Supplementary Materials for

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

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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)

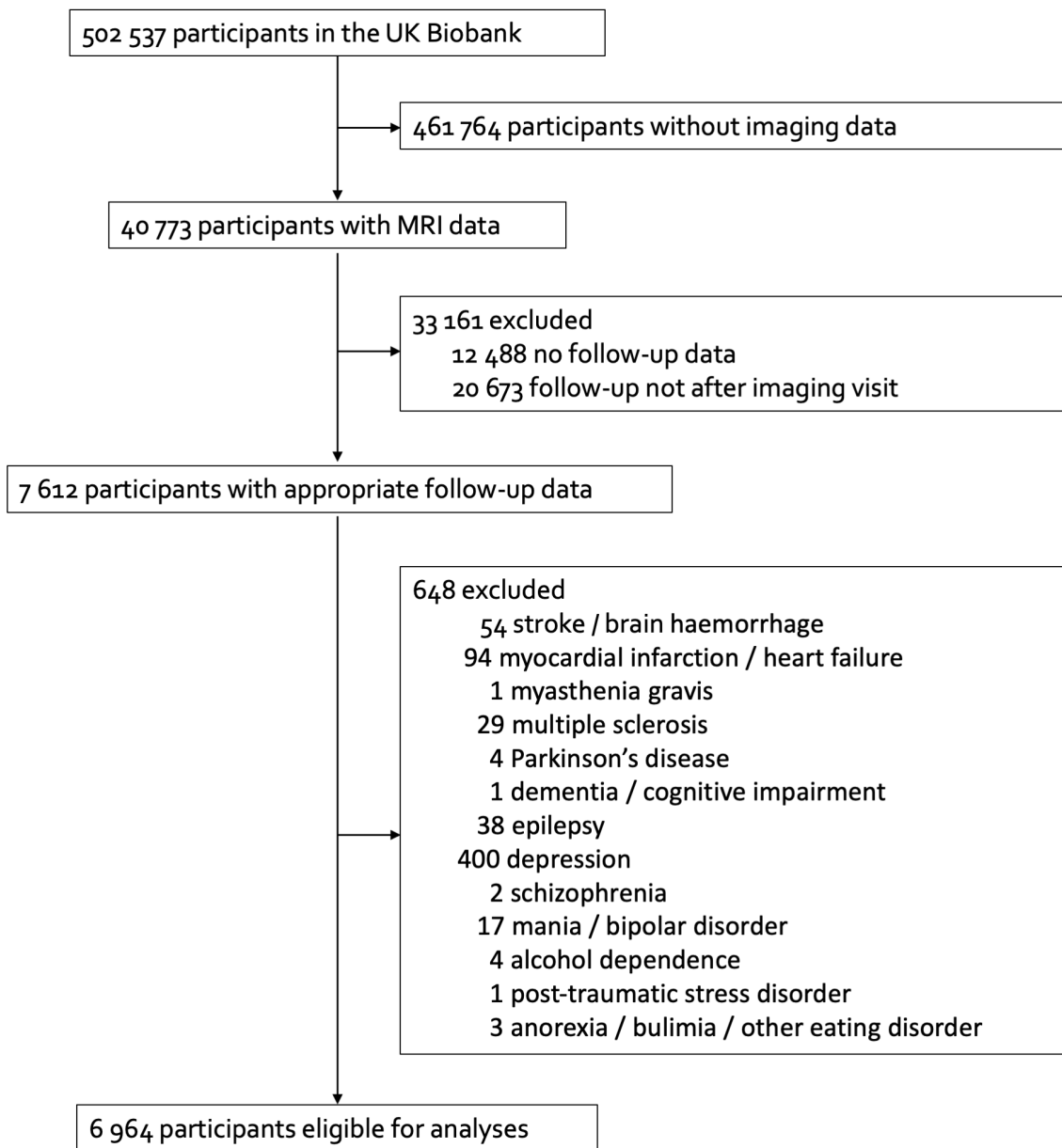**Figure S1.** Flowchart of participant exclusion and inclusion.

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┌─────────────────────────────────────────┐
│ 502 537 participants in the UK Biobank   │
└─────────────────────────────────────────┘
        │
        │        ┌────────────────────────────────────────────┐
        ├───────▶│ 461 764 participants without imaging data   │
        │        └────────────────────────────────────────────┘
        ▼
┌────────────────────────────────────┐
│ 40 773 participants with MRI data  │
└────────────────────────────────────┘
        │
        │        ┌────────────────────────────────────────────┐
        ├───────▶│ 33 161 excluded                             │
        │        │    12 488 no follow-up data                 │
        │        │    20 673 follow-up not after imaging visit │
        │        └────────────────────────────────────────────┘
        ▼
┌──────────────────────────────────────────────────┐
│ 7 612 participants with appropriate follow-up data│
└──────────────────────────────────────────────────┘
        │
        │        ┌────────────────────────────────────────────────────────┐
        │        │ 648 excluded                                            │
        │        │     54 stroke / brain haemorrhage                       │
        │        │     94 myocardial infarction / heart failure            │
        │        │      1 myasthenia gravis                                │
        │        │     29 multiple sclerosis                               │
        │        │      4 Parkinson's disease                              │
        ├───────▶│      1 dementia / cognitive impairment                  │
        │        │     38 epilepsy                                         │
        │        │    400 depression                                       │
        │        │      2 schizophrenia                                    │
        │        │     17 mania / bipolar disorder                         │
        │        │      4 alcohol dependence                               │
        │        │      1 post-traumatic stress disorder                   │
        │        │      3 anorexia / bulimia / other eating disorder       │
        │        └────────────────────────────────────────────────────────┘
        ▼
┌─────────────────────────────────────────┐
│ 6 964 participants eligible for analyses │
└─────────────────────────────────────────┘
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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	Sex/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, sex/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.