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

Maria Blöchl[1,2,3], H. Lina Schaare[4,5], Deniz Kumral[6,7], Michael Gaebler[1,8,9], Steffen Nestler[3] and 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]Clinical Psychology and Psychotherapy Unit, Institute of Psychology, University of Freiburg, Freiburg, Germany; [8]Faculty of Philosophy, Humboldt-Universität zu Berlin, 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 and [11]Center for Stroke Research Berlin, Charité – Universitätsmedizin Berlin, Berlin, Germany

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Author for correspondence:
Maria Blöchl, E-mail: bloechl@cbs.mpg.de

Abstract

Background. Cumulative burden from vascular risk factors (VRFs) has been associated with an increased risk of depressive symptoms in mid- and later life. It has been hypothesised that this association arises because VRFs disconnect fronto-subcortical white matter tracts involved in mood regulation, which 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.
Methods. 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.
Results. VRF burden showed a small association with 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).
Conclusions. Our 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.

Introduction

Vascular risk factors (VRFs), such as hypertension, obesity, hypercholesterolemia, diabetes, and smoking, are common in patients with depression (Molero et al., 2017; Valkanova & Ebmeier, 2013). Although the relationship between depression and VRFs seems complex and bidirectional (Hare, Toukhsati, Johansson, & Jaarsma, 2014; Penninx, 2017), previous research has shown that VRFs are associated with higher risk for depression in mid- and later life (Blöchl, Schaare, Kunzmann, & Nestler, 2021; Kivimäki et al., 2012; Valkanova & Ebmeier, 2013) and that this association is particularly strong for cumulative burden from multiple VRFs (Blöchl et al., 2021; Valkanova & Ebmeier, 2013).

A prevailing hypothesis posits the association between VRF burden and depressive symptoms in later adulthood might be due to cerebrovascular pathology (Alexopoulos, 1997). 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 (Catani & Ffytche, 2005; Taylor, Aizenstein, & Alexopoulos, 2013). 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 (Alexopoulos, 1997; Mather, 2012; Smagula & Aizenstein, 2016; Taylor et al., 2013).

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* (Chanraud, Zahr, Sullivan, & Pfefferbaum, 2010; Le Bihan, 2014). Abundant evidence using dMRI suggests that VRFs are associated with lower white matter microstructure integrity (Cox et al., 2019*a*, 2019*b*; Fuhrmann et al., 2018; Maillard et al., 2012; Power et al., 2017). 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) (Cox et al., 2019*a*, 2019*b*). A different line of research has furthermore reported altered white matter microstructure in fronto-subcortical regions of older people with depression (Brookes, Herbert, Lawrence, Morris, & Markus, 2014; Liao et al., 2013; Pasi et al., 2016; Reppermund et al., 2014; Shen et al., 2017; Wen, Steffens, Chen, & Zainal, 2014), 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 (Liao et al., 2013) 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 (Reppermund et al., 2014; Sheline et al., 2008). 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 (Taylor et al., 2013).

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 (see Fig. 1*a* for details on the study timeline). 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 (Hill, 1965; Maxwell & Cole, 2007; VanderWeele, Jackson, & Li, 2016). 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 (Cox et al., 2019*a*, 2019*b*; Fuhrmann et al., 2018; Maillard et al., 2012; Wang et al., 2015). 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 the average molecular diffusion rate in all directions and has also been associated with VRF burden (Cox et al., 2019*a*, 2019*b*; Power et al., 2017). 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 (Debette & Markus, 2010; Wardlaw, Valdés Hernández, & Muñoz-Maniega, 2015), have previously been implicated in the aetiology of depression in later life (Herrmann, Le Masurier, & Ebmeier, 2007; Sheline et al., 2008).

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 (Bycroft et al., 2018). 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 (SBP) 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 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 (Fig. 1*a*). 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 online Supplementary Table S1. The final sample included 6,964 participants. A flow chart detailing participant inclusion and exclusion can be found in online Supplementary Fig. 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 37 721. All participants provided informed consent to participate.

