Network Efficiency Mediates the Relationship Between Vascular Burden and Cognitive Impairment
A Diffusion Tensor Imaging Study in UK Biobank

Jun Shen, MSc; Daniel J. Tozer, PhD; Hugh S. Markus, FMedSci; Jonathan Tay©, PhD

Background and Purpose—Cerebrovascular disease contributes to age-related cognitive decline, but the mechanisms underlying this phenomenon remain completely understood. We hypothesized that vascular risk factors would lead to cognitive impairment through the disruption of brain white matter network efficiency.

Methods—Participants were 19,346 neurologically healthy individuals from UK Biobank that underwent diffusion MRI and cognitive testing (mean age=62.6). Global efficiency, a measure of network integration, was calculated from white matter networks constructed using deterministic diffusion tractography. First, we determined whether demographics (age, sex, ethnicity, socioeconomic status, and education), vascular risk factors (hypertension, hypercholesterolemia, diabetes mellitus, smoking, body mass index), and white matter hyperintensities were related to global efficiency using multivariate linear regression. Next, we used structural equation modeling to model a multiple regression. The dependent variable was a latent cognition variable using all cognitive data, while independent variables were a latent factor including all vascular risk factors (vascular burden), demographic variables, white matter hyperintensities, and global efficiency. Finally, we used mediation analysis to determine whether global efficiency explained the relationship between vascular burden and cognition.

Results—Hypertension and diabetes mellitus were consistently associated with reduced global efficiency even after controlling for white matter hyperintensities. Structural equation models revealed that vascular burden was associated with cognition (P=0.023), but not after adding global efficiency to the model (P=0.09), suggesting a mediation effect. Mediation analysis revealed a significant indirect effect of global efficiency on cognition through vascular burden (P<0.001), suggesting a partial mediation effect.

Conclusions—Vascular burden is associated with reduced global efficiency and cognitive impairment in the general population. Network efficiency partially mediates the relationship between vascular burden and cognition. This suggests that treating specific risk factors may prevent reductions in brain network efficiency and preserve cognitive functioning in the aging population. (Stroke. 2020;51:1682-1689. DOI: 10.1161/STROKEAHA.119.028587.)

Key Words: body mass index ■ cerebrovascular disease ■ diffusion tensor imaging ■ risk factors ■ stroke
Methods

Data Availability Statement
UK Biobank is an open access resource available to verified researchers upon application (https://www.ukbiobank.ac.uk/).

Study Participants
UK Biobank is a population-based cohort study comprising 500,000 men and women recruited across Great Britain (England, Scotland, and Wales) between 2006 and 2010. Following an initial assessment, a subset of participants returned for brain magnetic resonance imaging (MRI) an average of 7.7 (SD=1.4) years later. The data we analyze are from the visit for the MRI scan.

During the MRI visit, participants underwent a medical history review by a trained nurse. Participants were excluded if they reported a diagnosis of: Alzheimer disease or any other dementia, Parkinson disease, ischemic or hemorrhagic stroke, aneurysm, demyelinating disease including multiple sclerosis, chronic or degenerative neurological problems, neurological injury or trauma, head injury, infection of the nervous system, encephalitis, epilepsy, brain/intracranial abscess, cerebral palsy, or brain tumor.

UK Biobank received ethical approval from the Research Ethics Committee (reference 11/NW/0382), and all participants provided written informed consent. The present analyses were conducted under UK Biobank application 36509.

Demographic and Vascular Risk Factor Information
Sex and self-reported ethnic background were reported via touchscreen interview at the initial assessment. Ethnicity was recoded as a binary variable (White or not). The Townsend Deprivation Index was used to measure socioeconomic status and was automatically assigned to participants based on their postal codes. All other information was reported during the MRI visit. Educational qualifications and smoking status were recorded via touchscreen. Qualifications were recoded as a binary variable (College/University degree or not), while smoking status was an ordinal variable with 3 levels (never smoked/ex-smoker/current smoker). Body mass index (BMI) was calculated after removal of bulky items of clothing and shoes as participant weight (kg)/height² (m). Diagnoses of diabetes mellitus, hypertension, and hypercholesterolemia were obtained from the medical history interview. Two seated automated measurements of blood pressure were taken using the Omron HEM-7015IT device. These 2 measurements were averaged to provide mean systolic blood pressure and diastolic blood pressure.

