls-risk *z*-score (computed using visual contrast sensitivity, body sway, quadriceps strength, reaction time and lower limb proprioception)	9
David, 2016 [20]	141	63, range 59–69	76 (53.9%)	1.5T MRI	WMH grade (Fazekas score)	GAIT: Speed, 10 m	6
de Laat, 2010 [23]	431	65.2 (8.9)	195 (45.2%)	1.5T MRI	WMH volume; lacunar infarcts (presence/absence)	GAIT: Speed, stride length, cadence, stride width, double support percent; variability of stride length, stride time and stride width; Tinetti score and TUG test time, 5.6 m	9
de Laat, 2011a [22]	485	65.6 (8.8)	209 (43.10%)	1.5T MRI	WMH volume; infarcts number; CMB number	GAIT: Speed, stride length, cadence, stride width, double support percentage, 5.6 m	9
de Laat, 2011b [21]	429	65.2 (8.9)	194 (45.2%)	1.5T MRI	CSVD (WML or lacunar infarcts presence)	GAIT: Speed, stride length, stride width, cadence, 5.6 m	6
DiSalvio, 2020 [24]	70	76 (5)	40 (57.1%)	3.0T MRI	WMH volume	GAIT: Speed, lower extremity strength and functioning, dynamic gait and balance, and dynamic standing balance and motor planning, 6 m	5
Finsterwalder, 2019 [25]	39	CADASIL: 50.0 (8.1)	27 (69%)	3.0T MRI	Diagnosis of CADASIL; PSMD; WMH volume	GAIT: Pace (gait velocity, cadence and stride length), rhythm (double support phase and swing phase) and variability (stride time variability, stride length variability and base of support variability) domains; dual task cost was calculated for all of the domains for the three dual tasks: Serial 7's (calculatory dual task), naming animals (semantic dual task) and carrying a tray (motoric dual task), 6.7 m	6
Ghanavati, 2018 [26]	62	80.0 (4.2)	29 (46.8%)	3.0T MRI	WMH volumes, corrected for intercranial volume	GAIT: Time to complete single and dual task (reciting alternate letters of the alphabet) walks, 20 m FALLS: Fall risk assessment based on visual contrast sensitivity, proprioception, quadriceps strength, simple reaction time and postural sway	7

(continued)