Definition of VRF burden

We created three indicators to reflect overall VRF burden comprising VRFs that are commonly associated with (cerebro-)vascular health (Fuhrmann et al., 2018; Maillard et al., 2012; O'Donnell et al., 2016; Power et al., 2017). We first calculated the preregistered z-score index by summing the z-standardised values of

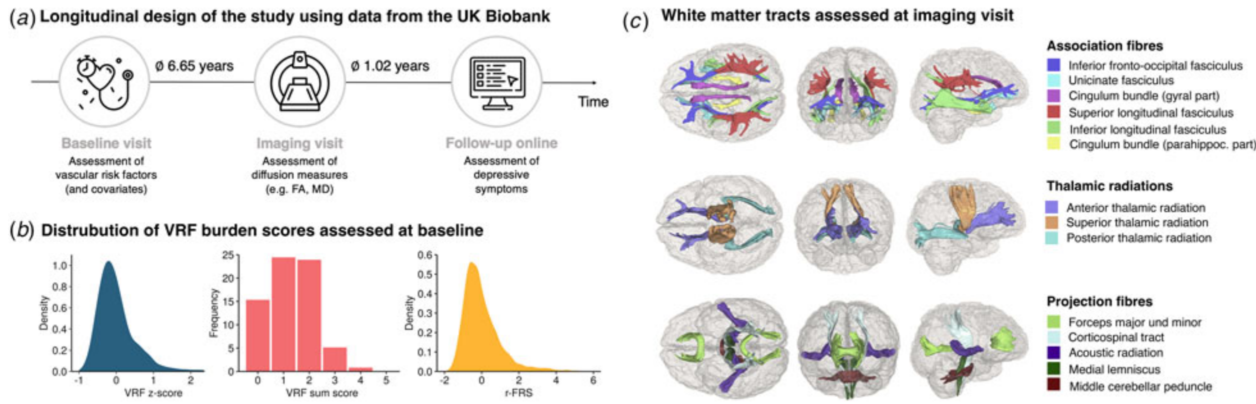

Fig. 1. Methodological details of the study. (a) Illustration of the longitudinal study design, which only included participants that consecutively participated in the baseline visit, the imaging visit, and the online follow-up (this figure contains resources from Flaticon.com). (b) Plots of the distribution 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 Cox, Ritchie, Fawns-Ritchie, Tucker-Drob, & Deary, 2019*b*). VRF, Vascular risk factor; FA, Fractional anisotropy; MD, Mean diffusivity; rFRS, revised Framingham Risk Score.

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 online Supplementary Table S2.

In addition to the preregistered 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 (Blöchl et al., 2021). It was calculated by summing dichotomised variables indicating the presence of different VRFs: SBP with self-reports of hypertension to indicate hypertension (0 = no, 1 = yes), a BMI $\geqslant$25 kg/m^2 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 (Dufouil et al., 2017; Wolf, D'Agostino, Belanger, & Kannel, 1991). The rFRS was calculated for women and men separately by combining information on several risk factors (age, sex/gender, SBP, 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. (Dufouil et al. 2017). VRF sum score and rFRS were not preregistered and hence used in exploratory analyses (see online Supplementary Table S3). The distributions of all VRF scores are shown in Fig. 1*b*.

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 = 92 ms) than a twice-refocused ('bipolar') sequence at the expense of stronger eddy current distortions (Alfaro-Almagro et al., 2018; Miller et al., 2016).

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 (Alfaro-Almagro et al., 2018). 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 (Fig. 1*c*). For both FA and MD, we pairwise excluded outliers as defined by datapoints being 2.2 interquartile ranges below first or above third quartile (Cox et al., 2016). 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) (Griffanti et al., 2016). Tract-based MD and global markers of white matter microstructure were not preregistered and hence used in exploratory analyses (see online Supplementary Table S3). Detailed UK Biobank variable codes for white matter variables used in the preregistered analysis are listed in online Supplementary 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 online Supplementary Table S2. A mean score of all items was derived with higher values indicating more severe depressive symptoms.

Covariates

Age, sex/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 (Alfaro-Almagro et al., 2021). Age (in years) was assessed at baseline. Sex/gender was defined as a dichotomous variable due to its binary assessment (women/men). Note that we refer to the variable sex/gender, since the UK Biobank assessed this variable by acquiring the recorded data from the National Health Service (NHS) but gave the participants the opportunity to update the information using self-report. The variable thus captures a mixture between sex and gender, although not capturing the full spectrum of gender. 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 Pound Sterling (£) ('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 (Morris & Carstairs, 1991; Townsend, 1987). 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 (Alfaro-Almagro et al., 2018). Detailed UK Biobank variable codes for covariates used in the preregistered analysis are listed in online Supplementary Table S2. Deviating from the preregistration, total brain volume was added as a covariate based on recommendations published after preregistering (Alfaro-Almagro et al., 2021).

