Impaired mobility and MRI markers of vascular brain injury: Atherosclerosis Risk in Communities and UK Biobank studies

Richa Sharma ![ORCID],[1] Adam de Havenon ![ORCID],[1] Cyprien Rivier,[1] Seyedmehdi Payabvash ![ORCID],[2] Rachel Forman,[1] Harlan Krumholz,[3] Guido J Falcone,[1] Kevin N Sheth,[1] Walter N Kernan[3]

[1]Department of Neurology, Yale School of Medicine, New Haven, Connecticut, USA
[2]Department of Radiology and Biomedical Imaging, Yale School of Medicine, New Haven, Connecticut, USA
[3]Department of Medicine, Yale School of Medicine, New Haven, Connecticut, USA

Correspondence to
Dr Richa Sharma;
richa.sharma@yale.edu

ABSTRACT

Background Vascular brain injury (VBI) may be an under-recognised contributor to mobility impairment. We examined associations between MRI VBI biomarkers and impaired mobility.

Methods We separately analysed Atherosclerosis Risk in Communities (ARIC) and UK Biobank (UKB) study cohorts. Inclusion criteria were no prevalent clinical stroke, and available brain MRI and balance and gait data. MRI VBI biomarkers were (ARIC: ventricular and white matter hyperintensity (WMH) volumes, non-lacunar and lacunar infarctions, microhaemorrhage; UKB: ventricular, brain and WMH volumes, fractional anisotropy (FA), mean diffusivity (MD), intracellular and isotropic free water volume fractions). Quantitative biomarkers were categorised into tertiles. Mobility impairment outcomes were imbalance and slow walk in ARIC and recent fall and slow walk in UKB. Adjusted multivariable logistic regression analyses were performed.

Results We included 1626 ARIC (mean age 76.2 years; 23.4% imbalance, 25.0% slow walk) and 40 098 UKB (mean age 55 years; 15.8% falls, 2.8% slow walk) participants. In ARIC, imbalance associated with four of five VBI measures (all p values<0.05), most strongly with WMH (adjusted OR, aOR 1.64; 95% CI 1.18 to 2.29). Slow walk associated with four of five VBI measures, most strongly with WMH (aOR 2.32; 95% CI 1.66 to 3.24). In UKB, falls associated with all VBI measures except WMH, most strongly with FA (aOR 1.16; 95% CI 1.08 to 1.24). Slow walking associated with WMH, FA and MD, most strongly with FA (aOR 1.57; 95% CI 1.32 to 1.87).

Conclusions VBI is associated with mobility impairment in community-dwelling, clinically stroke-free cohorts. Consequences of VBI may extend beyond clinically apparent stroke to include mobility.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Impairment of mobility is associated with significant disability. Clinical stroke is a known cause of mobility impairment, but there is a paucity of evidence linking vascular brain injury (VBI) evident on brain MRI and mobility impairment in stroke-free individuals. Furthermore, no study to date has assessed this association while accounting for the contribution of disorders external to the central nervous system on mobility impairment.

WHAT THIS STUDY ADDS

⇒ In an analysis of two population-based cohorts of stroke-free individuals in the Atherosclerosis Risk in Communities and UK Biobank (UKB) Studies, MRI biomarkers of VBI were significantly associated with mobility impairment outcomes in both cohorts. In a subanalysis of the UKB cohort, this significant relationship between MRI biomarkers of VBI and mobility impairment remained even on adjusting for conditions external to the central nervous system that may contribute to impaired mobility.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Understanding the link between VBI and mobility impairment may have significant implications such as inclusion of mobility impairment as an outcome in trials of interventions aiming to modify vascular risk factors.

INTRODUCTION

Impaired mobility, characterised by imbalance, slow walk speed and falls, is common and disabling.[1] Nearly, 20% of participants in the 2008 National Health Interview Survey reported imbalance, of whom 27% indicated that it prevented participation in activities including exercise and social events.[2] Slow gait is frequent with a prevalence of 43% in individuals over age 65 and has been associated with difficulty in performing daily functions and fall risk.[3] Preventing mobility impairment may preserve independence and social participation, and reduce falls, the leading cause of fatal and non-fatal injuries among older adults.[4]

Mobility impairment can result from disorders of the cerebral vasculature, vestibular

system, visual system, spinal cord, peripheral nerves, muscles and joints. Often, the aetiological diagnosis of mobility impairment is uncertain because of no apparent or multiple potential aetiologies. Clinical stroke is a well-known cause of mobility impairment. Clinically inapparent vascular brain injury (VBI), defined by the presence of asymptomatic but radiographically evident infarcts and small vessel disease, also associated with disability. These forms of VBI are being established as contributors to cognitive impairment with comparable effects to clinical stroke on quality of life.[5] Studies have demonstrated associations between biomarkers of VBI and measures of mobility impairment but have been limited by narrow ranges of neuroimaging biomarkers assessed in individual studies, evaluations in single cohorts, inclusion of participants with prior history of clinical stroke and not accounting for non-neurological contributors to mobility impairment.[6 7]

We aimed to evaluate the association between MRI biomarkers of VBI and mobility impairment in stroke-free participants of two large epidemiological studies: the Atherosclerosis Risk in Communities (ARIC) study and the UK Biobank (UKB) study. We hypothesise that MRI biomarkers of VBI are independently associated with mobility impairment among stroke-free adults.