Table 2. Continued

First author, year	Sample size	Age, mean (SD)	Female, number (%)	Neuroimaging modality	CSVD markers	Gait and falls measures	Quality score
Gouw, 2006 [27]	574	74 (5)	314 (55%)	0.5T and 1.5T MRI	WMH grade (Fazekas score, Scheltens scale and volume)	GAIT: SPPB	7
Griebe, 2011 [28]	34	69.4 (7.0)	23 (68%)	3.0T MRI	WMH (ARWMC scale; probability map for volume of lesions)	GAIT: SPPB	6
Guttmann, 2000 [29]	28	81 (5.9)	16/28 (57%)	1.5T MRI	WMH volume	GAIT: SPPB, stabilogram diffusion analysis, altered sensory input test, post-translation stability test, functional base of support, gait speed and single-leg stance time	8
Hashimoto, 2014 [30]	201	67.8 (6.5)	109 (54.2%)	1.5T MRI	WMH grade (Fazekas scale)	GAIT: TUG test, TUG test with dual task (serial 3's)	9
Hou, 2021 [61]	224	60.6 (10.5)	80 (35.7%)	3.0T MRI	CSVD score (4-point scale)	GAIT: speed, stride length, cadence, stride width, Tinetti test, TUG test, SPPB, 4 m	6
Jayakodi, 2021 [58]	408	72.0 (7.0)	176 (43.1%)	1.5T MRI	CSVD score (4-point scale)	GAIT: Double support time variability, 4.6 m	7
Jenkins, 2020 [59]	144	56 (4), range 48–63	61 (42.4%)	3.0T MRI	WMH volume	GAIT: speed, cadence and stride width, 40 feet	8
Jokinen, 2021 [11]	152	70.6 (2.9)	95 (62.5%)	3.0T MRI	WMH volume	GAIT: speed, single leg stance time, TUG test, SPPB, subjective walking difficulty, 8 m FALLS: falls in past 12 months	7
Karim, 2020 [31]	269	82.9 (2.7)	146 (57%)	3.0T MRI	WMH volume	GAIT: Speed, 20 m	9
Kim, 2016 [32]	129	73.8 (6.8)	77 (59.7%)	3.0T MRI	WMH volume; lacune number; CMB number	GAIT: Gait abnormality and gait severity	9
Koo, 2012 [33]	125	71.9 (7.8)	91 (72.8%)	1.5T MRI	WMH volume	FALLS: Risk of falls	6
Li, 2020 [34]	314	59.6 (2.7)	54.10%	3.0T MRI	CSVD score (4-point scale); WMH grade (Fazekas scale); Lacunes (presence/absence); CMB (presence/absence); PVS (presence/absence)	GAIT: Speed, stride time, cadence, stance phase time %, max swing velocity, stride length, heel strike angle, toe-off angle; Tinetti score and TUG test, 10 m	8
Ma, 2022 [60]	CSVD: 46; NC: 22	CSVD: 71.2 (8.2); NC: 70.2 (6.7)	33 (48.5%)	3.0T MRI	WMH grade (Fazekas scale)	GAIT: Speed, stride time, stride length, cadence, swing time, stride time variability, stride length variability, speed variability, swing time variability, gait asymmetry, phase coordination index, 25 strides	6
Moscufo, 2011 [35]	99	83 (4)	57 (57.6%)	3.0T MRI	WMH fraction (WMH volume/intracranial cavity)	GAIT: SPPB	7
Murray, 2010 [36]	148	median 79, IQR 76–83	83 (56.1%)	3.0T MRI	WMH proportional volume (WMH volume/total WM volume*100)	GAIT: UPDRS gait and postural stability, speed, stride length, 4.88 m	6
Nadkarni, 2016 [37]	179	83.1 (2.7)	104 (58.1%)	3.0T MRI	WMH volume, normalised to brain volume	GAIT: Speed, 4 m	7
Ogama, 2022 [62]	91	73.2 (4.9)	53 (58.2%)	1.5T MRI	WMH volume	GAIT: Pace (speed, cadence, stride length), rhythm (stride time, double leg support time), postural control (walking angle, step width), variability (gait speed variability), 6.4 m	7
Pinter, 2017 [12]	678	72.5 (0.7)	319 (47.1%)	1.5T MRI	CSVD score (4-point scale); WMH volume	GAIT: Speed, chair stands, standing balance, 6 m	6
Rasmussen, 2019 [38]	904	45 (by study design)	449 (49.7%)	3.0T MRI	WMH volume	GAIT: Speed, 6 m	9

(continued)

