Vascular risk factors, white matter microstructure, and depressive symptoms: A longitudinal analysis in the UK Biobank

Authors

Maria Blöchl[1,2,3], H. Lina Schaare[4,5], Deniz Kumral[6,7], Michael Gaebler[1,8,9], Steffen Nestler[3], Arno Villringer[1,10,11]

[1] Department for Neurology, Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany

[2] International Max Planck Research School: Neuroscience of Communication: Structure, Function, and Plasticity, Leipzig, Germany

[3] Department of Psychology, University of Münster, Münster, Germany

[4] Otto Hahn Group Cognitive Neurogenetics, Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany

[5] Institute of Neuroscience and Medicine (INM-7: Brain and Behaviour) Research Centre Jülich, Germany

[6] Institute of Psychology, Neuropsychology, University of Freiburg, Freiburg, Germany

[7] Institute of Psychology, Clinical Psychology and Psychotherapy Unit, University of Freiburg, Freiburg, Germany

[8] Humboldt-Universität zu Berlin, Faculty of Philosophy, Berlin School of Mind and Brain, MindBrainBody Institute

[9] Max Planck Dahlem Campus of Cognition, Berlin, Germany

[10] Clinic for Cognitive Neurology, University Clinic Leipzig, Leipzig, Germany

[11] Center for Stroke Research Berlin, Charité – Universitätsmedizin Berlin, Berlin, Germany

Corresponding Author

Maria Blöchl, Max Planck Institute for Human Cognitive and Brain Sciences, 04103 Leipzig, Germany. Email: bloechl@cbs.mpg.de

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Abstract

Cumulative burden from vascular risk factors (VRFs) has been associated with an increased risk of depressive symptoms in mid- and later life, but the mechanisms underlying this link are still unclear. One hypothesis is that VRFs disconnect fronto-subcortical white matter tracts that underlie mood and emotion regulation, which in turn puts older adults at higher risk of developing depressive symptoms. However, evidence for the hypothesis that disconnection of white matter tracts underlies the association between VRF burden and depressive symptoms from longitudinal studies is scarce. This preregistered study analysed longitudinal data from 6,964 middle-aged and older adults from the UK Biobank who participated in consecutive assessments of VRFs, brain imaging, and depressive symptoms. Using mediation modelling, we directly tested to what extend white matter microstructure mediates the longitudinal association between VRF burden and depressive symptoms. Our results showed small associations between VRF burden and depressive symptoms at follow-up. However, there was no evidence that fractional anisotropy (FA) of white matter tracts mediated this association. Additional analyses also yielded no mediating effects using alternative operationalisations of VRF burden, mean diffusivity (MD) of single tracts, or overall average of tract-based white matter microstructure (global FA, global MD, white matter hyperintensity volume). Taken together, these results lend no support to the hypothesis that disconnection of white matter tracts underlies the association between VRF burden and depressive symptoms, while highlighting the relevance of using longitudinal data to directly test pathways linking vascular and mental health. Future studies should examine alternative mechanisms and potentially more fine-grained associations between VRFs and depressive symptoms using similar longitudinal study designs.

Introduction

Vascular risk factors (VRFs), such as hypertension, obesity, hypercholesterolemia, diabetes, and smoking, are common in patients with depression [1, 2]. Although the relationship between depression and VRFs seems complex and bidirectional [3, 4], previous research has shown that VRFs are associated with higher risk for depression in mid- and later life [2, 5, 6] and that this association is particularly strong for cumulative burden from multiple VRFs [2, 5].

A prevailing hypothesis posits the association between VRF burden and depressive symptoms in later adulthood might be due to cerebrovascular pathology [7]. Specifically, it has been suggested that VRF burden slowly leads to white matter disconnection, a microstructural deterioration of the brain's fronto-subcortical connective pathways through processes such as axonal demyelination that reduces information transfer efficiency [8, 9]. This loss of white matter microstructure, which disconnects brain regions involved in mood and emotion regulation, is thought to make older adults with higher VRF burden more vulnerable to develop depressive symptoms [7, 9–11].

The concept of disconnection relies on the analysis of diffusion magnetic resonance imaging (dMRI), a non-invasive, quantitative neuroimaging method that exploits the Brownian motion of water molecules, allowing inferences about the underlying microstructure of brain white matter *in vivo* [12, 13]. Abundant evidence using dMRI suggests that VRFs are associated with lower white matter microstructure integrity [14–17]. For example, a recent study in the UK Biobank suggested that burden from multiple VRFs is associated with altered white matter microstructure in association and thalamic pathways as assessed by fractional anisotropy (FA) and mean diffusivity (MD) [14]. A different line of research has furthermore reported altered white matter microstructure in fronto-subcortical regions of older people with depression [18–23], providing evidence for white matter disconnections in depression.

However, direct evidence for the hypothesis that white matter disconnection underlies the link between VRFs and depressive symptoms is still scarce given that longitudinal studies directly testing this pathway are lacking. Moreover, other findings exist that challenge the proposed mechanisms: For example, altered white matter microstructure has also been described in younger depressed patients that have low VRF burden [22] and studies have shown lower FA and more white matter hyperintensities (WMH) in older depressed compared to non-depressed participants – even after matching both

groups on VRFs [21, 24]. Thus, a longitudinal study is needed to directly examine the mediating pathway between VRF burden, white matter integrity, and depressive symptoms that has previously been hypothesised [9].

This preregistered study aimed to fill this gap by leveraging the longitudinal data of 6,964 middle-aged and older adults from the UK Biobank, who participated in consecutive assessments of VRF burden, white matter microstructure, and depressive symptoms over the course of about 8 years. We used mediation models to (1) establish the association between VRF burden and depressive symptoms, and (2) test whether white matter disconnections mediate this association. The longitudinal design ensured the temporal ordering of the variables under study, which is important when aiming to investigate potentially causal effects [25–27]. Our preregistered analyses focused on tract-based FA as an indicator of white matter microstructure. FA indicates the directional diffusion of water molecule diffusion along white matter bundles and has been shown to be sensitive to the influence of VRFs [14, 15, 17, 28]. We examined the robustness of our results in a range of exploratory analyses. First, we analysed two additional markers of VRF burden. Second, we explored effects when using tract-based MD as an indicator of white matter microstructure; MD indicates molecular diffusion rate and has also been associated with VRF burden [14, 16]. Finally, we explored global markers of white matter disconnection (grand-mean FA and MD across all tracts, WMH volume) as potential mediators of the association between VRF burden and depressive symptoms. Particularly WMH, which are diffuse regions of high signal intensity on T2-weighted magnetic resonance imaging (MRI) scans and of presumed vascular origin [29, 30], have previously been implicated in the aetiology of depression in later life [24, 31].

Methods

Preregistration, Data Access, Materials

We preregistered our core hypotheses and analysis plans on the Open Science Framework (OSF) in January 2019 (https://osf.io/8gjsa). We were granted access to the UK Biobank's data resource in May 2018 after an initial application, but embargoed data access until after preregistration. All data used in this study are publicly available from the UK Biobank upon registration (http://www.ukbio-bank.ac.uk/). The code to perform all the analyses is publicly available on the OSF (https://osf.io/fskgj/).