METHODS
Study design and participants
We separately performed cross-sectional analyses to evaluate the association between brain MRI markers of VBI and measures of mobility impairment in the ARIC and UKB cohorts.

ARIC is a population-based, prospective cohort study which recruited 15 792 participants ages 44–66 years from 1987 to 1989 to evaluate risk factors and clinical outcomes associated with atherosclerosis.[8 9] Participants were recruited from four US communities (Washington County, Maryland; Jackson, Mississippi; Forsyth County, North Carolina and Minneapolis suburbs in Minnesota) and underwent interviews and clinical examinations during six in-person visits (visit 2 1990–1993, visit 3 1993–1995, visit 4 1996–1999, visit 5 2011–2013 and visit 6 2016–2017). A subset of ARIC participants were eligible for a visit 5 brain MRI in the ancillary ARIC-Neurocognitive Study if there was no contraindication and they met one of the following criteria: (1) had a prior study MRI from 2004 to 2006 (visit 3), (2) had either low cognitive scores or decline on longitudinally administered tests and (3) were from an age-stratified random sample of remaining participants.[10] We included participants in the ARIC-Neurocognitive Study with (1) an in-person visit 5 examination, (2) a visit 5 brain MRI, (3) documented ability to ambulate and (4) availability of balance and 4 min walk speed data from visit 5. Patients with a history of stroke per self-report were excluded. The time from visit 5 to visit 5 MRI is not available.

UKB is a prospective cohort study which enrolled 502 480 individuals ages 40–69 in the UK from 2006 to 2010.[11 12] Demographic, clinical and biological sample data were collected at baseline. A subset of participants underwent a brain MRI at an average of 4.15 (SD 0.91) years after recruitment. The average age of participants at the time of brain MRI was 61.72 years (SD 7.47 years). We included UKB participants who were (1) able to walk, (2) answered the query, 'How would you describe your usual walking pace' and (3) answered the query, 'In the last year, have you had any falls?'. Participants were deemed unable to walk if the response to the query, 'number of days walked per weekend' was 'unable to walk'.[13] Participants with a history of clinical stroke, ascertained using self-reports or electronic health records (EHR), were excluded.

ARIC and UKB datasets are publicly available by application request to respective study committees. This research has been conducted using the UK Biobank Resource under Application Number 58743.

Outcome measures
In ARIC, individual outcomes reflecting mobility impairment included (1) impaired balance and (2) slow walk speed. Balance was classified as impaired at visit 5 if a participant scored <2 on the five-level ordinal composite balance score extracted from the Short Physical Performance Battery or SPPB (range 0–4; 0 indicates poorest and 4 indicates best).[14] The balance score was derived from observed performance on the during standing from a chair, tandem gait, semitandem gait and side-by-side stand tests.[15] The 4 m walk time was averaged over two trials at visit 5 and the walk speed was calculated by dividing 4 m by the average walk time. Slow walk speed was then defined by the lowest quartile.

In UKB, the individual, self-reported outcomes studied were participant selections from a multiple choice list describing (1) at least one fall in the past year and (2) slow compared with normal or fast walk speed. In the absence of a balance variable in the UKB database, we studied recent falls given the association between fall risk and balance demonstrated in the literature.[12–14]

MRI Biomarkers of VBI in ARIC
In ARIC, 3 Tesla brain MRI scans with 3.3 mm slices were obtained at imaging centres near each study field centre and read centrally at the Mayo Clinic (Rochester, Minnesota).[15] Sequences relevant to this study were MP RAGE, axial T2* GRE and axial fluid-attenuated inversion recovery (FLAIR) images.

We analysed five biomarkers of VBI in ARIC: (1) white matter hyperintensity (WMH) volume, (2) ventricular volume (VV), (3) any infarct, (4) lacunar infarct and (5) microbleed (CMB) presence. Previous research has demonstrated their importance to cerebrovascular health.[16–18] Axial FLAIR images were centrally segmented by an automated algorithm into voxels to derive WMH volume measures and both ventricular and

total intracranial volumes were calculated from preprocessed MP RAGE pulse sequence with Freesurfer.[16] These measures are available as numerical fields in the ARIC dataset. We normalised WMH and VV for intracranial volume. The presence of infarct and type and presence of CMB were centrally read and available as categorical variables in the dataset. Radiographic lacunar infarcts were 3–20 mm in maximal dimension and located in a subcortical region while non-lacunar infarctions were infarcts that did not meet this criteria. CMBs were defined as homogeneous lesions of haemosiderin deposits <10 mm in diameter detected by trained imaging analysts and confirmed by a radiologist. MRI exposures of VBI were (1) top tertile of VV defined by the distribution of the full cohort, (2) top tertile of WMH volume in the full cohort, (3) prior non-lacunar infarct, (4) prior lacunar infarct and (5) CMB presence.