Table 2. Continued

First author, year	Sample size	Age, mean (SD)	Female, number (%)	Neuroimaging modality	CSVD markers	Gait and falls measures	Quality score
Rosano, 2006 [39]	321	79.1	195 (60.7%)	0.35T and 1.5T MRI	WMH grade (CVHS scale); Infarcts (presence/absence)	GAIT: Speed, stride length, base of support, double support time and latency, 4 m	7
Rosano, 2007 [40]	331	78.3 (4.0)	Not reported	0.35T and 1.5T MRI	WMH grade (10-point scale); infarcts (presence/absence)	GAIT: Step length variability, step width variability and stance time variability, 4 m	9
Rosario, 2016 [41]	265	82.9 (2.7)	152 (57%)	3.0T MRI	WMH volume	GAIT: Speed, 4 m	8
Rosso, 2014 [42]	265	82.9 (2.7)	152 (57.4%)	3.0T MRI	WMH volume	GAIT: Speed, step length, step length variability, 8 m	8
Sakakibara, 1999 [43]	63	73	35 (55.6%)	1.5T MRI	WMH grade (Brant-Zawadzki scale)	GAIT: Gait disorder	2
Sakurai, 2021 [44]	34	78.4 (4.2)	23 (54.8%)	1.5T MRI	WMH volume normalised to ICV	GAIT: Speed, variability of double support time, stride time, stride length and step length, 5 m	8
Sartor, 2017 [45]	101	yPn = 57, range 50–69; oPn = 77, range 70–89	47 (46.5%)	Unknown	WMH grade (Fazekas score)	GAIT: Speed, dual task cost (serial 7s), 20 m	7
Seiler, 2017 [46]	230	70.2 (4.9)	153 (66.5%)	3.0T MRI	WMH volume	GAIT: Speed; SPPB, 8 m	6
Smith, 2015 [47]	803	58 (8)	474 (59%)	1.5T and 3.0T MRI	Lacunes (presence/absence, number and location); CMB (presence/absence, number and location); WMH volume, normalised to sex-specific average intracranial volume	GAIT: TUG test	9
Sorond, 2011 [48]	42	78.3 (6.5)	23 (54.8%)	1.5T and 3.0T MRI	WMH volume	GAIT: Speed, 4 m	5
Starr, 2003 [49]	97	78–79 years	39 (40.2%)	1.0T MRI	WMH grade (Fazekas scale)	GAIT: Time able to balance on one leg, walking time, unspecified walking distance	7
Stijntjes, 2016 [50]	297	65.4 (6.8)	150 (50.5%)	3.0T MRI	WMH volume; CMB (presence/absence); lacunar infarcts (presence/absence)	GAIT: Standing balance duration, chair rise duration, speed, 4 m	8
Su, 2017 [52]	770	57.2 (9.3)	501 (65.1%)	3.0T MRI	WMH grade (Fazekas scale); Lacunes (presence/absence); CMB (presence/absence); perivascular spaces (4-point scale)	GAIT: SPPB	8
Su, 2018 [51]	770	57.2 (9.3)	501 (65.1%)	3.0T MRI	CSVD group: High WMH (Fazekas scale ≥2) and ≥1 lacune: Controls remainder of the population	GAIT: SPPB	5
Valkanova, 2018 [3]	178	69 (5.1)	44 (25%)	3.0 T MRI	WMH volume	GAIT: Speed, stride length, stride time, gait speed variability, stride length variability, stride time variability and double stance percent, 10 m	7
Verlinden, 2016 [53]	2,330	65.9 (9.2)	1,283 (55.1%)	1.5T MRI	WMH volume	GAIT: 7 gait domains: rhythm (cadence and single support time), phases (double support time and single support %), variability (stride length and time), pace (stride length and velocity), tandem (errors in tandem walking), turning (turning time and step count) and base of support (stride width and its variability), 4.88 m	9
Verwer, 2018 [54]	133	71.0 (9.3)	55 (41%)	3.0T MRI	WMH grade (Fazekas scale); lacunar infarcts (presence/absence); CMB (presence/absence)	GAIT: SPPB	7
Wang, 2021 [55]	579	67.6 (7.6)	339 (58.5%)	3.0T MRI	WMH volume; CMB number; enlarged PVS (presence/absence)	GAIT: Speed, 6 m	9
Willey, 2018 [56]	616	74.3 (8.6)	419 (62.7%)	1.5T MRI	WMH volume; SI (presence/absence)	GAIT: SPPB	9
Windham, 2016 [57]	1960	61.2 (10.0)	1,267 (64.6%)	1.5T MRI	WMH volume	GAIT: Speed; subjective gait difficulty in walking half a mile, 25 feet	9

ARWMC, age-related white matter changes; ICV, intracranial volume; IQR, interquartile range; oPn, older adults without Parkinson's disease; PSMD, peak width of skeletonised mean diffusivity; SI, silent infarct; UPDRS, Unified Parkinson's Disease Rating Scale and yPn, young adults without Parkinson's disease.