Sample and Participants

The UK Biobank is a large, ongoing cohort study that aims to follow the health and well-being of middle-aged and older adults [32]. Between 2006 and 2010, about 500,000 community-dwelling middle aged and older adults were recruited from across the United Kingdom (UK) to participate in the study. The baseline assessment comprised the measurement of a broad range of demographic and health factors, which included assessments of VRFs (e.g. systolic blood pressure measures, questions about smoking history, and questions on diabetes diagnoses; for details see below). Between 2015 and 2019, a subset of participants (N = 22,484) underwent a second assessment including head magnetic resonance imaging (MRI). Finally, a third mental health assessment was conducted online between 2016 and 2017 and comprised a depressive symptoms questionnaire (for details see below).

To ensure a longitudinal design of the study, we only included participants that successively participated in the (1) baseline assessment, (2) the neuroimaging assessment, and (3) the online follow-up (**Figure 1a**). Moreover, we excluded participants with manifest vascular diseases (e.g. stroke, myocardial infarction), neurodegenerative disorders (e.g. dementia, Parkinson's disease) or severe neuropsychiatric disorders (e.g. epilepsy, schizophrenia, bipolar disorder). Detailed UK Biobank variable codes for these exclusion criteria are listed in **Table S1** in the Supplementary Material. The final sample included 6,964 participants. A flow chart detailing participant inclusion and exclusion can be found in **Figure S1**.

The UK Biobank received ethical approval from the North West Multi-Centre Research Ethics Committee (MREC; reference 11/NW/0382). The present analyses were conducted under UK Biobank application number 37721. All participants provided informed consent to participate.

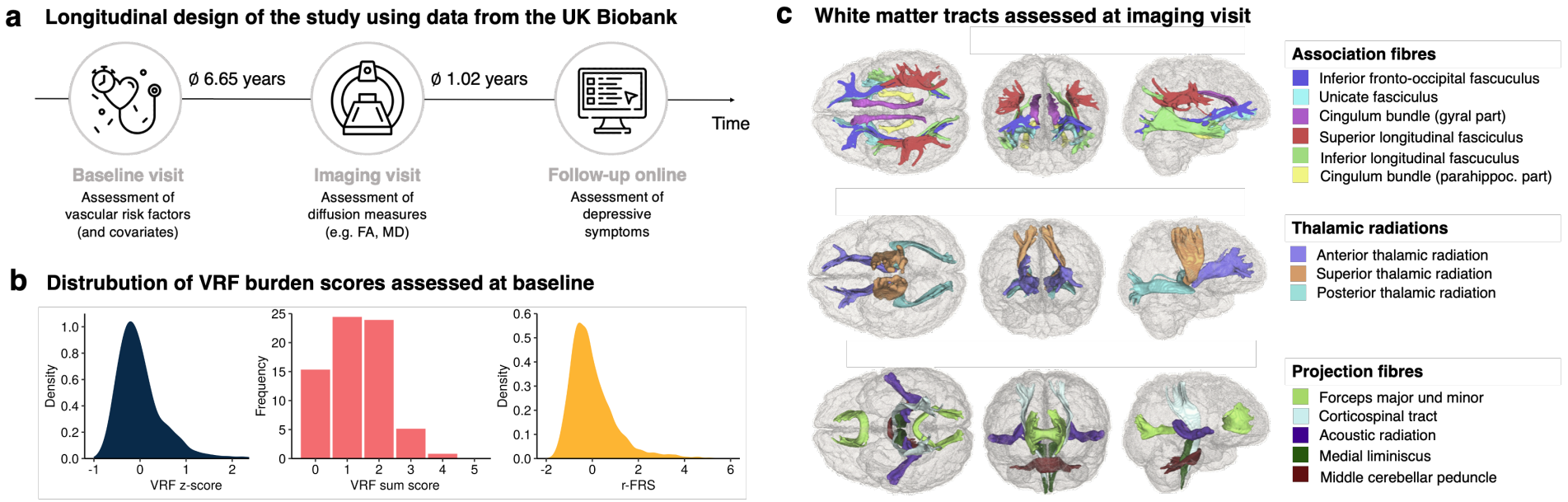

Figure 1. Methodological details of the study. **a** Illustration of the longitudinal study design, which only included participants that consecutively participated in the baseline visit, the imaging visit, and the online follow-up (this figure contains resources from Flaticon.com). **b** Plots of the distribution of the three VRF burden scores used in this study, preregistered VRF z-score (blue), VRF sum score (pink), and rFRS score (yellow). Note that the VRF z-score was preregistered. **c** White matter tracts assessed at the imaging visit (adapted from [33]). VRF: Vascular risk factor, FA: Fractional anisotropy, MD: Mean diffusivity, rFRS: revised Framingham Risk Score.

Definition of VRF burden

We created three indicators to reflect overall VRF burden comprising VRFs that are commonly associated with (cerebro-)vascular health [15–17, 34]. We first calculated the pre-registered z-score index by summing the z-standardised values of systolic blood pressure (SBP), body mass index (BMI), self-reported diagnosis of high cholesterol, presence of diabetes, and current smoking. SBP and BMI entered as continuous variables, while high cholesterol, diabetes, and smoking entered as dichotomous variables (0 = no, 1 = yes). Detailed UK Biobank variable codes for variables used to construct the preregistered VRF score are listed in **Table S2**.

In addition to the pre-registered z-score, we calculated two VRF burden indices that are commonly used: a VRF sum score and the revised Framingham Risk Score (rFRS). The VRF sum score indicates the number of VRFs per person and has been established as a predictor of depressive symptoms [5]. It was calculated by summing dichotomised variables indicating the presence of different VRFs: systolic blood pressure with self-reports of hypertension to indicate hypertension (0 = no, 1 = yes), a BMI ≥ 25kg/m² to indicate the presence of obesity (0 = no, 1 = yes), self-reported diagnosis of high cholesterol (0 = no, 1 = yes), self-reported diagnosis of diabetes (0 = no, 1 = yes), and current smoking (0 = no, 1 = yes). The FRS is a common tool to predict the risk for vascular diseases and the revised FRS (rFRS) was developed to predict stroke [35, 36]. The rFRS was calculated for women and men separately by combining information on several risk factors (age, sex, systolic blood pressure, use of antihypertensives, prevalent cardiovascular disease, current smoking status, current/previous atrial fibrillation, and diabetes mellitus [DM]) to predict 10-year probability of stroke as detailed in Dufouil et al. [36]. VRF sum score and rFRS were not pre-registered and hence used in exploratory analyses (see **Table S3** in the Supplementary Material). The distributions of all VRF scores are shown in **Figure 1b**.

Diffusion imaging and white matter data

White matter data were derived from the UK Biobank brain imaging data. All brain MRI data were acquired on a Siemens Skyra 3 T scanner with a standard Siemens 32-channel head coil and data acquisition followed the open-access protocol (http://www.fmrib.ox.ac.uk/ukbiobank/protocol/V4_23092014.pdf). Diffusion MRI (d-MRI) data was acquired with two b-values (b = 1000 and 2000 s/mm^2) at 2 mm spatial resolution, with multiband acceleration factor of 3. For each diffusion-weighted shell, 50 distinct diffusion-encoding directions were acquired (covering 100 distinct directions

over the two b-values), resulting in 2 mm isotropic voxels. The diffusion preparation was a standard ("monopolar") Stejskal-Tanner pulse sequence, which enabled higher SNR due to a short echo time (TE = 92ms) than a twice-refocused ("bipolar") sequence at the expense of stronger eddy current distortions [37, 38].