Preregistered statistical analyses

To assess whether white matter microstructure mediates the association of VRF burden with depressive symptoms, we used mediation models (Fig. 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 (MacKinnon, 2008). 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 (Enders, 2001). 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 0.97) between the tracts. Our preregistration also detailed analyses to compare mediating effects of different tracts, which aimed to test whether specific white matter tracts had a stronger mediating effect on the association between VRF burden and depressive symptoms than other white matter tracts (i.e. planned comparisons to test whether mediating effects of white matter tracts connecting brain regions underlying mood are larger than mediating effects of other tracts). However, because our results yielded no evidence for mediating effects of any tract, the premise of these preregistered comparisons was not met (i.e. there can be no locally specific mediating effects if there are none at all). Hence, we did not perform these preregistered comparisons.

All analyses were performed using R (version 4.1.1); mediation models were estimated using lavaan (Rosseel, 2012).

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 × 15 tracts × 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

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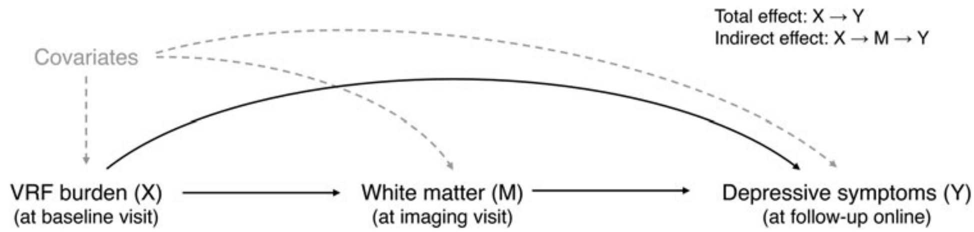

Fig. 2. Illustration of the mediation model and estimated pathways. The indirect effect reflects the effect of X on Y through M. The total effect reflects the sum of the direct effect of X on Y and the indirect effect.

entered as mediators into the longitudinal mediation models, which yielded an additional 9 models (3 VRF burden scores × 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 online Supplementary Table S1.

Results

Sample characteristics

The study included 6,964 participants with longitudinal data on VRFs, white matter tract microstructure, and depressive symptoms (see online Supplementary Fig. S1 for flow chart). Table 1 shows the sample characteristics at baseline. Of the 6964 participants included in the analyses, 3,694 (53%) were women and the average age at baseline was 55.47 years (s.d. = 7.41, range = 40–70 years). The neuroimaging assessment took place on average 6.65 years (s.d. = 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 Fig. 1*a*).

Table 1. Baseline characteristics of participants ($n = 6964$)

Variable	*n*	Mean ± s.d. or *n* (%)
Age in years	6,964	55.47 ± 7.42
Sex/Gender	6,964	
Women		3694 (53%)
Men		3270 (47%)
Racial-ethnic background	6,940	
White		6765 (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%)
18000–30999 £		1489 (21%)
31000–51999 £		1928 (28%)
52000–1 00 000 £		1660 (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 (Fig. 3*a*, 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 (Fig. 3*b*, 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 to 0.001, cingulate bundle gyral part) to 0.001 (bootstrapped 99% CI −0.001 to 0.003, corticospinal tract). The mean indirect effect across 15 tracts was −0.0001 (s.d. = 0.0006).

We further examined the two paths constituting the indirect effects in all models. There were significant negative associations for the VRF z-score → FA path for 6 white matter tracts (gyral part of the cingulum bundle, forceps minor, inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, posterior thalamic radiation, and superior longitudinal fasciculus). These results indicate that higher VRF burden was associated with lower FA in these tracts. However, there were no significant associations for the FA → depressive symptom path in all tracts, suggesting that FA in white matter tracts was not associated with depressive symptoms after accounting for VRF burden and covariates (see online Supplementary 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–