Table 3. Study characteristics of longitudinal studies

First author, year	Study duration	Sample size	Age, mean (SD)	Female, number (%)	Neu-roimaging modality	CSVD markers	Gait and falls measures	Quality score
Baloh, 2003 [63]	8–10 years	59	78.5 (3.7)	25 (42.4%)	1.5T MRI	WMH volume and grade (Victoroff scale)	GAIT: Tinetti score	7
Briley, 2000 [64]	6–36 months	221	67.6 (10.8)	3 (1%)	CT	WMH grade (Rotterdam Study scale); infarcts (size, vascular distribution and type [i.e. cortical versus subcortical only])	GAIT: Gait score	6
Callisaya, 2013 [66]	30.6 months, SD 4.9	225	71.4 (6.8)	98 (45.6%)	1.5T MRI	WMH volume; infarcts (number)	GAIT: Speed, step length, cadence, step width, 4.6 m	10
Callisaya, 2014 [82]	12 months	655	74.5 (6.7)	319 (48.7%)	1.5T MRI	WMH volume; infarcts (number)	FALLS: Number of falls	8
Callisaya, 2015 [65]	2.5 years, SD 0.4	187	70.5 (6.5)	68 (50.0%)	1.5T MRI	WMH volume	GAIT: Speed, 4.6 m FALLS: Number of falls over 12 months	7
Heiland, 2021 [81]	6.0 years, SD 1.4	331	68.9 (8.3)	198 (58.3%)	1.5T MRI	CSVD score (3-point scale), WMH volume, PVS grade, lacune count	GAIT: Speed, 2.44 m	9
Kreisel, 2013 [67]	3 years	639	74.1 (5.0)	351 (54.93%)	0.5T and 1.5T MRI	ARWMC grade (Fazekas scale)	GAIT: SPPB	7
Moscufo, 2012 [68]	1.9 years, SD 0.4	77	82 (4)	46 (60%)	3.0T MRI	WMH volume, as % ICV	GAIT: Tinetti score; SPPB	9
Pinter, 2018 [69]	3 years	443	72.5 (0.7)	199 (44.9%)	1.5T MRI	WMH volume	GAIT: Speed, chair stand time, standing balance time, 6 m	8
Rosano, 2005 [70]	4 years	2,450	74.4 (4.7)	1,397 (57%)	0.35T and 1.5T MRI	WMH (10-point visual rating scale); Small brain infarcts (presence/absence)	GAIT: Motor performance (speed, timed chair stand); self-reported physical impairment (difficulty walking half a mile or with one or more activities of daily living), 15 feet	8
Rosso, 2017 [71]	6 years	2,703	74.4 (4.8)	1,521 (56.3%)	1.5T and 3.0T MRI	WMH (10-point visual rating scale)	GAIT: Speed, self-reported mobility disability defined as unable to walk 0.8 km, 15 feet	8
Silbert, 2008 [72]	9.1 years, SD 4.0	104	85.1 (5.6)	64 (61.50%)	1.5T MRI	WMH volume	GAIT: Tinetti score; time to walk, number of steps, 9 m	6
Soumare, 2009 [73]	8 years	1702	72.4 (4.1)	1,031 (60.6%)	1.5T MRI	WMH volume; lacunar infarcts (presence/absence)	GAIT: Time to walk, gait speed; Tinetti score, 6 m	9
Srikanth, 2009 [74]	12 months	294	73.0 (7.0)	131 (44.6%)	1.5T MRI	WMH volume	GAIT: Speed, cadence, step length, step width, double support time, variability of stride, 4.2 m length, time and width FALLS: Incident falls (first fall in 12 months after study onset)	8
Sullivan, 2021 [75]	6.51 years	1859	median 76.7, IQR 72.0 to 80.0	1,115 (60%)	3.0T MRI	WMH volume; Infarct (presence/absence); CMB (number)	GAIT: Speed, 4 m	9
van der Holst, 2017 [77]	5.4 years SD 0.2	310	63.3 (8.4)	137 (44.2%)	1.5T MRI	WMH volume; lacunes (number); CMB (number)	GAIT: Speed, stride length and cadence, 5.6 m	10
van der Holst, 2018 [76]	5.4 SD 0.2	275	62.5 (8.20	120 (43.6%)	1.5T MRI	WMH volume; lacunes (number); CMB (number)	GAIT: Speed, stride length, cadence, 5.6 m	9
Willey, 2013 [78]	2 years	701	80.3 (5.6)	471 (67.2%)	1.5T MRI	WMH volume; silent brain infarcts (presence/absence)	GAIT: Speed, 4 m	9
Wolfson, 2005 [79]	19–22 months	*Control*: 7; *Impaired Mobility:* 7	*Control*: 81 (1.7); *Impaired Mobility*: 84 (3.4)	*Control*: 1 (14.3%); *Impaired Mobility*: 4 (57.1%)	1.5T MRI	Volume of WM signal abnormalities normalised to ICV	GAIT: SPPB; single stance time, tandem stance time, functional base of support and gait velocity	8
Zhang, 2020 [80]	1 year	*Fallers*: 16; *Non-fallers*: 78	*Fallers*: 76.6 (7.2); *Non-fallers*: 68.4 (7.4)	*Fallers*: 7 (43.8%); *Non-Fallers*: 43 (55.1%)	3.0T MRI	WMH grade (Fazekas score)	GAIT: Tinetti score, Berg Balance Scale score and TUG test	8

ARWMC, age-related white matter changes; ICV, intracranial volume.

[39, 40], Rotterdam Study scale [85, 86], Scheltens scale [27, 87] and Wahlund's age-related white matter changes scale [88]).