MRI biomarkers of VBI in UKB

In the UKB, brain MRI scans were acquired by 3T scanners (Siemens Skyra with a 32-channel RF receive head coil).[13] UKB procedures for acquisition and quality check of imaging have been previously described.[19] T1-weighted MRI with an MP RAGE sequences were obtained with 1 mm isotropic resolution and field-of-view 208×256×256. The resolution of the T2 FLAIR was 1.05×1×1 mm where the T2* values were approximated by magnitude images at two echo times. Diffusion tensor imaging (DTI) sequences were obtained using two b-values (b=1000, 2000 s/mm^2) at isotropic resolution of 2 mm and multiband acceleration factor of 3. For each of the two shells, 50 diffusion-encoding directions were acquisitioned.

We analysed MRI biomarkers of VBI in UKB which were centrally quantified: (1) WMH volume, (2) VV, (3) brain volume, (4) fractional anisotropy (FA), (5) mean diffusivity (MD), (6) intracellular volume fraction (ICVF) (an index of white matter neurite density) and (7) isotropic or free water volume fraction (ISOVF). We normalised the non-DTI measures for intracranial volume. WMH volume was quantified using the Brain Intensity Abnormality Classification Algorithm, a part of the FMRIB Software library. We categorised exposure to each continuous non-DTI MRI biomarker by tertiles (top tertile for WMH, bottom tertile for brain volume and top tertile for VV).

DTI markers were explored in UKB because white matter structural integrity has been associated with vascular risk factors and risk of incident stroke and dementia.[20 21] Studies suggest that alterations in white matter that appear normal by T2 FLAIR but abnormal by DTI represent an early phase of injury, while WMH represents a late phase arising from the same pathophysiologic mechanism.[22] UKB dataset includes quantitative data from central image processing previously described.[10 21 22] FSL software was employed to calculate diffusion tensor and scalar parameters with the b=1000 shell (50 directions) and DTIFIT (diffusion tensor imaging fit). Neurite orientation dispersion and density modelling were performed with the Accelerated

Microstructure imaging via Convex Optimisation tool to produce voxel-based parameters of ICVF and IsoVF. FMRIB Software Library's Diffusion Toolbox for diffusion modelling and tractography analysis was used to correct noise in DTI data from distortions, eddy currents and head movement.[23 24] DTI maps generated were employed as inputs for tract-based spatial statistics processing.

We calculated mean DTI measures from each of 48 standard space tracts per participant.[25] In accordance with a published methodology of analysing DTI measures in UKB,[26] we performed principal component analyses on each DTI measure aggregated over 48 tracts using the 'stats' package in R. We classified participants into tertiles of FA, MD, ICVF and ISOVF by principal component 1. The top tertile for each sequence in the full cohort was designated as the exposure for each DTI marker.

Covariates

We evaluated variables that may confound associations between MRI biomarkers and mobility impairment: age, sex, race, hypertension (defined as a measured diastolic blood pressure >90 mm Hg or use of a medication for high blood pressure), use of anticholesterol medication, diabetes (defined by glucose value >140 mg/dL, non-fasting glucose value >200 mg/dL, use of medication for diabetes or self-reported diagnosis of diabetes), body mass index (BMI) (kg/m^2) and current smoking.[27] In UKB, models were further adjusted for comorbidities that impact organs external to the central nervous system (CNS) which may also contribute to mobility impairment. These conditions were identified using International Classification of Diseases or ICD-10 codes for diseases of the eye and adnexa (H00–H59), the inner ear (H80–H83), the peripheral nervous system (G50–G73), peripheral vasculature (I73), and musculoskeletal system and connective tissue (M00–M99).

Statistical analysis

We compared characteristics of eligible participants in the ARIC and UKB datasets. Mann-Whitney U and χ^2 tests were used as appropriate. We fit separate logistic regression models to examine the association between the presence of individual MRI biomarker of VBI and the outcomes in each cohort. We also adjusted for covariates that were significant in descriptive analysis at a prespecified p<0.05. Unadjusted associations were studied in all eligible participants. For the adjusted analyses, we excluded participants with any missing covariate. We adjusted for two sets of covariates in UKB. Similar to analyses in ARIC, we adjusted for demographics and clinical covariates. We then further adjusted for disorders of organs external to the CNS. We examined two-way interactions between each pairwise combination of MRI biomarkers as a product term in the adjusted logistic regression analyses for the individual outcomes. To evaluate the links between microstructural white matter changes and mobility impairment, we calculated the OR of DTI MRI biomarkers of VBI and each outcome among