Cognitive Assessment
The cognitive tests used in our study were administered via touchscreen during the MRI visit. Fluid intelligence was assessed using a numeric memory test, which required participants to remember a 2-digit number after a pause, with digits increasing by one until the participant made an error or reached 12 digits. The reliability and longitudinal stability of these tests has been previously reported. In brief, the protocol included a T1-weighted anatomic image, a T2-weighted fluid attenuated inversion recovery image to quantify white matter hyperintensities (WMHs), and a diffusion MRI sequence to measure white matter microstructural properties. The diffusion MRI sequence included 105 volumes acquired at 2 mm³ resolution, with 5 at b=0 s/mm², 50 at b=1000 s/mm², and 50 at b=2000 s/mm².

Brain Volumetry
Brain volumetry was calculated using tools from FSL as previously described. In brief, total brain volumes (TBVs) were estimated from the T1-weighted images using the Structural Image Evaluation, Using Normalization, of Atrophy for Cross-Sectional Measurement (SIENAX) method, while WMH volumes were automatically calculated from fluid attenuated inversion recovery images using the Brain Intensity Abnormality Normalisation Classification Algorithm (BIANCA). TBV and WMH were then normalized for differences in head size by multiplying the raw volumes by a scaling parameter estimated in SIENAX.

Diffusion MRI Preprocessing and Tractography
Raw diffusion data were corrected for eddy currents, head motion, outlier slices, and gradient distortion. Diffusion tensors were then fit using the b=1000 s/mm² shell, yielding a scalar fractional anisotropy (FA) image. This FA image was then nonlinearly warped to standard space. Full details on the diffusion processing pipeline and the software used by the UK Biobank imaging team have been published elsewhere.

The FA image in native diffusion space was used for deterministic diffusion tensor tractography using MRtrix3. Streamlines were seeded on a 0.5 mm grid for every voxel with FA ≥0.15 and propagated in 0.5 mm steps using fourth-order Runge-Kutta integration. Termination criteria included the following: streamline length <20 or >250 mm, turning angle >45°, or voxel FA <0.15.

Network Analysis
Following tractography, a connectivity matrix was generated for each participant using nodes derived from the Automated Anatomic Labeling (AAL) atlas. The AAL is widely used in network analysis studies and consists of 90 manually labeled cortical and subcortical areas (45 per hemisphere) in standard space. These 90 regions exclude cerebellar regions in the AAL as tractography algorithms perform poorly in these areas.

The warp field calculated from each participant’s FA image to standard space was inverted and applied to the AAL using nearest neighbor interpolation, bringing the AAL into native diffusion space (where streamlines were computed). Two areas in the AAL were considered connected if joined by the end points of a reconstructed streamline, resulting in a nonzero edge in the connectivity matrix. Edges were weighted according to the number of streamlines connecting 2 regions multiplied by the inverse average streamline length, as longer streamlines are seeded multiple times. Streamlines that terminated in the same AAL region they were initiated in were excluded, and edge weights <1 were set to 0 to minimize noise-related false positives. This yielded a zero-diagonal symmetrical 90x90 undirected connectivity matrix for each participant. An illustration of how connectivity matrices are derived is shown in Figure 1.

Finally, network measures were calculated for each connectivity matrix using the Brain Connectivity Toolbox. We chose to focus on weighted global efficiency, $E^w$, which is the average inverse shortest path length, $d_{ij}^w$, between a pair of nodes, $i$ and $j$, for the set of all nodes in a network, $N$, such that:

$$E^w = \frac{1}{N} \sum_{i \in N} \sum_{j \neq i} \frac{d_{ij}^w}{n-1}$$

with $n$ being the total number of nodes. A more formal mathematical description of this measure can be found elsewhere. The global
efficiency of brain white matter networks has been shown to be a strong predictor of cognitive deficits, dementia, and mortality in patients with cerebrovascular disease.5,18

**Statistical Analysis**

All analyses were conducted in R 3.6.2 with the lavaan package 0.6-5. Unless otherwise specified, all tests were 2-tailed with $\alpha=0.05$. 