White matter markers analysed in this study have been generated from the raw d-MRI data by the UK Biobank team and were made available as imaging-derived phenotypes (IDPs). The full details of the image processing and quality control pipeline are described elsewhere [37]. In brief, the analyses rely on probabilistic tractography-based analysis, which has been used to map major white matter tracts using standard mask. For each tract, a weighted-mean value of FA and MD within each tract was computed (the weighting was determined by the tractography probabilistic output), which reflects structural connectivity between pairs of brain regions. These estimates were provided for 15 major white matter tracts (**Figure 1c**). For both FA and MD, we pairwise excluded outliers as defined by datapoints being 2.2 interquartile ranges below first or above third quartile [39]. FA and MD markers of the left and right hemisphere were averaged for bilateral white matter tracts (all tracts except for forceps major, forceps minor). Besides tract-based markers, we also explored the role of overall FA, overall MD, and whole-brain WMH load as global markers of white matter microstructure: We calculated global FA and global MD by summing all tract-based FA and MD integrity measures, respectively. We refer to these measures as "global measures" to highlight that the overall measure has very little spatial sensitivity, although it has to be noted that these measures are not brain-wide measures of FA and MD, respectively. The volume of WMH was calculated from the T1-weighted and fluid-attenuated inversion recovery images using Brain Intensity Abnormality Classification Algorithm (BIANCA) of the FMRIB Software Library (FSL) [40]. Tract-based MD and global markers of white matter microstructure were not pre-registered and hence used in exploratory analyses (see **Table S3** in the Supplementary Material). Detailed UK Biobank variable codes for white matter variables used in the preregistered analysis are listed in **Table S2**.

Assessment of depressive symptoms

Depressive symptoms were measured using the Patient Health Questionnaire 9 question version (PHQ-9). The PHQ-9 comprised 9 items asking whether participants experienced feelings of depression, feelings of inadequacy, tiredness or low energy, lack of interest or pleasure in doing things, poor appetite or overeating, thoughts of suicide or self-harm, trouble concentrating, trouble falling asleep or sleeping too much,

changes in speed or amount of moving over the past two weeks. Answers were given on a scale from 1 (“not at all”) to 4 (“nearly every day”). Detailed UK Biobank variable codes for depressive symptoms used in the preregistered analysis are listed in **Table S2**. A mean score of all items was derived with higher values indicating more severe depressive symptoms.

Covariates

Age, gender, racial-ethnic background, educational attainment, household income, Townsend deprivation index, baseline depressed mood, and total brain volume were included as covariates in all models [41]. Age (in years) was assessed at baseline. Gender was defined as a dichotomous variable due to its binary assessment (women / men). Racial-ethnic background was defined as a dichotomous variable (White / People of Colour [including people who identified as Asian or Asian British, Black or Black British, Chinese, Mixed, or Other]) since the vast majority of the sample (97%) identified themselves as "White". Educational attainment was defined as a dichotomous variable ("College or university degree" / "No college or university degree"). Household income was assessed as a categorial variable indicating pre-tax total household income in Sterling Pound ("Less than 18,000" / "18,000 to 30,999" / "31,000 to 51,999" / "52,000 to 100,000" / "Greater than 100,000"). Townsend deprivation index is a measure of the level of material deprivation in which the participant lives and was assessed as a continuous variable with higher values indicating greater deprivation [42, 43]. Baseline depressed mood was calculated as the average score of four items assessing mood symptoms at baseline: frequency of depressed mood, frequency of unenthusiasm / disinterest, frequency of tenses/restlessness, frequency of tiredness. Answers ranged from 1 (not at all) to 4 (nearly every day).Total brain volume was defined as a ratio that shows the volumetric scaling from the T1 head image to MNI standard atlas [37]. Detailed UK Biobank variable codes for covariates used in the preregistered analysis are listed in **Table S2**. Deviating from the preregistration, total brain volume was added as a covariate based on recommendations published after preregistering [41].

Preregistered statistical analyses

To assess whether white matter microstructure mediates the association of VRF burden with depressive symptoms, we used mediation models (**Figure 2**). In these models, VRF burden at baseline was defined as the exposure (X), white matter tract microstructure indices at the neuroimaging assessment as the mediators (Ms), and

depressive symptoms at the online follow-up as the outcome (Y). To estimate the mediation model, we relied on a path analytic framework, which simultaneously estimates the direct, indirect, and total effect using several regressions models [44]. The direct effect reflects the association between the exposure VRF burden at baseline (X) and the outcome depressive symptoms at follow-up (Y). It is the regression coefficient estimated by regressing X on Y while accounting for covariates. The indirect effect reflects the part of the association between X and Y that is mediated by white matter indices (M). It is the coefficient of two regression coefficients: the coefficients from regressing X on M, and the coefficients from regressing M on Y while accounting for X and all covariates. The total effect is the sum of the direct and the indirect effect and reflects the association between X and Y that is direct and mediated via M. The models were estimated using full information maximum likelihood (FIML) to account for missing data under the assumption of data missing at random [45]. Confidence intervals (CI) were calculated using bootstrapping (with 1,000 bootstrapping samples). Given the relatively large sample size and number of models, effects were considered significant when the 99% CI did not contain zero.

Based on our preregistration, we estimated mediation models using the VRF burden z-score for each of the 15 white matter tracts separately. Although we initially specified to perform a multiple mediation model, in which FA values of all 15 tracts were entered simultaneously as mediators, we simplified our model as detailed in our preregistered analysis plan. This was done given that the large model failed to converge due to very high intercorrelations (all *r*s between 0.99 and .97) between the tracts. Moreover, while our preregistration detailed analyses to compare the sizes of different mediating effects based (between white matter tracts connecting brain regions underlying mood and emotion regulation and other tracts), these comparisons were not performed because of the limited evidence for any mediating effects.

All analyses were performed using R (version 4.1.1); mediation models were estimated using lavaan [46].

Exploratory analyses

In addition to our preregistered analyses, we explored whether similar results were obtained when using either the VRF sum score or the rFRS to indicate VRF burden. We therefore fitted the same models as described above using the VRF sum score and the rFRS. We also repeated all analyses using MD as marker of local white matter structure (see above for descriptions of these variables). Overall, we fitted 90 models

using tract-based white matter indices as mediators (3 VRF burden scores x 15 tracts x 2 white matter markers), of which 75 models were exploratory.

Finally, we performed further exploratory mediation analyses to examine whether global white matter microstructure mediated the association between VRF burden and depressive symptoms. To this end, global FA, global MD, and WMH volume were entered as mediators into the longitudinal mediation models, which yielded an additional 9 models (3 VRF burden scores x 3 markers of global white matter microstructure). An overview of the used predictors (Xs) and mediators (Ms) in the longitudinal mediation models can be found in **Table S1** in the Supplementary Material.