Most cross-sectional studies (36/47) found that WMH was associated with worse gait performance and history of falls (see Appendices G and H). The majority of studies (30/47) adjusted for age. During single task walks, greater WMH was associated with worse performance on several gait measures (i.e. gait speed, stride length, stride width, stride time, single-leg stance time, and variability of gait speed and stride length) [12, 13, 17, 21, 28–31, 34, 36, 37, 40, 41, 44, 47, 52, 54, 56, 57, 60, 62], gait scales (i.e. SPPB, Tinetti test, TUG test, chair stand, overall gait score, walking score, global gait) [11, 13–15, 27, 29, 30, 32, 35, 47, 52, 53, 56], gait disorders [43] and subjective mobility difficulty [57]. Greater WMH volume was also associated with higher odds of poor gait speed, double support time, step length variability, stance time variability, SPPB, TUG test and chair stand [23, 39, 48, 54]. On dual task walks, greater WMH severity was associated with slower gait speed [20, 26, 38]. One study examining falls found that individuals with a history of falls had greater WMH severity, based on a visual rating scale [16].

Of the 11 studies that did not find associations between WMH and gait, 10 failed to find significant associations between WMH severity and gait [3, 18, 24, 42, 45, 46, 49, 50, 55, 59], and one failed to find differences in WMH volume between individuals with and without risk of falls [33].

Longitudinal studies

Of the 20 longitudinal studies of gait and falls outcomes reporting on WMH, 16 examined associations with changes in gait and 4 examined associations with incident falls (see Supplementary Appendix I available in *Age and Ageing* online). Most studies (15/20) examined baseline WMH as a predictor of change in gait or new falls, while 5/20 correlated change in WMH with changes in gait. Longitudinal measurements of WMH severity were done volumetrically [65, 66, 68, 69, 72–79, 81] or using a visual rating scale (Fazekas scale [67, 70, 80, 83], Rosano scale [70], Rotterdam Study scale [86] and Victoroff scale [89]).

Of the 16 studies on change in gait over time, 12 measured WMH at baseline only and 4 correlated change in WMH with change in gait over time. Of the 12 studies that measured WMH at baseline, 10 found that higher WMH at baseline was associated with worsening of gait speed ($n = 5$) [70, 71, 73, 78, 81], greater time to walk a specified distance ($n = 1$) [72], decreased number of steps to walk a specified distance ($n = 1$) [72], lower summary scores of gait and gait variability ($n = 1$) [73], and worse performance on Tinetti test ($n = 1$) [63], SPPB ($n = 1$) [67] and chair rise ($n = 1$) [68]. Two studies failed to find associations between baseline WMH volume and gait impairment when examining gait speed, cadence and stride length [75, 77]. Of the four studies that examined the association of change in WMH over time with change in gait over time, three found that an increase in WMH volume was associated with worse gait (measured by gait speed ($n = 2$) [66, 69], step length ($n = 1$) [66] and SPPB score ($n = 1$) [79]; while one study failed to find an association between change in WMH and change in gait [76].

Four of the 20 longitudinal studies examined relationships between WMH and incident falls, of which three measured WMH at baseline and one measured WMH change over time. The three studies reporting baseline WMH found that baseline WMH grade or volume was predictive of future falls [64, 80, 82]. The study that examined the change in WMH volume over time found that an increase in WMH volume was associated with a greater risk for multiple future falls [65].

Meta-analysis

Thirteen cross-sectional studies [11, 23, 24, 28, 31, 36, 38, 39, 44, 48, 50, 54, 55] with sufficiently reported data on gait speed and WMH volume were meta-analysed using a random-effects model to assess the overall relationship between WMH volume and gait speed (see Supplementary Appendix G available in *Age and Ageing* online), of which six studies controlled for age [11, 23, 31, 39, 44, 50], six controlled for sex [11, 23, 38, 39, 44, 50] and seven controlled for other factors [11, 23, 31, 38, 39, 44, 50] (five of the seven studies controlled for age, sex and other factors [11, 23, 39, 44, 50]; one controlled for age without sex, including other factors [31] and one controlled for sex without age, including other factors [38]). Of note, 24 of the remaining 34 non-meta-analysed cross-sectional studies reporting WMH volume did adjust for age. Nine studies were considered high quality [11, 23, 31, 38, 39, 44, 50, 54, 55] and four were moderate quality [24, 28, 36, 48] based on the Newcastle–Ottawa scale (see Supplementary Appendix D available in *Age and Ageing* online). The estimated pooled partial correlation between WMH volume and gait speed was −0.23 (95% confidence interval [CI]: −0.33 to −0.14, $P < 0.0001$; see Figure 2A). When restricted to the studies adjusting for age, the pooled partial correlation was attenuated but still significant ($r = -0.21$, 95% CI: −0.36 to −0.05, $P < 0.05$; see Figure 2B).