Table 1 Characteristics of ARIC participants (N=1626) stratified by balance and walk speed at visit 5

Characteristic	Full cohort (N=1626)	No imbalance (n=1245)	Imbalance (n=381)	P value*	Normal or fast walk speed (n=1222)	Slow walk speed (n=404)	P value†
Visit 5 demographic and clinical characteristics							
Age (years)	76.2±5.3	75.4±5.0	78.9±5.3	<0.001	75.6±5.0	78.2±5.5	<0.001
Age groups				<0.001			<0.001
60–69	168 (10.3%)	151 (12.1%)	18 (4.7%)		144 (11.8%)	24 (5.9%)	
70–79	981 (60.3%)	812 (65.2%)	169 (44.4%)		780 (63.8%)	201 (49.8%)	
80–90	477 (29.4%)	283 (22.7%)	194 (50.9%)		298 (24.4%)	179 (44.3%)	
Female sex	942 (57.9%)	698 (56.1%)	140 (63.8%)	0.008	667 (54.6%)	275 (68.1%)	<0.001
Black race	419 (25.8%)	301 (24.2%)	118 (31.0%)	0.008	268 (21.9%)	151 (37.4%)	<0.001
Hypertension	1085 (67.6%)	818 (65.7%)	282 (74.0%)	0.003	794 (65.0%)	305 (75.6%)	<0.001
Cholesterol medication use	897 (55.3%)	675 (54.2%)	225 (59.1%)	0.092	670 (54.8%)	230 (57.0%)	0.439
Diabetes	476 (29.6%)	342 (27.5%)	138 (36.2%)	0.001	329 (26.9%)	153 (37.8%)	<0.001
Body mass index (kg/m^2)	28.4±5.4	28.2±5.1	29.1±6.3	0.004	28.1±4.9	29.6±6.7	<0.001
Current smoking	83 (5.2%)	780 (5.6%)	14 (3.7%)	0.150	55 (4.5%)	29 (7.1%)	0.048
Visit 5 MRI Biomarkers							
Ventricular volume (mL)	34.5, 24.5–48.4	32.9, 23.6–46.9	38.8, 28.0–51.2	<0.001	33.4, 24.0–46.9	37.1, 27.2–51.0	<0.001
White matter hyperintensity volume (mL)	11.6, 6.4–21.6	10.7, 5.8–19.6	15.9, 8.8–30.5	<0.001	10.4, 5.8–19.5	15.8, 9.3–27.0	<0.001
Presence of prior infarct	398 (24.5%)	279 (22.4%)	119 (31.2%)	<0.001	267 (21.0%)	142 (35.2%)	<0.001
Prior lacunar infarct	278 (17.1%)	188 (15.1%)	90 (23.6%)	<0.001	169 (13.8%)	109 (27.0%)	<0.001
Microhaemorrhage	369 (22.9%)	265 (21.3%)	107 (28.0%)	0.006	266 (21.8%)	106 (26.3%)	0.064

Values are n (percentage) for categorical variables or median (IQR) for continuous variables.
*P values comparing participants with and without imbalance.
†P values comparing participants with and without slow gait.
ARIC, Atherosclerosis Risk in Communities.

a subgroup of participants with the lowest tertile of WMH burden. Statistical analyses were performed in Stata V.17.1 (StataCorp) and R.

RESULTS
ARIC cohort
There were 1626 eligible participants (table 1). Mean age was 76.2 years (SD 5.2 years). Of these participants, 381 (23.4%) had impaired balance and 404 (25.0%) had slow walk speed. Median SPPB score was 2 (IQR 1–2) among participants with impaired balance and 4 (IQR 4–4) among participants with preserved balance. Median 4 m walk speed was 0.64 m/s (IQR 0.54–0.70) among participants with slow walk speed and 0.94 m/s (IQR 0.85–1.06) among participants with normal walk speed. Participants with impaired balance were significantly older (79 vs 75 years, p<0.001) and more likely to be female, black, and have hypertension, diabetes, and elevated BMI. Participants with slow walk speed were significantly older (78 vs 75 years, p<0.001), female, black, and had hypertension, diabetes, and elevated BMI. Characteristics of participants who did and did not meet inclusion criteria are in online supplemental table 1. Excluded participants were younger and less likely to be black.

The prevalence of each MRI biomarkers of VBI was significantly higher in patients with impaired versus preserved balance (top tertile of VV 40% vs 31% with respect to the full cohort; top tertile of WMH volume 45% vs 30%; prior infarct 31% vs 22%; prior lacunar infarct 24% vs 15%; CMB 28% vs 21%; all p values<0.05). The prevalence of each MRI biomarker of VBI except CMB was significantly higher among participants with slow versus normal or fast walk speed (top tertile of VV 39% vs 31% with respect to the full cohort; top tertile WMH volume 45% vs 29%; prior infarct 35% vs 21%; prior lacunar infarct 27% vs 14%; all p values<0.01).