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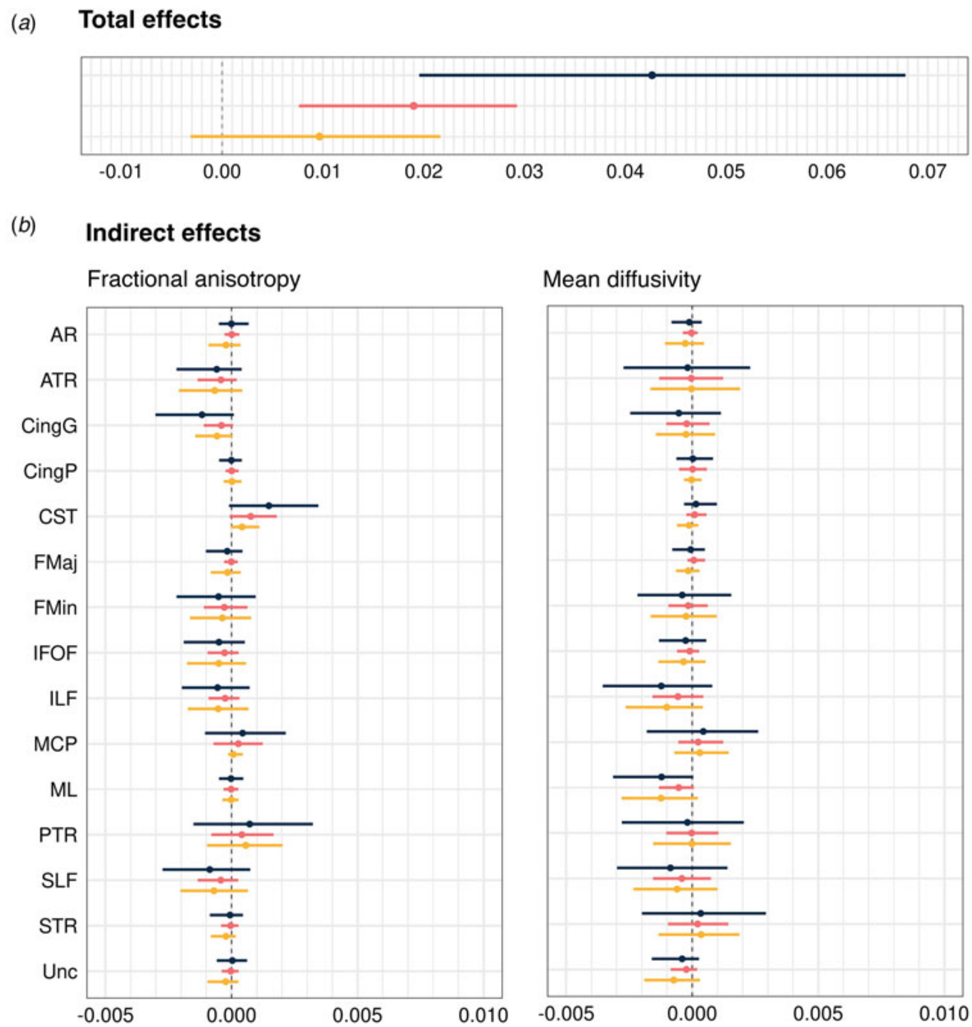

Fig. 3. Total and indirect effect estimates of longitudinal mediation models of FA and MD of single white matter tracts as mediators. (a) Total effects (and 99% CIs) of the preregistered VRF z-score (blue), the VRF sum score (pink), and the revised FRS (yellow) on depressive symptoms at follow-up. Note 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 of single white matter tracts. (c) Indirect effects (and 99% CIs) of FA of single white matter tracts. 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, Interior 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, Unicate fasciculus.

0.029; Figure 3*a*, 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 (Fig. 3*b*, pink bars). Estimated indirect effects were small with narrow CIs, ranging from −0.001 (bootstrapped 99% CI −0.001 to 0.001, superior longitudinal fasciculus) to 0.001 (bootstrapped 99% CI −0.001 to 0.002, corticospinal tract). The mean indirect effect across 15 tracts was −0.0001 (s.d. = 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 to 0.043; Figure 3*a*, yellow bar). Indirect effects of these models similarly yielded no evidence for indirect effects for FA of any of the 15 white matter tracts (Fig. 3*b*, yellow bars). Estimated indirect effects were small with narrow CIs, ranging from −0.001 (bootstrapped 99% CI −0.002 to 0.001, superior longitudinal fasciculus) to 0.001 (bootstrapped 99% CI −0.001 to 0.002, posterior thalamic radiation). The mean indirect effect across 15 tracts was −0.0002 (s.d. = 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 Fig. 3*a*). 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 (Fig. 3*b*). 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 to 0.001 medial lemniscus for rFRS) to 0.001 (bootstrapped 99% CI −0.003 to 0.001, middle cerebellar peduncle for VRF z-score). The mean indirect effect across 15 tracts was −0.0003 (s.d. = 0.0005) for the VRF z-score, −0.0001 (s.d. = 0.0002) for VRF sum score, and −0.0003 (s.d. = 0.0004) for rFRS.

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 2. 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.