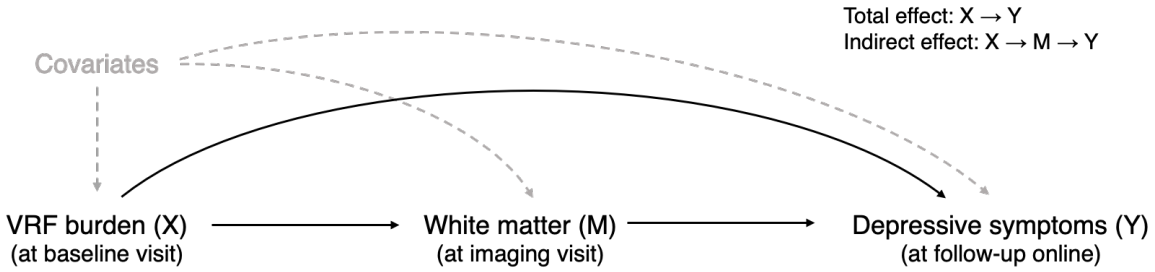

Figure 2. Illustration of the mediation model and estimated pathways. The indirect effect reflects the effect of X on Y through M. The total effect reflects the sum of the direct effect of X on Y and the indirect effect.

Results

Sample characteristics

The study included 6,964 participants with longitudinal data on vascular risk factors, white matter tract microstructure, and depressive symptoms (see **Figure S1** for flow chart). **Table 1** shows the sample characteristics at baseline. Of the 6,964 participants included in the analyses, 3,694 (53%) were women and the average age at baseline was 55.47 years (*SD* = 7.41, range = 40 – 70 years). The neuroimaging assessment took place on average 6.65 years (SD = 1.04, range = 4.29 – 10.81 years) after the baseline assessment, and the online-follow up was conducted on average 1.02 years after the neuroimaging assessment (see also **Figure 1a**).

Table 1. Baseline Characteristics of Participants (*n* = 6,964).

Variable	*n*	Mean ± *SD* or *n* (%)
Age in years	6,964	55.47 ± 7.42
Gender	6,964	
Women		3694 (53%)
Men		3270 (47%)
Racial-ethnic background	6,940	
White		6,765 (97%)
People of Colour[a]		175 (3%)
Education	6,838	
No university degree		3729 (54%)
University degree		3109 (45%)
Income	6,247	
< 18,000 £		770 (11%)
18,000 – 30,999 £		1,489 (21%)
31,000 – 51,999 £		1,928 (28%)
52,000 – 100,000 £		1,660 (24%)
> 100,000 £		400 (6%)
Townsend deprivation index	6,961	-2.02 ± 2.60
VRF z-score	6,941	0.00 ± 0.50
VRF sum score	6,941	1.30 ± 0.93
rFRS	6,806	0.02 ± 0.02
Depressive symptoms	6,964	1.26 ± 0.36

Note: VRF = vascular risk factor; rFRS = revised Framingham Risk Score.

[a] Includes people who identify as “Asian or Asian British”, “Black or Black British”, “Chinese”, “Mixed”, or “Other ethnic group”.

Preregistered analyses: Mediation of the association between VRF burden and depressive symptoms by FA of white matter tracts

We first assessed the total effect of our mediation analysis to investigate whether the VRF z-score at baseline was associated with depressive symptoms at follow-up. Mediation analyses revealed that the total effect was 0.042 (bootstrapped 99% CI [0.020, 0.068]), which indicates that for the VRF z-score, higher VRF burden at baseline predicted more severe depressive symptoms about 8 years later (**Figure 3a,** blue bar). We next examined indirect effects of the mediation analyses to test whether FA of 15 white matter tracts mediated the association between the VRF z-score and depressive symptoms. Results of the mediation models yielded no evidence for indirect effects for FA of any of the 15 white matter tracts (**Figure 3b,** blue bars). Of the 15

indirect effects, 0% were considered statistically different from zero. Estimated indirect effects were small with narrow CIs, ranging from -0.001 (bootstrapped 99% CI [-0.003, 0.001], cingulate bundle gyral part) to 0.001 (bootstrapped 99% CI [-0.001, 0.003], corticospinal tract). The mean indirect effect across 15 tracts was -0.0001 (*SD* = 0.0006). Examining the components of the indirect revealed significant negative associations for the VRF z-score → FA of 6 white matter tracts paths, indicating that higher VRF burden was associated with lower FA for the gyral part of the cingulum bundle, forceps minor, inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, posterior thalamic radiation, superior longitudinal fasciculus. However, there were no significant associations for the FA → depressive symptom path, suggesting that FA in white matter tracts was not associated with depressive symptoms after accounting for VRF burden and covariates (see Table S4 for detailed results).

Exploratory analyses

VRF sum score. First, we explored the robustness of our results for VRF sum score as an alternative measure of VRF burden. These analyses revealed a significant total effect with 0.019 (bootstrapped 99% CI [0.008, 0.029]; **Figure 3a,** pink bar), suggesting an association between higher VRF burden at baseline and depressive symptoms at follow-up. Of the 15 indirect effects assessing whether FA of 15 white matter tracts mediated this association, 0% were considered statistically different from zero (**Figure 3b,** pink bars). Estimated indirect effects were small with narrow CIs, ranging from -0.001 (bootstrapped 99% CI [-0.001, 0.001], superior longitudinal fasciculus) to 0.001 (bootstrapped 99% CI [-0.001, 0.002], corticospinal tract). The mean indirect effect across 15 tracts was -0.0001 (*SD* = 0.0003).

R-FRS score. Next, we explored the robustness of our results for rFRS as an alternative measure of VRF burden. Exploratory mediation analysis revealed that higher rFRS was associated with higher depressive symptoms at follow-up, but this effect was not statistically significant (*b* = 0.018, bootstrapped 99% CI [-0.007, 0.043]; **Figure 3a,** yellow bar). Indirect effects of these models similarly yielded no evidence for indirect effects for FA of any of the 15 white matter tracts (**Figure 3b**, yellow bars). Estimated indirect effects were small with narrow CIs, ranging from -0.001 (bootstrapped 99% CI [-0.002, 0.001], superior longitudinal fasciculus) to 0.001 (bootstrapped 99% CI [-0.001, 0.002], posterior thalamic radiation). The mean indirect effect across 15 tracts was -0.0002 (*SD* = 0.0004).

MD of white matter tracts. Next, we explored the robustness of our results by re-running the mediation models using all three VRF burden markers with MD of 15 white matter tracts as mediators. These analyses yielded similar total effects for the VRF z-score, the VRF sum score, and the rFRS score as the mediation models with FA (see **Figure 3a**). The mediation models furthermore yielded no evidence for indirect effects of MD of any of the 15 white matter tracts neither for the VRF z-score, the VRF sum score, nor the rFRS (**Figure 3b**). Of the 45 indirect effects, 0% were considered statistically different from zero. Estimated indirect effects were small with narrow CIs, ranging from -0.001 (bootstrapped 99% CI [-0.003, 0.001] medial lemniscus for rFRS) to 0.001 (bootstrapped 99% CI [-0.003, 0.001], middle cerebellar peduncle for VRF z-score). The mean indirect effect across 15 tracts was -0.0003 (*SD* = 0.0005) for the VRF z-score, -0.0001 (*SD* = 0.0002) for VRF sum score, and -0.0003 (*SD* = 0.0004) for rFRS.