Imbalance was significantly associated with four out of five MRI biomarkers of VBI (table 2). Adjusted ORs were 1.73 (95% CI 1.23 to 2.45) for top tertile of VV, 1.64 (95% CI 1.18 to 2.29) for top tertile of WMH and 1.46 (95% CI 1.07 to 1.99) for a radiographic lacunar infarct (table 2). The interaction of WMH tertile and CMB on the outcome of imbalance was statistically significant (p=0.03; online supplemental table 2). The remainder of the two-way interaction analyses of imbalance was not significant. Slow walk speed was significantly associated with four of five biomarkers of VBI (table 3). Adjusted ORs were 2.12 (95% CI 1.51 to 2.98) for top tertile of VV, 2.32 (95% CI 1.66 to 3.24) for top tertile of WMH and 2.17 (95% CI 1.61 to 2.93) for a radiographic lacunar infarct (table 3). There were no significant interactions

Table 2 Associations between imbalance and MRI biomarkers of vascular brain injury in ARIC visit 5

MRI biomarker	Category	Unadjusted OR for imbalance	95% CI	P value*	Adjusted OR for imbalance†	95% CI	P value‡
Ventricular volume§	Tertile 1	Reference	–	–	–	–	–
	Tertile 2	1.66	1.23 to 2.24	0.001	1.43	1.03 to 1.99	0.035
	Tertile 3	1.92	1.43 to 2.57	<0.001	1.73	1.23 to 2.45	0.002
White matter hyperintensity volume§	Tertile 1	Reference	–	–	–	–	–
	Tertile 2	1.82	1.34 to 2.48	<0.001	1.37	0.98 to 1.91	0.063
	Tertile 3	2.66	1.98 to 3.59	<0.001	1.64	1.18 to 2.29	0.004
Prior infarct		1.57	1.22 to 2.03	<0.001	1.37	1.04 to 1.81	0.027
Prior lacunar infarct		1.74	1.31 to 2.31	<0.001	1.46	1.07 to 1.99	0.016
Microhaemorrhage		1.44	1.11 to 1.88	0.006	1.33	1.00 to 1.77	0.052

*P values comparing participants with and without imbalance.
†Adjusted for age, sex, race, hypertension, diabetes, body mass index at ARIC visit 5.
‡P values comparing participants with and without slow gait.
§Further adjusted for total brain volume in tertiles, n=1583.
ARIC, Atherosclerosis Risk in Communities.

between pairs of MRI biomarkers and slow walk speed (online supplemental table 2).

UKB cohort

Of 500 271 UKB participants, 41 443 were enrolled in the MRI neuroimaging study, of whom 1345 were excluded due to prevalent stroke, resulting in a cohort of 40 098 eligible participants. Mean age of participants was 56.5 years (SD 8.10 years). There were 6316 participants (15.8%) who reported falling in the past year and 1112 participants (2.8%) with slow walk speed. Participants with recent fall were significantly more likely to be older, female and have hypertension, dyslipidaemia, diabetes, elevated BMI and disorders of organs external to the CNS (table 4). Participants with slow walk speed were significantly more likely to be older, female and have hypertension, dyslipidaemia, diabetes, elevated BMI and disorders of organs external to the CNS. Characteristics of all and only eligible UKB participants are presented in online supplemental table 3. Eligible participants were

significantly younger and had less vascular risk factors compared with the full cohort.

The prevalence of each MRI biomarker of VBI was significantly higher among participants with versus without recent fall (top tertile of VV 35% vs 33% with respect to the full cohort; bottom tertile of brain volume 36% and 33%; top tertile of WMH volume 37% and 33%; top tertile of FA 38.3% vs 32.2%; top tertile of MD 37.2% vs 32.5%; top tertile of ICVF 37.0% vs 32.5%; top tertile of ISOVF 36.4% vs 32.6%; all p values<0.01; table 5).

The prevalence of each MRI biomarker of VBI was significantly higher among participants with slow versus normal or fast walk speed (top tertile of VV 37% and 33%; bottom tertile of brain volume 38% and 33%; top tertile of WMH volume 47% and 33%; top tertile of FA 46% vs 33%; top tertile of MD 41% vs 33%; top tertile of ICVF 40% vs 33%; top tertile of ISOVF 40% vs 33%; all p values<0.01). There were no significant interactions between pairs of MRI

Table 3 Associations between slow walk speed and MRI biomarkers of vascular brain injury in ARIC visit 5