High heterogeneity was observed between studies ($I^2 = 82.95\%$; tau^2 = 0.02; $Q = 79.37$, $P < 0.0001$). The leave-one-out method, wherein each study was removed from the meta-analysis one at a time, found that overall results and heterogeneity were not influenced by any one study. A meta-regression found that heterogeneity was not explained by whether a study was age-adjusted ($R^2 = 0.00\%$, $Q = 0.33$, $P = 0.56$), participants' age ($R^2 = 12.03\%$, $Q = 2.19$, $P = 0.14$), sex ($R^2 = 0.00\%$, $Q = 0.14$, $P = 0.71$) or study quality (age: $R^2 = 15.94\%$, $Q = 2.25$, $P = 0.13$). Heterogeneity was also not explained by subgroup analysis of studies that did adjust for age versus those that did not adjust for age (age-adjusted:

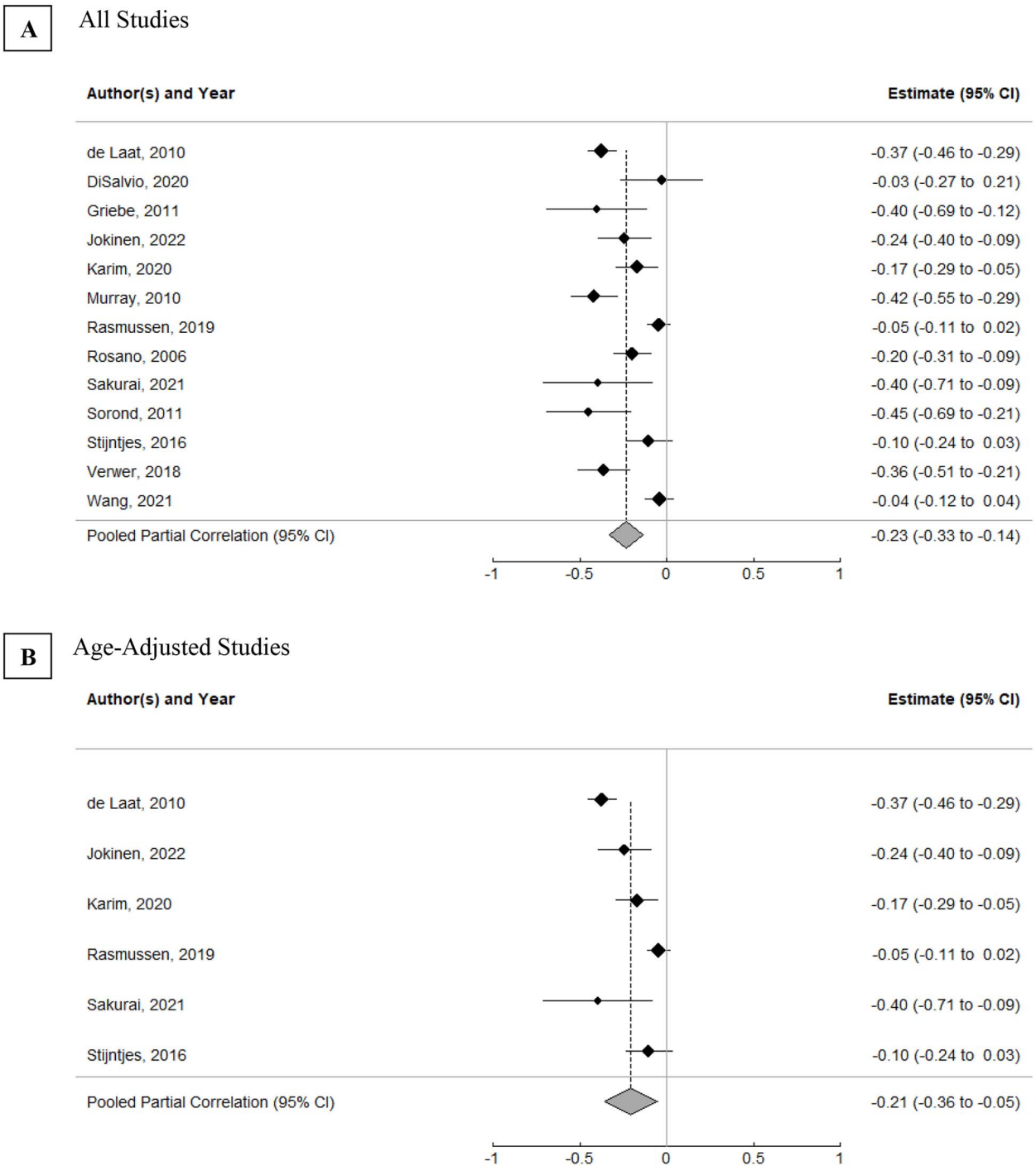

Figure 2. Correlations between WMH volume and gait speed. (A) All studies. (B) Age-adjusted studies. Estimates reflect partial correlation coefficients, with the position of the markers denoting the estimate, the horizontal lines representing 95% CI and the size of markers indicative of weight of the corresponding study. Summary scores indicate pooled partial correlation coefficients of included studies. Supplementary Appendix G describes study outcomes for the included studies.