**Figure 1.** White matter network construction. A network consists of nodes and connecting edges. Using magnetic resonance imaging, nodes can be defined using an a priori neuroanatomical parcellation, while edges can be defined using tractography on diffusion tensor images. Co-registering the parcellation and tractography image yields information on how gray matter regions are connected by the white matter. This is the basis of the connectivity matrix, which represents white matter network connectivity.
All reported \( P \) values were adjusted for multiple comparisons on a model-wise basis using the false discovery rate.\(^{20}\) Variables with positive skew were transformed using log \(_e\) transformations, with the prior addition of a scalar constant if values were <1. Variables transformed included Townsend Deprivation Index, BMI, reaction time, and visual memory.

Our analysis attempted to answer 3 following inter-related questions: (1) are vascular risk factors related to global efficiency; (2) does global efficiency explain variance in general cognitive function after controlling for vascular risk factors; and (3) does global efficiency mediate the relationship between vascular risk factors and cognition?

To answer the first question, whether vascular risk factors were related to global efficiency, we modeled 2 multivariate linear regressions with global efficiency as the dependent variable. In the first model, age, sex, ethnicity, education, Townsend Deprivation Index, normalized TBV, and the vascular risk factors were regressed on global efficiency, allowing us to assess the individual contributions of each vascular risk factor on global efficiency. The second model included all the terms in the first while adding normalized WMH volume as an additional covariate to control for SVD severity. These models were then compared using a likelihood ratio test. A significant difference in these models would indicate that WMH explains additional variance in global efficiency beyond the vascular risk factors alone. Given the potential importance of blood pressure for affecting global efficiency, we repeated the analyses by replacing hypertension with systolic blood pressure.

To answer the second question, whether global efficiency explained additional variance in general cognitive function after controlling for vascular risk factors, we used structural equation modeling. Structural equation modeling allows for the modeling of directed (regression) and undirected (correlation) relationships between observed and unobserved (latent) variables. A latent variable is not directly measured in an experiment but rather inferred through other measured variables. Latent variables can then be regressed on other observed or unobserved variables, making it a useful approach to dimensionality reduction.\(^{21}\)

Two latent variables were defined: a vascular factor (henceforth referred to as vascular burden), which included smoking, BMI, hypertension, hypercholesterolemia, and diabetes mellitus; and a factor representing general cognitive function, which included numeric memory, prospective memory, fluid intelligence, reaction time, and visual memory. The psychometric characteristics and longitudinal stability of this single-factor cognitive construct have been previously validated in this cohort.\(^{9}\) These latent variables were then used in another series of multiple regressions, modeled within the structural equation modeling framework. In the first model, vascular burden, demographic variables, and WMH burden was regressed on the general cognitive factor. The second model included all the terms of the first but added global efficiency as a predictor of cognition.

To answer the third question, which was whether global efficiency mediated the relationship between vascular risk factors and cognition, we used mediation analysis, a technique used to determine if the association between variables can be partially explained by the effect of a third, or mediating, variable.\(^{22}\) In this mediation model, vascular burden was used as the independent variable, cognition the dependent variable, and global efficiency the mediating variable. In mediation analyses, the total effect is the original relationship between vascular burden and cognition, unadjusted for the mediator. The direct effect is the effect of vascular burden after adjusting for the mediator, while the indirect effect, also called the mediation effect, is the effect of global efficiency on cognition through vascular burden. A significant indirect effect is indicative of a mediation effect.

To account for sporadic missing data, all structural equation models were fit using full information maximum likelihood. Full information maximum likelihood uses all available information to estimate models, thereby leveraging information in partially complete cases without imputing missing values.\(^{23}\) All reported \( \beta \)'s presented are standardized regression coefficients and are thus directly comparable, while reported \( P \) values have been adjusted for multiple comparisons on a model-wise basis using the false discovery rate method.

**Results**

Following exclusions due to neurological diseases, MR scans of inadequate quality for analysis, and failures of the MRI analysis pipeline, a total of 19 364 participants had usable diffusion MRI data. Descriptive statistics for this subset of participants are reported in Table 1.