MRI biomarker	Category	Unadjusted OR for slow walk speed	95% CI	P value	Adjusted OR for slow walk speed	95% CI	P value‡
Ventricular volume§	Tertile 1	Reference	–	–	–	–	–
	Tertile 2	1.50	1.12 to 1.99	0.006	1.53	1.11 to 2.12	0.010
	Tertile 3	1.73	1.31 to 2.30	<0.001	2.12	1.51 to 2.98	<0.001
White matter hyperintensity volume§	Tertile 1	Reference	–	–	–	–	–
	Tertile 2	2.24	1.65 to 3.05	<0.001	1.83	1.31 to 2.56	<0.001
	Tertile 3	3.13	2.31 to 4.22	<0.001	2.32	1.66 to 3.24	<0.001
Prior infarct		2.05	1.60 to 2.62	<0.001	1.98	1.51 to 2.60	<0.001
Prior lacunar infarct		2.30	1.75 to 3.03	<0.001	2.17	1.61 to 2.93	<0.001
Microhaemorrhage		1.28	0.99 to 1.66	0.064	1.19	0.89 to 1.59	0.242

‡ Adjusted for age, sex, race, hypertension, diabetes, and body mass index at ARIC Visit 5.
§ Further adjusted for total brain volume in tertiles, n=1,583.
ARIC, Atherosclerosis Risk in Communities.

Table 4 Characteristics of UKB participants (N=40 098) stratified by recent fall history and walk speed

Characteristics	No recent fall (n=33 782)	Recent fall (n=6316)	P value*	Normal/fast walk (n=38 986)	Slow walk (n=1112)	P value†
Age (years)	54.77 (7.53)	55.97 (7.40)	<0.001	54.92 (7.53)	56.46 (7.10)	<0.001
Female sex	17 165 (50.8%)	4113 (65.1%)	<0.001	20 592 (52.8%)	686 (61.7%)	<0.001
Black race	220 (0.7%)	35 (0.6%)	0.416	245 (0.6%)	10 (0.9%)	0.342
Hypertension	6106 (18.1%)	1372 (21.7%)	<0.001	7065 (18.1%)	413 (37.1%)	<0.001
Cholesterol medication use	2798 (8.3%)	615 (9.7%)	<0.001	3245 (8.3%)	168 (15.1%)	<0.001
Diabetes	841 (2.5%)	193 (3.1%)	0.01	944 (2.4%)	90 (8.1%)	<0.001
Current smoking	2057 (6.1%)	403 (6.4%)	0.391	2381 (6.1%)	79 (7.1%)	0.193
BMI 25–30 kg/m²	14 471 (42.9%)	2651 (42.1%)	<0.001	16 741 (43.0%)	381 (34.4%)	<0.001
BMI>30 kg/m²	5644 (16.7%)	1355 (21.5%)		6450 (16.6%)	549 (49.5%)	
Diseases of peripheral nervous system, eye and inner ear	12 054 (35.7%)	2488 (39.4%)	<0.001	14 057 (36.1%)	485 (43.6%)	<0.001
Peripheral vascular disease	534 (1.6%)	128 (2.0%)	0.012	635 (1.6%)	27 (2.4%)	0.052
Diseases of musculoskeletal system and connective tissue	19 653 (58.2%)	4102 (64.9%)	<0.001	22 919 (58.8%)	836 (75.2%)	<0.001

Values are n (percentage) for categorical variables or median (IQR) for continuous variables.
*P values comparing participants with and without recent fall.
†P values comparing participants with and without slow gait.
BMI, body mass index; UKB, UK Biobank.

biomarkers and slow walk speed (online supplemental table 4).

VV (OR 1.11; 95% CI 1.02 to 1.19), brain volume (OR 1.10; 95% CI 1.02 to 1.19) and each of the DTI measures (FA OR 1.16; 95% CI 1.08 to 1.24) were significantly associated with recent fall in adjusted analyses (table 6). WMH volume (OR 1.48; 95% CI 1.24 to 1.76) and FA (OR 1.57; 95% CI 1.32 to 1.87) were significantly associated with slow walk speed. There were no significant interactions between pairs of MRI biomarkers and recent fall (online supplemental table 4).

We evaluated the associations between the microstructural DTI markers of VBI and outcomes among participants without established macrostructural white matter disease. Among UKB participants in the lowest WMH tertile, the top tertile of the principal component of ICVF was significantly associated with recent fall (adjusted OR 1.17, p=0.015, online supplemental table 5). No other DTI markers associated with either outcome of interest.

DISCUSSION

MRI biomarkers of VBI were common and associated with measures of mobility impairment, even after adjusting for demographics and clinical comorbidity, in stroke-free participants from two community-dwelling populations. Our results suggest that clinically unrecognised VBI confers an independent risk for mobility impairment.