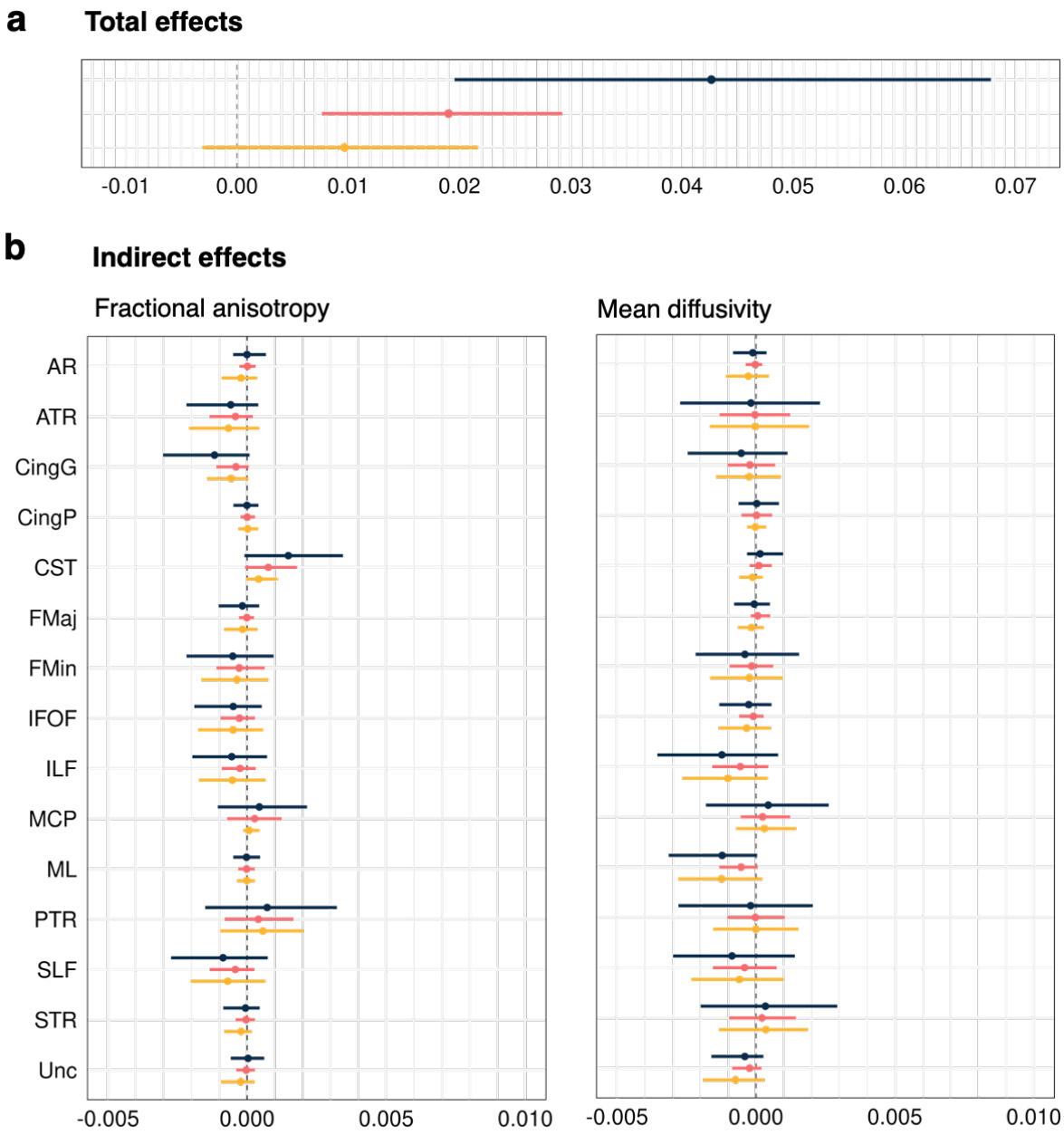

Figure 3. Total and indirect effect estimates of mediation models of FA and MD of single white matter tracts as mediators. **a** Total effects (and 99% CIs) of the pre-registered VRF z-score (blue), the VRF sum score (pink), and the revised FRS (yellow) on depressive symptoms at follow-up. Note that the total effects are very similar for each of the 90 longitudinal mediation models estimated, so only estimates from the first models (FA of AR) were plotted. **b** Indirect effects (and 99% CIs) of FA and MD of single white matter tracts. FA = Fractional anisotropy, MD = Mean diffusivity, AR = Acoustic radiation, ATR = Anterior thalamic radiation, CingG = Cingulate bundle (gyral part), CingP = Cingulate bundle (parahippocampal part), CST = Corticospinal tract, FMaj = Forceps major, FMin = Forceps minor, IFOF = Inferior fronto-occipital fasciculus, ILF = Inferior longitudinal fasciculus, MCP = Middle cerebellar peduncle, ML = Medial lemniscus, PTR = Posterior thalamic radiation, SLF = Superior longitudinal fasciculus, STR = Superior thalamic radiation, Unc = Uncinate fasciculus.

Global white matter markers. Finally, we explored whether markers of global white matter microstructure would mediate the association between VRF burden and depressive symptoms. Results of longitudinal mediation models using averaged FA and MD combining information from all tracts and WMH volume as mediators are detailed in **Table 3**. Results suggested that higher VRF burden was associated with more depressive symptoms at follow-up (except for the rFRS). Again, the 99% CIs of indirect effects of all models contained zero, yielding no evidence for a mediating effect of any of these global white matter indicators on the relationship between VRFs and depressive symptoms.

Table 3. Results of longitudinal mediation analyses using global white matter indices.

	VRF z-score			VRF sum score			rFRS		
	b	99% CI lower	99% CI upper	b	99% CI lower	99% CI upper	b	99% CI lower	99% CI upper
Global FA									
Total effect	**0.0426**	**0.0191**	**0.0669**	**0.0190**	**0.0081**	**0.0311**	0.0179	–0.0060	0.0412
Direct effect	**0.0431**	**0.0194**	**0.0668**	**0.0192**	**0.0082**	**0.0314**	0.0194	–0.0042	0.0428
Indirect effect	–0.0005	–0.0017	0.0004	–0.0002	–0.0007	0.0002	–0.0015	–0.0041	0.0008
Global MD									
Total effect	**0.0426**	**0.0175**	**0.0653**	**0.0189**	**0.0064**	**0.0304**	0.0180	–0.0074	0.0461
Direct effect	**0.0435**	**0.0198**	**0.0668**	**0.0193**	**0.0071**	**0.0307**	0.0198	–0.0076	0.0460
Indirect effect	–0.0009	–0.0029	0.0008	–0.0003	–0.0012	0.0003	–0.0018	–0.0056	0.0023
WMH volume									
Total effect	**0.0425**	**0.0189**	**0.0673**	**0.0190**	**0.0066**	**0.0301**	0.0176	–0.0072	0.0432
Direct effect	**0.0408**	**0.0164**	**0.0664**	**0.0180**	**0.0058**	**0.0292**	0.0146	–0.0100	0.0406
Indirect effect	0.0018	–0.0012	0.0051	0.0010	–0.0006	0.0027	0.0030	–0.0010	0.0076