Discussion

In this preregistered 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 preregistered 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 (Blöchl et al., 2021; Kivimäki et al., 2012; Valkanova & Ebmeier, 2013). 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 (Valkanova & Ebmeier, 2013). 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 (Long et al., 2015) is less clear than the association between obesity and depression (Luppino et al., 2010; Tyrrell et al., 2019). Some studies have even suggested that people with higher SBP tend to have fewer depressive symptoms (Berendes, Meyer, Hulpke-Wette, & Herrmann-Lingen, 2013; Montano, 2020; Schaare et al., 2022). 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 (Cox et al., 2019*a*, 2019*b*; Maillard et al., 2012), 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 (Alexopoulos, 1997; Taylor et al., 2013). This hypothesis has been ubiquitous in the literature on vascular and mental health (Aizenstein et al., 2016; Ikram et al., 2010; Valkanova & Ebmeier, 2013). 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, previously reported white matter disconnections in later-life depression may have been 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 (Borsboom, Cramer, & Kalis, 2018; Schmaal et al., 2020; Shen et al., 2019; Winter et al., 2022), which are however stronger in clinical compared to population-based samples (Binnewies et al., 2022). 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 in a population-based sample. While it remains to be investigated whether mediating effects might be observed in clinical samples, it is also possible that the link 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 (Gustavson et al., 2019; Zhao et al., 2021*b*) and the link between white matter changes and depression might rather be attributed to their genetic correlations (Rutten-Jacobs et al., 2018; Zhao et al., 2021*a*; Zhao et al., 2021*b*). Future studies in clinical and population-based samples, which account for confounders as well as genetic links, would be needed to more clearly establish the potential causal links between VRFs, white matter, and depressive symptoms.

Another major factor that might influence links between VRF burden, white matter, and depressive symptoms is the timing and spacing of the assessments across the lifespan. One possibility is that the follow-up period in our study was too short for strong effects to have occurred. For example, previous studies have shown stronger links between vascular risk and white matter microstructure with a follow-up of about 20 years (Suri et al., 2019; Zsoldos et al., 2018, 2020). Similarly, we might have not detected a relationship between white matter microstructure and depressive symptoms due to the limited interval of about one year. Effects between VRFs, white matter, and depression might need longer to unfold and would be stronger in studies with longer follow-ups.

Future studies are also needed to clarify precisely how the links between VRF burden, white matter changes, and depressive symptoms change across the lifespan. Damages to white matter microstructure increase with age (Cox et al., 2016; de Leeuw et al., 2001; Liu et al., 2017) and might be a stronger mediator in the link between VRFs and depression in later life compared to midlife. Moreover, further investigating the role of age will be essential because the VRF-depression link might vary across the

Table 2. 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.

lifespan. Some studies pointed to the possibility that the link between VRFs and depressive symptoms is strongest in older samples (Mast, Azar, & Murrell, 2005; Molero et al., 2017). However, we have recently shown that the association between VRFs and depressive symptoms is in fact stronger in middle-aged compared to older adults after accounting for age-related increases in diseases (e.g. stroke) and disabilities (Blöchl et al., 2021). This observation is in line with current evidence establishing a link between vascular and mental health as early as in adolescence and young adulthood (Chaplin et al., 2021*a*; Chaplin, Smith, Jones, & Khandaker, 2021*b*). Lifespan studies including younger, middle-aged, and older individuals are needed to systematically assess the role of age in the links between vascular risk, white matter, and depression.

Finally, certain VRFs may act through other mediating mechanisms than the disconnection of white matter tracts. As argued above, classical VRFs, such as hypertension and blood pressure, are strongly associated with white matter microstructure. Yet, they might be less important in their association to depressive symptoms. Instead, metabolic-related VRFs, such as BMI or obesity, might play a bigger role and drive the association between composite VRF scores and depressive symptoms. Recently, it has been suggested that such metabolic VRFs contribute to depressive symptoms via inflammatory pathways (Milaneschi, Lamers, Berk, & Penninx, 2020). Although inflammatory markers have also been previously suggested to contribute to vascular depression (Taylor et al., 2013), 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 (Nosek, Ebersole, DeHaven, & Mellor, 2018), 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 (Fry et al., 2017). Thus, selection effects might bias our estimated associations and limits generalisability of our findings (Munafò, Tilling, Taylor, Evans, & Davey Smith, 2018). 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, it is possible that effects in this study were underestimated because of the use of a population-based sample, the short spacing between assessments, and the age range of participants. As previously discussed, future studies will be needed to systematically address whether studies in clinical samples, with longer follow-up times, and at specific times during the lifespan reveal the hypothesised mediating effects. Third, 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

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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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