Our study provides compelling evidence confirming the association between VBI and mobility impairment in two large, stroke-free cohorts. WMH burden has been most frequently studied[24–30] and linked with mobility impairment. In the Cardiovascular Health Study, participants with worsening WMH lesions between serial MRI brain imaging over 5 years had a decline in gait speed.[7] In the Leukoaraiosis AND DISability or LADIS study of 639 older participants, WMH severity was associated with gait speed and balance.[6] Low FA was associated with gait function in 173 elderly individuals, in patients who fell among 94 individuals and with slow walk speed in 68 older adults.[28 29] Our study confirms these results and extends

Table 5 MRI biomarkers of vascular brain injury of UKB participants stratified by recent fall history and walk speed

MRI biomarker	No recent fall (n=33 782)	Recent fall (n=6316)	P value*	Normal/fast walk (n=38 986)	Slow walk (n=1112)	P value†
Ventricular volume‡ (mL)	42.91 (32.83, 56.68)	43.96 (33.51, 57.38)	0.001	43.03 (32.87, 56.74)	44.93 (35.00, 59.95)	<0.001
Brain volume‡ (mL)	1159.12 (1084.08, 1237.68)	1131.13 (1060.21, 1210.16)	<0.001	1155.84 (1080.97, 1234.55)	1118.03 (1048.68, 1192.92)	<0.001
White matter hyperintensity volume‡ (mL)	3.64 (1.97, 7.33)	4.17 (2.19, 8.59)	<0.001	3.69 (1.98, 7.44)	5.29 (2.74, 11.21)	<0.001

*P values comparing participants with and without recent fall.
†P values comparing participants with and without slow gait.
‡Median and IQR.
UKB, UK Biobank.

Table 6 Associations between recent fall and slow walk speed and MRI biomarkers of vascular brain injury in the UKB

MRI biomarker (N=40 098)	Category	OR of recent fall* (95% CI), p value	OR of recent fall† (95% CI), p value	OR of slow walk speed* (95% CI), p value	OR of slow walk speed† (95% CI), p value
Ventricular volume	Tertile 1	Reference	Reference	Reference	Reference
	Tertile 2	1.07 (1.00–1.15), 0.060	1.07 (1.00–1.15), 0.049	1.09 (0.92–1.28), 0.313	1.10 (0.93–1.29) 0.26
	Tertile 3	1.10 (1.02–1.19), 0.015	1.11 (1.02–1.19), 0.010	1.12 (0.94–1.33), 0.202	1.14 (0.96–1.36) 0.138
Brain volume	Tertile 1	Reference	Reference	Reference	Reference
	Tertile 2	1.07 (1.00–1.15), 0.065	1.07 (1.00–1.15), 0.054	1.11 (0.94–1.30), 0.230	1.11 (0.94–1.31) 0.203
	Tertile 3	1.09 (1.01–1.19), 0.025	1.10 (1.02–1.19), 0.018	1.04 (0.87–1.24), 0.692	1.05 (0.88–1.26) 0.593
WMH volume	Tertile 1	Reference	Reference	Reference	Reference
	Tertile 2	0.99 (0.93–1.07), 0.889	0.99 (0.93–1.07), 0.866	1.17 (0.98–1.39), 0.083	1.16 (0.98–1.38) 0.090
	Tertile 3	1.05 (0.97–1.13), 0.241	1.05 (0.97–1.13), 0.242	1.47 (1.24–1.76), <0.001	1.48 (1.24–1.76) <0.001
FA PC1	Tertile 1	Reference	Reference	Reference	Reference
	Tertile 2	1.03 (0.96–1.11), 0.487	1.03 (0.96–1.10), 0.530	1.31 (1.10–1.55), 0.002	1.30 (1.09–1.54) 0.003
	Tertile 3	1.17 (1.09–1.25), <0.001	1.16 (1.08–1.24), <0.001	1.58 (1.33–1.88), <0.001	1.57 (1.32–1.87) <0.001
MD PC1	Tertile 1	Reference	Reference	Reference	Reference
	Tertile 2	1.01 (0.95–1.09), 0.357	1.01 (0.94–1.09), 0.357	0.98 (0.84–1.15), 0.815	0.98 (0.84–1.15) 0.806
	Tertile 3	1.14 (1.07–1.23), <0.001	1.14 (1.06–1.23), <0.001	1.15 (0.98–1.34), 0.085	1.14 (0.98–1.34) 0.093
ICVF PC1	Tertile 1	Reference	Reference	Reference	Reference
	Tertile 2	1.03 (0.96–1.10), 0.357	1.02 (0.96–1.10), 0.357	0.98 (0.84–1.15), 0.815	0.98 (0.84–1.15) 0.806
	Tertile 3	1.14 (1.07–1.23), <0.001	1.14 (1.07–1.23), 0.001	1.15 (0.98–1.34), 0.085	1.14 (0.98–1.34) 0.093
ISOVF PC1	Tertile 1	Reference	Reference	Reference	Reference
	Tertile 2	1.09 (1.02–1.17), 0.015	1.09 (1.02–1.17), 0.015	1.24 (1.05–1.47), 0.010	1.39 (0.95–2.11) 0.105
	Tertile 3	1.13 (1.04–1.22), 0.002	1.13 (1.05–1.23), 0.002	1.35 (1.13–1.62), 0.001	1.36 (0.94–2.05) 0.119

*Adjusted for age, sex, race, hypertension, diabetes and body mass index.
†Adjusted for age, sex, race, hypertension, diabetes, body mass index, diseases of the peripheral nervous system, eye, and ear, peripheral vascular disease, diseases of the musculoskeletal system and connective tissue.
FA, fractional anisotropy; ICVF, intracellular volume fraction; IsoVF, isotropic volume fraction; MD, mean diffusivity; PC1, principal component 1; UKB, UK Biobank; WMH, white matter hyperintensity.

the literature with findings of associations between additional MRI VBI biomarkers and measures of mobility impairment in two clinically stroke-free, community-based cohorts.