$I^2 = 83.10\%$; $\text{tau}^2 = 0.02$; $Q = 41.43$, $P < 0.0001$; not age-adjusted: $I^2 = 82.24\%$; $\text{tau}^2 = 0.02$; $Q = 37.52$, $P < 0.0001$). No evidence of publication bias was detected through visual inspection of funnel plot (see Supplementary Appendix Q available in *Age and Ageing* online) or Egger's linear regression test ($z = -1.57$, $P = 0.15$).

Lacunar infarcts

Cross-sectional studies

Studies examining lacunar infarcts had mixed results (see Supplementary Appendix J available in *Age and Ageing* online), with 8 of 14 studies reporting some associations

between lacunar infarcts and gait and falls. Of these eight studies, four found that infarct presence was associated with impaired gait measures (gait speed, cadence, step and stride length, step and stride width, double support, and variability of step length, stride time and stance time) [23, 39, 40, 50], three studies found that infarct presence was associated with gait scales (Tinetti test, TUG test and chair stands) [15, 47, 54] and one study found that silent lacunar infarcts were associated with greater falls risk [19].

However, 6 of 14 studies found no significant links between lacunar infarcts and gait when examining several gait measures (gait speed, cadence, stride time, stride length, stance phase time and maximum swing velocity) and gait scales (chair stands, summary gait scores and overall assessments of gait impairment on single and dual task walks) [12, 30, 32, 34, 46, 52].

Longitudinal studies

Seven longitudinal studies of gait and falls outcomes examined the presence of lacunar infarcts, of which six studies reported associations with changes in gait and one study reported associations with incident falls (see Supplementary Appendix K available in *Age and Ageing* online). Only one study examined the association with incident lacunar infarcts.

Of the six studies examining changes in gait, five studies assessed lacunar infarct presence at baseline and one study measured change in lacunar infarct presence over time. Of the five studies reporting baseline lacunar infarcts, two studies found that baseline presence of lacunes was associated with risk of incident walking speed limitation (gait speed <0.8 m/s; $n = 1$) [81] and decline in gait speed ($n = 1$) [70]. Three studies found that baseline infarct presence was not associated with declines in gait speed ($n = 3$) [73, 75, 77], cadence ($n = 1$) [77] or stride length ($n = 1$) [77]. The one study that examined the association of new lacunes (defines as the appearance of one or more lacunes at follow-up) with change in gait failed to find an association with changes in gait speed, cadence or stride length; however, the number of patients with incident lacunes was small (17/61 [27.9%] with lacunes at follow-up) [76].

The one study, out of seven longitudinal studies, that reported associations of baseline lacunar infarcts with incident multiple falls found a linear trend for higher risk of falls with increasing number of baseline infarcts (categorised as none, one, two, or three or more) with a significant association between three or more infarcts at baseline and incident multiple falls [82].

CMB

Cross-sectional studies

There were mixed findings with respect to CMBs and gait (see Supplementary Appendix L available in *Age and Ageing* online). Six of 12 studies found associations between the presence of CMB and gait measures (i.e. gait speed, cadence, stride length, stride width, double support time and stance phase time percent) or Tinetti test [19, 22, 34, 46, 50, 55]. However, six of 12 studies found no associations between CMB presence and gait speed, SPPB, TUG test, chair stand or summary gait scores [12, 30, 32, 47, 52, 54, 55].

No studies reported associations between CMBs and falls.

Longitudinal studies

Three studies examined CMBs in relation to gait performance over time (see Supplementary Appendix M available in *Age and Ageing* online), of which two studies measured baseline CMB count and one study measured change in CMB count over time. The two studies that examined baseline CMB count failed to find associations with change in gait speed ($n = 2$) [75, 77], cadence ($n = 1$) [77] or stride length ($n = 1$) [77]. One study examined the impact of change in CMB count on change in gait and also did not find associations with changes in speed, stride length or cadence [76]; however, the number of patients with incident CMBs was small (17/56 [30.4%] with CMBs at follow-up).