**Vascular Risk Factors Are Associated With White Matter Network Global Efficiency**

The results of the regression analyses on global efficiency are shown Table 2. The first regression, which included demographic variables, vascular risk factors, and TBV as covariates showed that all variables except hypercholesterolemia were associated with global efficiency. Age, TBV, and sex explained the most variability, with all other variables explaining relatively small amounts of variance.

### Table 1. Descriptive Statistics for Included Participants

| Demographic variables                     | Mean (SD) or Count (%) N |
|-------------------------------------------|-------------------------|
| Age                                       | 62.6 (7.4) 19 346       |
| Sex, female (%)                           | 9108 (47.1) 19 346      |
| Ethnicity, white (%)                      | 18 786 (97.4) 19 285    |
| Education, College or University (%)      | 9000 (46.5) 19 346      |
| Townsend Deprivation Index                | –2.0 (2.6) 19 329       |
| Vascular risk factors                     |                         |
| Smoking (never/ex/current)                | 11 982 (62.6)/6444 (33.7)/724 (3.8) 19 150 |
| BMI, mm/kg\(^2\)                          | 26.6 (4.4) 18 871       |
| Hypertension (%)                          | 3924 (20.3) 19 346      |
| SBP, mm/Hg                                | 136.8 (17.8) 16 351     |
| Diabetes mellitus (%)                     | 891 (4.6) 19 346        |
| Hypercholesterolemia (%)                  | 2265 (11.7) 19 346      |
| Neuroimaging variables                    |                         |
| TBV, mm\(^3\)                             | 502 645.4 (72.588.0) 19 346 |
| WMH, mm\(^3\)                             | 4530.2 (5850.0) 19 303  |
| Global efficiency                         | 6.6 (1.3) 19 346        |
| Cognitive variables                       |                         |
| Numeric memory                            | 6.8 (1.3) 8509          |
| Fluid intelligence                        | 6.8 (2.1) 17 437        |
| Reaction time, ms                         | 588.5 (106.1) 17 827    |
| Prospective memory, correct first try (%) | 15 474 (86.5) 17 880    |
| Visual memory                             | 3.5 (2.8) 17 897        |

TBV and WMH have been adjusted for head size. BMI indicates body mass index; SBP, systolic blood pressure; TBV, total brain volume; TDI, Townsend Deprivation Index; and WMH, white matter hyperintensity volume.
We then added WMH volume to this regression model to determine whether vascular risk factors were merely causing SVD, which in itself leads to network disruption. As predicted, WMH was associated with global efficiency after controlling for all other variables. The addition of WMH to the model attenuated many coefficients from the original, leading smoking and BMI to become nonsignificant. Hypertension and diabetes mellitus remained significant, however, suggesting that some vascular risk factors predict global efficiency even after taking WMH into account. The inclusion of WMH increased the adjusted R² of the model, and a likelihood ratio test confirmed that the full model was an improvement ($F=1224.3$; $P<0.001$). This pattern of results was identical after replacing hypertension with systolic blood pressure (Table 3).

### Vascular Burden Is Not Associated With Cognition After Controlling for Global Efficiency

The results of the structural equation modeling-based regressions are in Table 4. Model 1 revealed that all variables, including vascular burden, demographic variables, and WMH, were associated with the latent cognition

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**Table 2. Multivariate Linear Regressions Showing Associations Between Risk Factors and Global Efficiency, With and Without WMH (n=18592)**