Note. Effects that are considered significant (99% CI does not contain zero) are marked in bold. VRF = Vascular risk factors, CI = Confidence interval, rFRS = revised Framingham risk score, FA = Fractional anisotropy, MD = Mean diffusivity, WMH = White matter hyperintensities

Discussion

In this pre-registered study, we used longitudinal data from a large sample of middle aged and older adults, who participated in consecutive assessments of VRFs, white matter microstructure, and depressive symptoms in the UK Biobank. Our main aim was to test the hypothesis that the association between VRF burden and depressive symptoms is mediated by disconnection of white matter tracts. Our pre-registered analyses suggest a small association between VRF burden at baseline and the severity of depressive symptoms about 8 years later. There was, however, no evidence that FA of any white matter tract mediated this association. Extensive exploratory analyses, which included two alternative indicators of VRF burden and MD of white matter tracts yielded similar results for different operationalisations of VRF burden and white matter microstructure.

The results of our study are largely consistent with findings showing small associations between higher VRF burden and depressive symptoms [2, 5, 6]. However, it has to be noted that the association between rFRS and depressive symptoms was not statistically significant in this sample, while significant associations were found for the VRF z-score and sum score. This finding is in line with a meta-analysis suggesting that composite scores of VRFs, but not Framingham Risk Scores, are linked to later life depression [2]. It is possible that effects of certain VRFs show a closer, weaker, or perhaps even reverse association with depression. For example, the association between hypertension and depression [47] is less clear than the association between obesity and depression [48, 49]. Some studies have even suggested that people with higher systolic blood pressure tend to have fewer depressive symptoms [50, 51]. Notably, hypertension and blood pressure are important variables contributing to the rFRS, which might explain why no significant association of this score was observed in this study.

Importantly, we found no evidence that disconnection of white matter tracts mediated the association between VRF burden and depressive symptoms. Despite evidence for an association between VRF burden and white matter microstructure as previously reported [14, 17], we found that neither tract-based FA and MD nor overall markers of white matter damage (including WMH) underlie the link between VRF burden and depressive symptoms. These results lend no support to the prevailing hypothesis that VRFs lead to depressive symptoms because they disconnect fronto-subcortical

pathways [7, 9]. This hypothesis has been ubiquitous in the literature on vascular and mental health [2, 52, 53]. Yet, direct evidence has remained scare. Our study fills this gap in understanding the associations between VRFs, white matter, and depressive symptoms and highlights the importance of directly examining proposed mechanisms using longitudinal data.

Our findings offer several avenues of future research into the temporal and causal relationships between vascular risk, white matter microstructure, and depression. First, it is possible that previously reported white matter disconnections in later-life depression were overestimated because of small sample sizes or lack of appropriate control for socioeconomic factors. In the past years, these issues are increasingly recognised and more recent studies with larger samples suggest only small neural correlates of depression [54–57]. Results of our mediation models accounting for VRF burden, demographic, and socioeconomic covariates yielded no evidence for an association between white matter and subsequent depressive symptoms. It is possible that these small associations between white matter and depression are not due to VRFs. Instead, a large part of the observed variance in white matter microstructure might be explained by genetic factors [58, 59] and the link between white matter changes and depression might rather be attributed to their genetic correlations [58, 60, 61].

Another explanation is that certain VRFs, which show stronger associations with depressive symptoms, act through other mediating mechanisms than disconnection of white matter tracts. As argued above, classical VRFs, such as hypertension and blood pressure, which are strongly associated with white matter microstructure, might be less important in their association to depressive symptoms. Instead, metabolic-related VRFs, such as BMI or obesity, might make a stronger contribution to the association between certain composite VRF scores and depressive symptoms. Recently, it has been suggested that these metabolic VRFs might contribute to depressive symptoms, mainly via inflammatory pathways [62]. Although inflammatory markers have also been previously suggested to contribute to vascular depression [9] they have so far received relatively little attention. Future studies should aim to test whether such alternative physiological pathways might underly the relation between VRF burden and depressive symptoms.

This study extends our understanding of the links between VRFs burden, white matter microstructure, and depressive symptoms by leveraging a longitudinal study design, a large sample of middle aged and older adults, and mediation models to directly test longitudinal relationships between our variables of interest. Our main analyses were preregistered, which increases the credibility of our *a priori* research aims and better protects interpretations of results from biases [63], while extensive exploratory analyses supported the robustness of our results. However, our study had several limitations. First, the sample of the UK Biobank is relatively healthy, is less diverse, and has higher educational attainment compared to its target population [64]. Thus, selection effects might bias our estimated associations and limits generalisability of our findings [65]. While the UK Biobank offered a unique data source with extensive health data and longitudinal design for our study, future studies should replicate our results in more representative samples. Second, the quantification of white matter microstructure relied on tract-based measures, which limits spatial specificity. It is possible that more fine-grained mediation analyses of white matter would support mediation effects. Finally, the timing of the assessments time points varied between people. Some people might have had too short follow-up times, especially between the neuroimaging and mental health follow-up, which might have led to an underestimation of effects. Future studies should aim to include longer follow-up data to better understand the long-term associations between VRF burden and depressive symptoms and potential mediators underlying this association.

In this longitudinal study, we show an association between VRF burden and depressive symptoms in middle aged and older adults in the UK Biobank, but that this association is not mediated by tract-based or overall markers of white matter microstructure. Our results add to a better understanding of the relationship between VRF burden, white matter, and depressive symptoms in later adulthood, while lending no support to one prominent aetiological hypothesis of why VRFs and depression are linked. The present study also highlights the need for longitudinal data to directly test potential mediational pathways and points to the possibility that alternative mechanisms might link VRF burden and depressive symptoms in mid- and later life.

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Conflicts of Interest

On behalf of all authors, there are no conflicts of interests to declare.

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Supplementary Materials for

Vascular risk factors, white matter microstructure, and depressive symptoms: A longitudinal analysis in the UK Biobank

Maria Blöchl, H. Lina Schaare, Deniz Kumral, Michael Gaebler,
Steffen Nestler, Arno Villringer
Correspondence to: bloechl@cbs.mpg.de

This PDF file includes:

Table S1. List of variables used for excluding participants (incl. hyperlinks to the UK Biobank showcase).

Data ID	Data descriptor	Participant excluded if any of the following applied
6150	Vascular/heart problems diagnosed by doctor	[heart attack] [stroke]
20002	Non-cancer illness code, self-reported	[1075] heart attack/myocardial infarction [1076] heart failure/pulmonary oedema [1081] stroke [1083] subdural haemorrhage/haematoma [1259] motor neurone disease [1260] myasthenia gravis [1261] multiple sclerosis [1262] parkinsons disease [1263] dementia/alzheimers/cognitive impairment [1264] epilepsy [1286] depression [1289] schizophrenia [1291] mania/bipolar disorder/manic depression [1408] alcohol dependency [1409] opioid dependency [1410] other substance abuse/dependency [1469] post-traumatic stress disorder [1470] anorexia/bulimia/other eating disorder [1491] brain haemorrhage [1583] ischaemic stroke [1615] obsessive compulsive disorder (ocd)
20546	Substances taken for depression	Medication prescribed for you (for at least two weeks)

Figure S1. Flowchart of participant exclusion and inclusion.