Our study uniquely demonstrates a link between MRI biomarkers of VBI and mobility impairment on adjustment for disorders of non-CNS organs. Mobility requires complex integration of sensory inputs from the body and its surroundings and appropriate motor responses for control of body movements.[30] Balance is reliant on vision, coordination of vestibular and proprioception inputs and outputs, afferents to muscles, coordinated movement and reaction time. Reduced walk speed is associated with poor memory, executive function, processing speed and visuospatial ability.[31] Disorders of non-CNS organs can disrupt these pathways required for maintaining mobility.

One example of such a disorder is knee osteoarthritis. Furthermore, conditions external to the brain that impact mobility may also be associated with vascular risk factors, such as diabetic retinopathy and neuropathy. Our study uniquely isolates an independent association between VBI and mobility impairment adjusted for non-CNS disorders and vascular risk factors. Nevertheless, further study is necessary to definitively prove whether a true causal link exists between VBI and mobility impairment.

Among individuals without established white matter disease, microstructural white matter tract abnormalities were linked with recent fall. While WMH and lacunar infarcts are end-stage manifestations of ischaemic injury, DTI changes may represent microstructural damage even in 'normal-appearing white matter'. MRI markers of early microstructural injury that correlate with mobility

impairment indicate a potential window of opportunity in the absence of overt white matter disease markers. Since the compromise of the white matter susceptible to ischaemia may be mediated by cardiometabolic diseases,[32] removal of a vascular insult may prevent the progression of microstructural white matter pathology and facilitate mobility preservation. Although WMH was not associated with recent fall in the UKB, mean volume of WMH was relatively low (5.2±6.8 mL), likely reflecting the younger UKB cohort. The older ARIC cohort had a larger WMH mean volume (17.3±17.0 mL), which was associated with imbalance and walking speed. Because FA is a biomarker of future WMH development, it follows that the positive association with FA in the UKB reflects a similar finding to that of the ARIC cohort, although at an earlier and potentially intervenable stage.

The association between mobility impairment and VBI may be relevant to clinical trial design. Trial endpoints representing brain health may be improved by inclusion of important clinical events with shared causes relevant to an intervention.[33] Clinical stroke is included in the standard composite endpoint of major adverse cardiovascular events. The link between cognitive impairment and VBI is now also well established, with almost half of patients with Alzheimer's disease noted to have concomitant cerebrovascular disease.[34] About 5% of dementia is solely associated with cerebrovascular disease secondary to clinical stroke or WMH.[35] [36] Consequently, incident dementia is increasingly being incorporated as an outcome in cardiovascular trials.[37] Mobility is critical for maintaining functional independence but is under-represented in trials.[38] [39] Mobility impairment can lead to decreased movement due to fear of falling, resulting in a sedentary lifestyle and a worsening vascular health profile. Our results demonstrating high prevalence of MRI biomarkers of VBI among individuals with mobility impairment and their relatedness support considering the inclusion of mobility impairment in composite outcomes that reflect brain health.

Our study had limitations. It was subject to constraints inherent in a cross-sectional design. There were differences in availability and ascertainment of mobility impairment outcomes and MRI biomarkers of VBI in the two cohorts. There may be cultural and recall biases in self-reporting walk speed and falls. The two cohorts were dissimilar in age. Nevertheless, the relationships between MRI biomarkers of VBI and mobility impairment measures held, likely reflecting the robustness of the association. The cohorts were assembled on the basis of self-report of no history of stroke. If individuals with prior stroke were included in the sample erroneously due to recall bias, this may result in overestimation of the prevalence of MRI biomarkers of VBI in the target population of individuals free of a clinical stroke, potentially resulting in risk estimates that are biased away from the null.

CONCLUSION

Clinically unrecognised cerebrovascular disease detected on brain MRI is independently associated with mobility impairment. Along with clinical stroke and cognitive impairment, incorporation of mobility impairment in composite, patient-centred outcomes related to brain health may capture a broader spectrum of clinically meaningful disability due to cerebrovascular injury.

terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

ORCID iDs
Richa Sharma http://orcid.org/0000-0003-0798-2353
Adam de Havenon http://orcid.org/0000-0001-8178-8597
Seyedmehdi Payabvash http://orcid.org/0000-0003-4628-0370

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