Falls were not assessed in relation to CMBs.

PVS

Cross-sectional studies

Four studies reviewed the relationship between enlarged PVS and gait (see Supplementary Appendix N available in *Age and Ageing* online), all of which found no associations when measuring gait with gait speed, cadence, stride length, stride time, stance phase time percentage, maximum swing velocity and chair stands [12, 34, 52, 55].

None of the studies examined associations between PVSs and falls.

Longitudinal studies

One longitudinal study (see Supplementary Appendix O available in *Age and Ageing* online) found that greater baseline enlarged PVS presence was associated with a greater risk of incident walking speed limitation (gait speed <0.8 m/s) [81].

This study did not report findings relating to PVS and falls.

CADASIL

Cross-sectional studies

One study compared patients with the CSVD subtype, CADASIL, to healthy controls (see Supplementary Appendix P available in *Age and Ageing* online) and found that individuals with CADASIL had worse double support time and swing time during single task walks and worse velocity, cadence, swing time, stride length and double support time during dual task walks [25].

There were no reported associations between CADASIL and falls.

Longitudinal studies

None of the studies reported longitudinal associations.

Discussion

In this systematic review and meta-analysis, associations between measures of CSVD and gait and falls were analysed. Compared with prior reviews [4, 90], many more studies have been published recently including longitudinal studies of WMH progression and gait impairment. Overall, the data suggest that CSVD is adversely associated with gait and falls in the general population. The most data were available for WMH, where meta-analysis of cross-sectional studies showed that WMH volume was correlated with a mild, but highly statistically significant, decrease in gait speed. For other lesion types, such as infarcts and CMBs, the results were less consistent, and meta-analysis was not possible due to heterogeneity in CSVD assessment and gait measurement.

Previous systematic reviews have described the importance of examining gait and falls in older adults. One such review demonstrated associations between gait problems and increased frailty and falls, decreased cognition and overall lower life satisfaction [4], and another suggested that poor gait performance may predict the onset of dementia [91]. Similar to our findings in the general population, other reviews have found relationships between WMH and gait impairment in adults [90] and patients with Alzheimer's disease [92].

Gait impairment in CSVD is likely caused by interrupted frontal cortical–subcortical circuits [93]. Decreased connectivity of cerebral white matter tracts in older adults, as seen in CSVD, has been linked to gait impairment [5]. Further, slowed gait was linked to atrophy of the frontal cortex, basal ganglia, hippocampus and cerebellum and to damage of white matter circuits in frontal cortical regions and basal ganglia [5]. More studies are needed to comprehensively understand how the effects of different CSVD lesions on brain networks may contribute to gait decline.

One limitation of this review is that we searched for 'risk of falls' and synonyms, but we chose not to search for 'falls' as a keyword; this strategy probably increased the specificity of the returned results but may have missed some relevant papers. While we initially hoped to include multiple meta-analyses, we were limited by a lack of meta-analysable data for other CSVD lesion types and diagnoses. Further, there were much fewer studies on lacunes, CMBs and enlarged PVSs than WMH, and none on cSS. There were also fewer longitudinal studies than cross-sectional studies. These limitations, along with the heterogeneity in quantifying the amount of CSVD and harmonising methods across publications, made it difficult to synthesise information, ultimately restricting meta-analyses to just WMH volume and gait speed, the most commonly reported measures of CSVD and gait, respectively. The results, however, must be interpreted with caution as they showed significant heterogeneity that we were unable to explain statistically. In the future, pooling results across studies would be facilitated by greater consensus on standardised gait assessments such as that proposed by the Canadian Consortium on Neurodegeneration in Aging [94].

The applicability of the results must also be considered. The studies included were mostly done in the general population, where most participants would have had only mild covert age-related CSVD. Our review does not include the effects of more severe CSVD on gait and falls. Clinically, it is recognised that gait impairment is frequent in patients with severe symptomatic CSVD.

Although the effect of CSVD on gait and falls, as reflected in our meta-analysis of WMH and gait speed, is mild in strength, the overall public health impact of CSVD may be large because CSVD is so common with ageing. More studies are needed on the effect of CSVD on mobility-related quality of life, falls risk and injurious falls. Clinical trials of strategies to prevent CSVD are needed, and these trials should include the assessment of gait as an outcome. Prevention of CSVD should be part of a comprehensive strategy to improve mobility and reduce risk of falls in later life.

Supplementary Data: Supplementary data mentioned in the text are available to subscribers in *Age and Ageing* online.

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