|          | Model 1 | Model 2 |
|----------|---------|---------|
|          | $\beta$ (95% CI) | $P$ Value | $\beta$ (95% CI) | $P$ Value |
| Age      | $-0.26 \, (-0.28$ to $-0.25)$ | $<0.001$ | $-0.14 \, (-0.16$ to $-0.12)$ | $<0.001$ |
| Sex      | $0.36 \, (0.33$ to $0.39)$ | $<0.001$ | $0.34 \, (0.32$ to $0.37)$ | $<0.001$ |
| Ethnicity| $0.28 \, (0.20$ to $0.36)$ | $<0.001$ | $0.26 \, (0.18$ to $0.33)$ | $<0.001$ |
| Education| $0.05 \, (0.03$ to $0.08)$ | $<0.001$ | $0.05 \, (0.02$ to $0.07)$ | $<0.001$ |
| log$_{10}$(TDI) | $-0.02 \, (-0.03$ to $-0.01)$ | $0.002$ | $-0.02 \, (-0.03$ to $-0.01)$ | $0.001$ |
| Smoking | $-0.02 \, (-0.03$ to $-0.00)$ | $0.009$ | $-0.01 \, (-0.02$ to $0.01)$ | $0.29$ |
| log$_{10}$(BMI) | $-0.03 \, (-0.05$ to $-0.02)$ | $<0.001$ | $-0.01 \, (-0.02$ to $0.00)$ | $0.12$ |
| Hypertension | $-0.17 \, (-0.20$ to $-0.14)$ | $<0.001$ | $-0.11 \, (-0.15$ to $-0.08)$ | $<0.001$ |
| Diabetes mellitus | $-0.14 \, (-0.20$ to $-0.08)$ | $<0.001$ | $-0.09 \, (-0.15$ to $-0.03)$ | $0.003$ |
| Hypercholesterolemia | $-0.01 \, (-0.05$ to $0.03)$ | $0.71$ | $-0.01 \, (-0.05$ to $0.02)$ | $0.45$ |
| TBV      | $0.25 \, (0.23$ to $0.26)$ | $<0.001$ | $0.23 \, (0.22$ to $0.25)$ | $<0.001$ |
| WMH      | $-0.27 \, (-0.28$ to $-0.25)$ | $<0.001$ |

$\beta$ indicates standardized beta coefficient; BMI, body mass index; TBV, total brain volume; TDI, Townsend Deprivation Index; and WMH, white matter hyperintensity.

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**Table 3. Multivariate Linear Regressions With Blood Pressure Instead of Hypertension (n=15899)**

|          | Model 1 | Model 2 |
|----------|---------|---------|
|          | $\beta$ (95% CI) | $P$ Value | $\beta$ (95% CI) | $P$ Value |
| Age      | $-0.25 \, (-0.27$ to $-0.24)$ | $<0.001$ | $-0.13 \, (-0.15$ to $-0.11)$ | $<0.001$ |
| Sex      | $0.38 \, (0.35$ to $0.41)$ | $<0.001$ | $0.36 \, (0.33$ to $0.39)$ | $<0.001$ |
| Ethnicity| $0.29 \, (0.20$ to $0.37)$ | $<0.001$ | $0.25 \, (0.17$ to $0.34)$ | $<0.001$ |
| Education| $0.05 \, (0.03$ to $0.08)$ | $<0.001$ | $0.05 \, (0.02$ to $0.08)$ | $<0.001$ |
| log$_{10}$(TDI) | $-0.02 \, (-0.04$ to $-0.01)$ | $<0.001$ | $-0.03 \, (-0.04$ to $-0.01)$ | $<0.001$ |
| Smoking | $-0.01 \, (-0.03$ to $-0.00)$ | $0.044$ | $-0.00 \, (-0.02$ to $0.01)$ | $0.53$ |
| log$_{10}$(BMI) | $-0.03 \, (-0.05$ to $-0.02)$ | $<0.001$ | $-0.01 \, (-0.02$ to $0.01)$ | $0.17$ |
| SBP      | $-0.06 \, (-0.08$ to $-0.05)$ | $<0.001$ | $-0.03 \, (-0.05$ to $-0.02)$ | $<0.001$ |
| Diabetes mellitus | $-0.18 \, (-0.25$ to $-0.11)$ | $<0.001$ | $-0.12 \, (-0.19$ to $-0.06)$ | $<0.001$ |
| Hypercholesterolemia | $-0.04 \, (-0.08$ to $0.00)$ | $0.08$ | $-0.04 \, (-0.08$ to $0.00)$ | $0.10$ |
| TBV      | $0.25 \, (0.23$ to $0.27)$ | $<0.001$ | $0.23 \, (0.22$ to $0.25)$ | $<0.001$ |
| WMH      | $-0.27 \, (-0.28$ to $-0.25)$ | $<0.001$ |

$\beta$ indicates standardized beta coefficient; BMI, body mass index; SBP, systolic blood pressure; TBV, total brain volume; TDI, Townsend Deprivation Index; and WMH, white matter hyperintensity.
factor. In Model 2, which added global efficiency to Model 1, all variables remained significant except vascular burden, suggesting that the relationship between vascular burden and cognition may be mediated in part by global efficiency.