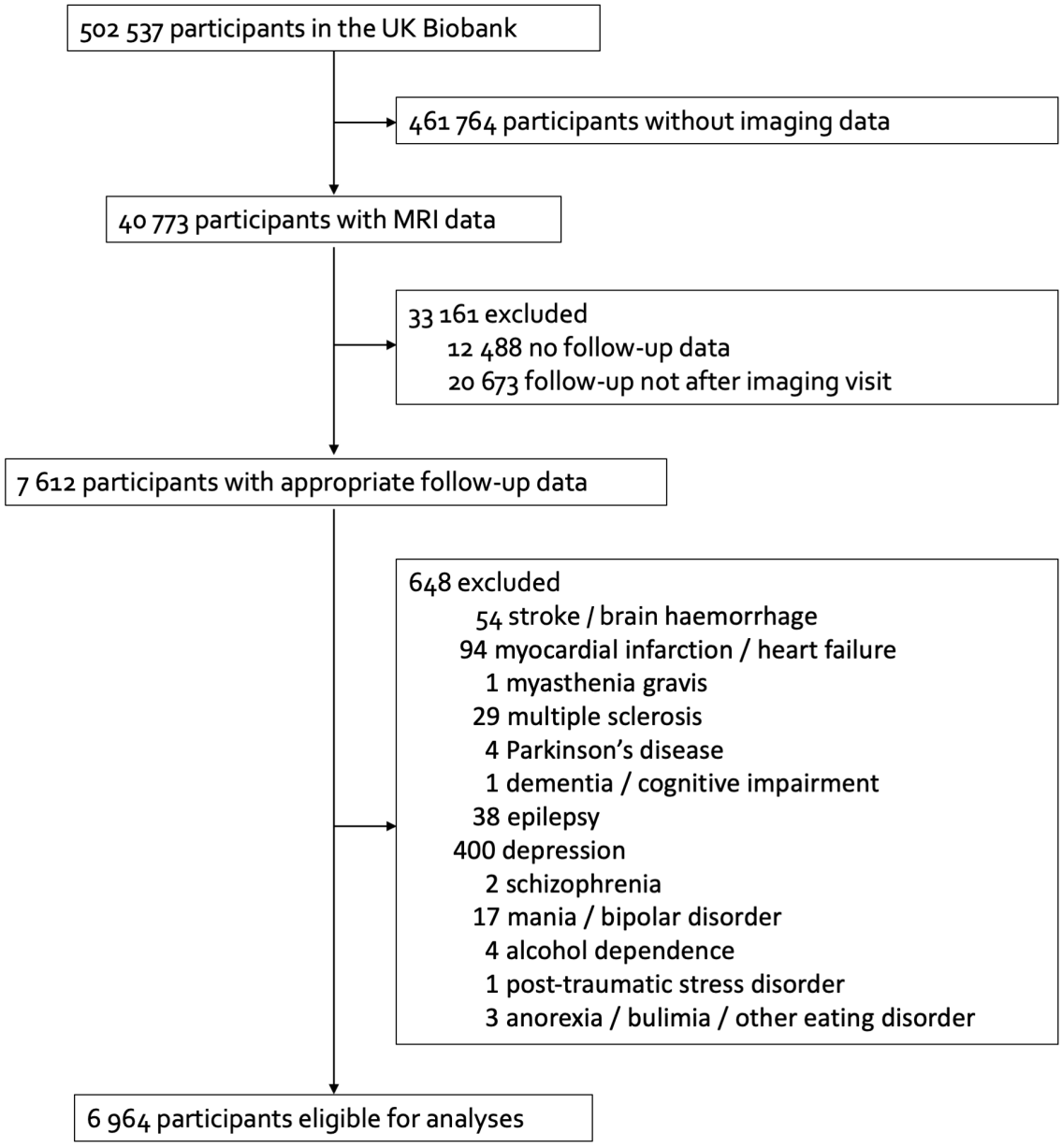

Table S2. List of relevant variables for pre-registered analyses.

Data ID	Data descriptor
Vascular risk factors	
4080	Systolic blood pressure, automated reading (mmHg)
93	Systolic blood pressure, manual reading (mmHg)
21001	Body mass index (kg/m²)
20002	Non-cancer illness code, self-reported [high cholesterol]
2443	Diabetes diagnosed by doctor
1239	Current tobacco smoking (yes, most or all days/only occasionally/no)
White matter markers	
25488	Weighted-mean FA in tract acoustic radiation (left)
25489	Weighted-mean FA in tract acoustic radiation (right)
25490	Weighted-mean FA in tract anterior thalamic radiation (left)
25491	Weighted-mean FA in tract anterior thalamic radiation (right)
25492	Weighted-mean FA in tract cingulate gyrus part of cingulum (left)
25493	Weighted-mean FA in tract cingulate gyrus part of cingulum (right)
25496	Weighted-mean FA in tract corticospinal tract (left)
25497	Weighted-mean FA in tract corticospinal tract (right)
25498	Weighted-mean FA in tract forceps major
25499	Weighted-mean FA in tract forceps minor
25500	Weighted-mean FA in tract inferior fronto-occipital fasciculus (left)
25501	Weighted-mean FA in tract inferior fronto-occipital fasciculus (right)
25502	Weighted-mean FA in tract inferior longitudinal fasciculus (left)
25503	Weighted-mean FA in tract inferior longitudinal fasciculus (right)
25505	Weighted-mean FA in tract medial lemniscus (left)
25506	Weighted-mean FA in tract medial lemniscus (right)
25504	Weighted-mean FA in tract middle cerebellar peduncle
25494	Weighted-mean FA in tract parahippocampal part of cingulum (left)
25495	Weighted-mean FA in tract parahippocampal part of cingulum (right)
25507	Weighted-mean FA in tract posterior thalamic radiation (left)
25508	Weighted-mean FA in tract posterior thalamic radiation (right)
25509	Weighted-mean FA in tract superior longitudinal fasciculus (left)
25510	Weighted-mean FA in tract superior longitudinal fasciculus (right)
25511	Weighted-mean FA in tract superior thalamic radiation (left)
25512	Weighted-mean FA in tract superior thalamic radiation (right)
25513	Weighted-mean FA in tract uncinate fasciculus (left)
25514	Weighted-mean FA in tract uncinate fasciculus (right)
Depressive symptoms	
20510	Recent feelings of depression
20507	Recent feelings of inadequacy

20519	Recent feelings of tiredness or low energy
20514	Recent lack of interest or pleasure in doing things
20511	Recent poor appetite or overeating
20513	Recent thought of suicide or self-harm
20508	Recent trouble concentrating on things
20517	Trouble falling asleep, or sleeping too much
20518	Recent changes in speed / amount of moving or speaking
Covariates	
21003	Age (in years)
31	Gender (male / female)
21000	Ethnic background
6138	Educational attainment
738	Household income
189	Townsend deprivation index
2050	Frequency of depressed mood in last 2 weeks
2060	Frequency of unenthusiasm / disinterest in last 2 weeks
2070	Frequency of tenseness / restlessness in last 2 weeks
2080	Frequency of tiredness / lethargy in last 2 weeks

Table S3. Overview of variables used in the longitudinal mediation models.