These models were then compared using the Akaike Information Criterion and Bayesian Information Criterion, 2 model selection indices where smaller values indicate better models. Model 2 minimized the Akaike Information Criterion (Model 1: 67384, Model 2: 67324, ΔAIC = −60) and Bayesian Information Criterion (Model 1: 67671, Model 2: 67619, ΔBIC = −52), suggesting that it was the better overall model.

**Global Efficiency Partially Mediates the Relationship Between Vascular Risk Factors and Cognition**

The results of the mediation analysis are shown in Figure 2. All regression paths were significant (P < 0.001). Mediation analysis showed that relationship between vascular burden and cognition was partially mediated by global efficiency, remaining significant even after controlling for global efficiency.

**Discussion**

We investigated the relationships between vascular burden, the global efficiency of white matter networks, and cognitive function in a large population-based cohort of neurologically healthy individuals. Our study yields 3 major findings. First, we showed that specific vascular risk factors were associated with reduced global efficiency, even after controlling for demographic variables and WMH volumes. Second, we demonstrated that vascular burden was associated with general cognitive function after controlling for demographic variables and WMH but not after adding global efficiency to the model. Third, we found that global efficiency partially mediated the relationship between vascular burden and cognition.

Analysis of individual vascular risk factors revealed that smoking, hypertension, diabetes mellitus, and BMI were associated with global efficiency, while hypercholesterolemia was not. This is consistent with research in smaller samples that show that patients with hypertension show reduced global efficiency, which may partially mediate the association between hypertension and executive function. Reduced global efficiency is also seen in diabetic patients. This suggests that treating specific vascular risk factors in the general population may prevent declines in global efficiency.

Furthermore, our study also showed that SVD-related pathology, as indicated by WMH volume, is associated with reduced global efficiency above and beyond the contributions of individual vascular risk factors. Indeed, the introduction of WMH to the model reduced many of the coefficients of individual vascular risk factors, leading to smoking status and BMI to become nonsignificant, suggesting that SVD-related processes play an important role in vascular alterations to white matter network topology. Previous studies have shown that WMH severity is associated with major symptoms of SVD, and that the relationship of WMH to these symptoms may be related to changes in the global efficiency of white matter networks. Importantly, however, WMH did not completely explain all the variance related to individual vascular risk factors, suggesting that vascular risk factors also result in network disruption via other mechanisms.

We also showed that vascular burden was related to general cognitive function, even after controlling for demographic variables and WMH volume. This relationship became nonsignificant after adding global efficiency to the model.

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**Table 4. Structural Equation Models Predicting Cognition, With and Without Global Efficiency**

|                      | Model 1 |           | Model 2 |           |
|----------------------|---------|-----------|---------|-----------|
|                      | β (95% CI) | P Value | β (95% CI) | P Value |
| Vascular burden      | −0.04 (−0.07 to −0.01) | 0.023 | −0.03 (−0.06 to 0.00) | 0.09 |
| Age                  | −0.21 (−0.24 to −0.18) | <0.001 | −0.19 (−0.22 to −0.16) | <0.001 |
| Sex                  | 0.15 (0.13 to 0.18) | <0.001 | 0.14 (0.12 to 0.16) | <0.001 |
| Ethnicity            | 0.22 (0.20 to 0.24) | <0.001 | 0.21 (0.19 to 0.24) | <0.001 |
| log10(TDI)           | −0.05 (−0.07 to −0.03) | <0.001 | −0.05 (−0.07 to −0.03) | <0.001 |
| Education            | 0.30 (0.28 to 0.32) | <0.001 | 0.30 (0.27 to 0.32) | <0.001 |
| log10(WMH)           | −0.10 (−0.13 to −0.08) | <0.001 | −0.08 (−0.10 to −0.05) | <0.001 |
| Global efficiency    | 0.10 (0.07 to 0.12) | <0.001 |
| BIC                  | 67384 |           | 67324 |           |
|                      | 67671 |           | 67619 |           |