Variable	Pre-registered or exploratory	Type of WM indicator	Detailed listing
Vascular risk factor burden (X)			
z-score	pre	–	–
sum Score	exp	–	–
revised FRS	exp	–	–
White matter microstructure (M)			
FA 15 single tracts	pre	local	AR, ATR, CingG, CingP, CST, FMaj, FMin, IFOF, ILF, MCP, ML, PTR, SLF, STR, Unc
MD 15 single tracts	exp	local	AR, ATR, CingG, CingP, CST, FMaj, FMin, IFOF, ILF, MCP, ML, PTR, SLF, STR, Unc
FA whole brain	exp	global	–
MD whole brain	exp	global	–
WMH volume	exp	global	–
Depressive symptoms (Y)			
Depressive symptoms	pre	–	–

Note: FA = Fractional anisotropy, MD = Mean diffusivity, FRS = Framingham Risk Score, WMH = White matter hyperintensities, pre = preregistered, exp = exploratory, WM = White matter, AR = Acoustic radiation, ATR = Anterior thalamic radiation, CingG = Cingulate bundle (gyral part), CingP = Cingulate bundle (parahippocampal part), CST = Corticospinal tract, FMaj = Forceps major, FMin = Forceps minor, IFOF = Inferior fronto-occipital fasciculus , ILF = Inferior longitudinal fasciculus, MCP = Middle cerebellar peduncle, ML = Medial lemniscus, PTR = Posterior thalamic radiation, SLF = Superior longitudinal fasciculus, STR = Superior thalamic radiation, Unc = Uncinate fasciculus.

Table S4. Results of pre-registered mediation analyses.

	estimate	lower 95% CI	upper 95% CI
Acoustic radiation			
Total effect	**0.043**	**0.020**	**0.068**
Direct effect	**0.043**	**0.020**	**0.068**
Indirect effect	-0.000	-0.000	0.000
VRFs → FA	0.000	-0.001	0.001
FA → depr. sympt.	0.220	-0.343	0.843
Anterior thalamic radiation			
Total effect	**0.043**	**0.021**	**0.064**
Direct effect	**0.043**	**0.021**	**0.065**
Indirect effect	-0.001	-0.002	0.000
VRFs → FA	0.001	-0.003	0.000
FA → depr. sympt.	0.415	-0.300	1.139
Cingulate bundle (gyral part)			
Total effect	**0.043**	**0.020**	**0.068**
Direct effect	**0.044**	**0.021**	**0.070**
Indirect effect	-0.001	-0.003	0.000
VRFs → FA	**-0.003**	**-0.005**	**-0.001**
FA → depr. sympt.	0.356	-0.034	0.732
Corticospinal tract			
Total effect	**0.043**	**0.020**	**0.067**
Direct effect	**0.041**	**0.018**	**0.065**
Indirect effect	0.001	-0.001	0.003
VRFs → FA	**0.003**	**0.001**	**0.004**
FA → depr. sympt.	0.542	-0.030	1.088
Forceps major			
Total effect	**0.043**	**0.019**	**0.065**
Direct effect	**0.043**	**0.019**	**0.065**
Indirect effect	0.000	-0.001	0.000
VRFs → FA	-0.001	-0.003	0.001
FA → depr. sympt.	0.131	-0.266	0.528
Forceps minor			
Total effect	**0.043**	**0.019**	**0.067**
Direct effect	**0.043**	**0.019**	**0.067**
Indirect effect	-0.001	-0.002	0.001
VRFs → FA	**-0.003**	**-0.004**	**-0.001**
FA → depr. sympt.	0.190	-0.382	0.702
Inferior fronto-occipital fasciculus			
Total effect	**0.043**	**0.019**	**0.067**
Direct effect	**0.043**	**0.020**	**0.067**
Indirect effect	0.000	-0.002	0.001
VRFs → FA	**-0.002**	**-0.003**	**-0.001**
FA → depr. sympt.	0.270	-0.328	0.874
Inferior longitudinal fasciculus			
Total effect	**0.043**	**0.020**	**0.067**
Direct effect	**0.043**	**0.020**	**0.068**
Indirect effect	-0.001	-0.002	0.001
VRFs → FA	**-0.002**	**-0.003**	**-0.001**
FA → depr. sympt.	0.292	-0.301	0.894

Medial lemniscus			
Total effect	**0.043**	**0.019**	**0.069**
Direct effect	**0.043**	**0.018**	**0.070**
Indirect effect	0.000	-0.000	0.000
VRFs → FA	-0.001	-0.002	0.001
FA → depr. sympt.	0.042	-0.490	0.567
Middle cerebellar peduncle			
Total effect	**0.043**	**0.019**	**0.068**
Direct effect	**0.042**	**0.019**	**0.068**
Indirect effect	0.000	-0.001	0.002
VRFs → FA	**0.004**	**0.002**	**0.006**
FA → depr. sympt.	0.120	-0.191	0.437
Cingulate (parahippocampal part)			
Total effect	**0.043**	**0.019**	**0.066**
Direct effect	**0.043**	**0.018**	**0.066**
Indirect effect	0.000	-0.000	0.000
VRFs → FA	0.000	-0.002	0.002
FA → depr. sympt.	-0.047	-0.544	0.412
Posterior thalamic radiation			
Total effect	**0.043**	**0.022**	**0.067**
Direct effect	**0.042**	**0.021**	**0.065**
Indirect effect	0.001	-0.002	0.003
VRFs → FA	**-0.004**	**-0.005**	**-0.003**
FA → depr. sympt.	-0.175	-0.732	0.357
Superior longitudinal fasciculus			
Total effect	**0.043**	**0.022**	**0.066**
Direct effect	**0.043**	**0.023**	**0.066**
Indirect effect	-0.001	-0.003	0.001
VRFs → FA	**-0.003**	**-0.004**	**-0.001**
FA → depr. sympt.	0.333	-0.258	0.896
Superior thalamic radiation			
Total effect	**0.043**	**0.020**	**0.065**
Direct effect	**0.043**	**0.020**	**0.065**
Indirect effect	0.000	-0.001	0.000
VRFs → FA	0.000	-0.001	0.001
FA → depr. sympt.	0.324	-0.275	0.968
Uncinate fasciculus			
Total effect	**0.043**	**0.018**	**0.065**
Direct effect	**0.043**	**0.018**	**0.065**
Indirect effect	0.000	-0.001	0.001
VRFs → FA	0.000	-0.001	0.001
FA → depr. sympt.	0.281	-0.337	0.843

Note. Estimates in bold are considered significant as their 99% CI does not contain zero. All associations are adjusted for covariates age, gender, racial-ethnic background, educational attainment, household income, Townsend deprivation index, and baseline depressive symptoms. CI = confidence interval. VRFs = vascular risk factors. FA = fractional anisotropy.