Lower AIC and BIC values indicate a better fitting model. β indicates standardized beta coefficient; AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; TDI, Townsend Deprivation Index; and WMH, white matter hyperintensity.
suggesting a partial mediation effect which was supported by our subsequent mediation analysis. This suggests that the effects of vascular risk factors on cognitive function cannot be fully explained by differences in demographic variables such as age, education or socioeconomic status, nor by subsequent SVD-related pathology such as WMH. The global efficiency of white matter networks, in addition to the abovementioned variables, may be necessary for a more complete description of how vascular burden leads to cognitive impairment.

Taken together, our results suggest that an important area for future work lies in elucidating the mechanisms that lead from vascular risk factors to network function to cognitive impairment. It is important to stress that the answer to this question may lie beyond currently observed cerebrovascular pathology, given that these results were observed after excluding participants with ischemic or hemorrhagic stroke and after controlling for an aspect of SVD-related pathology. For instance, it is possible that hypertension and diabetes mellitus may lead to increased arterial tortuosity. Although mild vessel tortuosity is considered asymptomatic, it is possible that it may lead to subtle ischemic changes in the brain that are not radiologically visible but still result in reduced global efficiency.

Increasing evidence suggests early management of vascular risk factors may delay or prevent white matter network damage, in turn delaying cognitive decline and possibly lowering dementia risk. Mounting evidence suggests that midlife vascular risk factor exposure accelerates rates of WMH volume progression, global brain, and hippocampal atrophy, and late-life cognitive impairment. Our study suggest that white matter network integrity may be a central mechanism, which underlies this association between vascular risk factors and cognition.

Future work may also expand on the potential interactions between vascular risk factors and demographic variables. For instance, we found that ethnicity was associated with both global efficiency and cognition after controlling for other variables. This effect may have been biased by our predominantly white sample but may also be indicative, or related to, ethnic differences in vascular risk factors and subsequent cerebrovascular complications. In a similar vein, our participants were mostly older individuals. Given the established inter-relationships between age and changes in white matter organization, vascular risk, and cognition, it is possible that the pattern and magnitude of our findings differ across the lifespan. Replicating these findings in different populations with more balanced subgroups may therefore yield additional insights into these complex relationships.

There are some limitations in this study. First, cognitive tests in the UK Biobank were conducted by participants themselves using a touch screen interface, rather than being administered by a trained examiner. The tests themselves, while assessing a broad range of cognitive functions, are not typically administered in clinical research. Second, this study was cross-sectional in nature, and only focused on middle-aged to elderly participants. Longitudinal research may be able to better indicate whether vascular risk factors lead to a change in the global efficiency of white matter networks, and whether this has consequent effects on cognition. Furthermore, a longitudinal sample that included younger individuals would be able to better determine how these effects might change across the lifespan.

### Summary

We have shown that community-dwelling individuals with higher vascular burden show increased white matter network disruption and cognitive impairment, and that white matter network disruption may mediate the association between vascular risk factors and cognitive impairment. This suggests that treating specific vascular risk factors may prevent reductions in white matter network global efficiency, potentially preserving cognitive function in aging individuals.

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J. Shen, H.S. Markus, and J. Tay conceived of the study. Drs Tozer and Tay analyzed the imaging data. J. Shen and Dr Tay conducted the statistical analysis and drafted the manuscript. J. Shen, Drs Tozer and Tay, and Prof Markus revised the manuscript for intellectual content. J. Shen acknowledges the support of his supervisor Junjian Zhang in Zhongnan Hospital of Wuhan University.

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### Disclosures

Prof Markus reports personal fees from BIBA outside the present study.

### References

1. Pantoni L. Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. *Lancet Neurol*. 2010;9:689–701. doi: 10.1016/S1474-4422(10)70104-6
2. van Leijsen EMC, Tay J, van Uden IWM, Kooijmans ECM, Bergkamp M, et al. Structural network changes in cerebral small vessel disease explained by temporal interactions between white matter hyperintensities and hippocampal atrophy. *Hippocampus*. 2019;29:500–510. doi: 10.1002/hipo.23039
3. Wardlaw JM, Smith C, Dichgans M. Small vessel disease: mechanisms and clinical implications. *Lancet Neurol*. 2019;18:684–696. doi: 10.1016/S1474-4422(19)30079-1
4. Laurent S, Boutourie P. The structural factor of hypertension: large and small artery alterations. *Circ Res*. 2015;116:1007–1021. doi: 10.1161/CIRCRESAHA.116.303596
5. Taladhar AM, Tay J, van Leijsen E, Lawrence AJ, van Uden IWM, Bergkamp M, et al. Structural network changes in cerebral small vessel disease. *J Neurol Neurosurg Psychiatry*. 2020;91:196–203. doi: 10.1136/jnnp-2019-321767
6. Bullmore E, Sporns O. Complex brain networks: graph theoretical analysis of structural and functional systems. *Nat Rev Neurosci*. 2009;10:186–198. doi: 10.1038/nrn2575
7. Hagmann P, Cammoun L, Gigandet X, Meuli R, Honey CJ, Wedeen VJ, et al. Mapping the structural core of human cerebral cortex. *PLoS Biol*. 2008;6:e159. doi: 10.1371/journal.pbio.0060159
8. Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLoS Med.* 2015;12:e1001779. doi: 10.1371/journal.pmed.1001779

9. Lyall DM, Cullen B, Allerhand M, Smith DJ, Mackay D, Evans J, et al. Cognitive Test Scores in UK Biobank: Data Reduction in 480,416 Participants and Longitudinal Stability in 20,346 Participants. *PLoS One.* 2016;11:e0154222. doi: 10.1371/journal.pone.0154222

10. Alfaro-Almagro F, Jenkinson M, Bangerter NK, Andersson JLR, Griffanti L, Douaud G, et al. Image processing and Quality Control for the first 10,000 brain imaging datasets from UK Biobank. *Neuroimage.* 2018;166:400–424. doi: 10.1016/j.neuroimage.2017.10.034

11. Smith SM, Zhang Y, Jenkinson M, Chen J, Matthews PM, Federico A, et al. Accurate, robust, and automated longitudinal and cross-sectional brain change analysis. *Neuroimage.* 2002;17:479–489. doi: 10.1006/nimg.2002.0978

12. Tournier J-D, Calamante F, Connelly A. MRtrix: Diffusion tractography using DT-MRI data. *Magn Reson Med.* 2004;52:1059–1069. doi: 10.1002/mrm.1040

13. Basser PJ, Pajevic S, Pierpaoli C, Duda J, Aldroubi A. In vivo fiber tractography using DT-MRI data. *Magn Reson Med.* 2000;44:625–632. doi: 10.1002/1522-2594(200010)44:4<625::aid-mrm17>3.0.co;2-o

14. Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, et al. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage.* 2002;15:273–289. doi: 10.1006/nimg.2001.0978

15. Hagmann P, Kurant M, Gigandet X, Thiran P, Wedeen VJ, Meuli R, et al. Mapping human whole-brain structural networks with diffusion MRI. *PLoS One.* 2007;2:e597. doi: 10.1371/journal.pone.0000597

16. Lawrence AJ, Chung AW, Morris RG, Markus HS, Barrick TR. Structural network efficiency is associated with cognitive impairment in small-vessel disease. *Neurology.* 2018;92:e1157–e1167. doi: 10.1212/WNL.00000000000612

17. Rubino M, Sporns O. Complex network measures of brain connectivity: uses and interpretations. *Neuroimage.* 2010;52:1059–1069. doi: 10.1016/j.neuroimage.2009.10.003

18. Lawrence AJ, Zeestraten EA, Benjamin P, Lambert CP, Morris RG, Barrick TR, et al. Longitudinal decline in structural networks predicts dementia in cerebral small vessel disease. *Neurology.* 2019;93:e1898–e1910. doi: 10.1212/WNL.000000000005551

19. Rosseel Y. lavaan: An R package for structural equation modeling and more. *J Stat Softw.* 2012;48:1–36.

20. Benjamini Y, Hochberg Y. Controlling the false discovery rate: A practical and powerful approach to multiple testing. *J R Stat Soc B.* 1995;57:289–300.