SUPPLEMENTARY INFORMATION

Mediation of the Association Between Vascular Risk Factors and Depressive Symptoms by C-Reactive Protein

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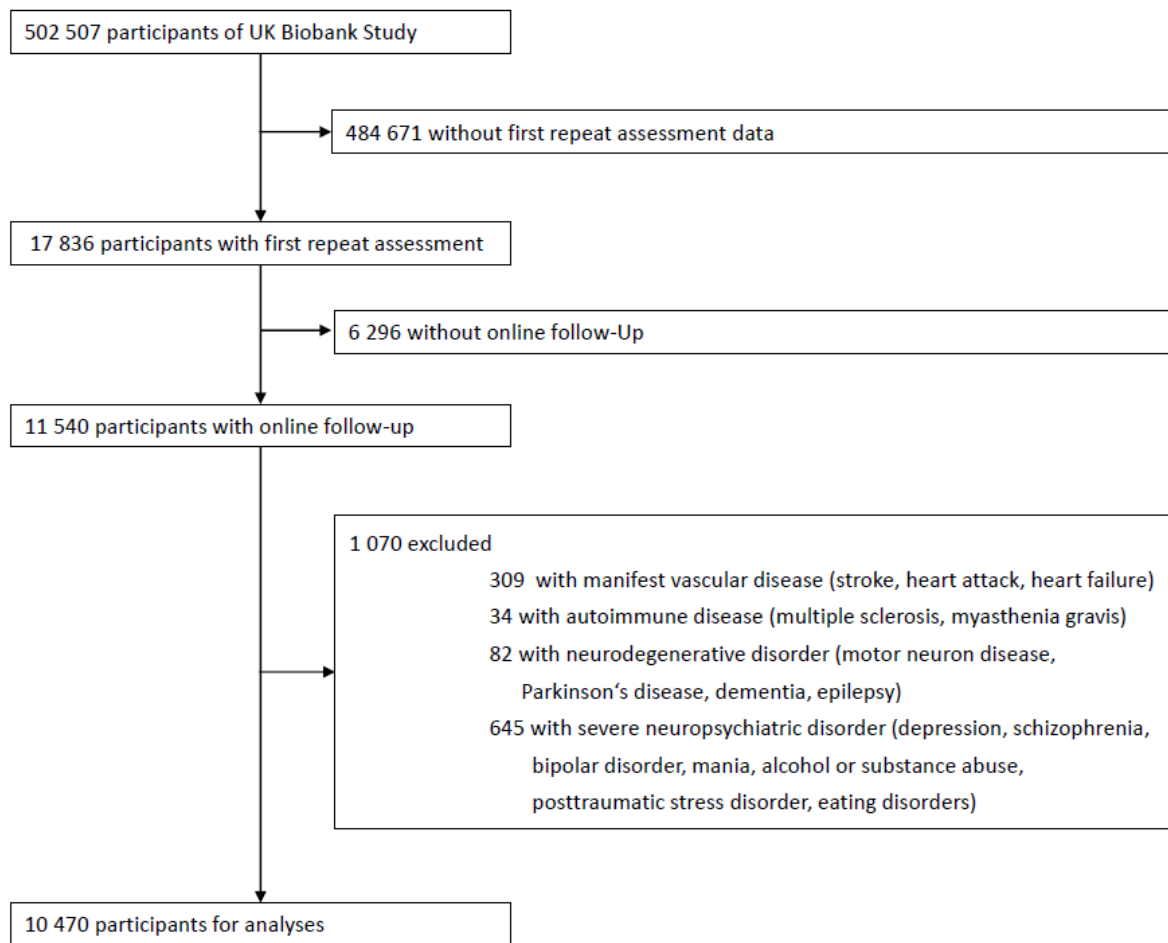
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Table S1

Variables for Exclusion Criteria with Hyperlinks to the UK Biobank Showcase

ID	Data descriptor	Excluded if one of the following applied	Item formulation / assessment method
6150	Vascular/heart problems diagnosed by doctor	[Heart attack]	Has a doctor ever told you that you have had any of the following conditions? (You can select more than one answer) (Heart attack / Angina / Stroke / High blood pressure / None of the above / Prefer not to answer)
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 neuron disease [1260] Myasthenia gravis [1261] Multiple sclerosis [1262] Parkinson's disease [1263] Dementia / Alzheimer's / 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	Tree-structured list used by clinic nurses to code non-cancer illness

Figure S1

Flowchart of UK Biobank participants included in the current study

502 507 participants of UK Biobank Study

→ 484 671 without first repeat assessment data

17 836 participants with first repeat assessment

→ 6 296 without online follow-Up

11 540 participants with online follow-up

→ 1 070 excluded

  309 with manifest vascular disease (stroke, heart attack, heart failure)

  34 with autoimmune disease (multiple sclerosis, myasthenia gravis)

  82 with neurodegenerative disorder (motor neuron disease, Parkinson's disease, dementia, epilepsy)

  645 with severe neuropsychiatric disorder (depression, schizophrenia, bipolar disorder, mania, alcohol or substance abuse, posttraumatic stress disorder, eating disorders)

10 470 participants for analyses

Supplementary Methods: Comparison of included and excluded UK Biobank participants

Our final sample included 10,470 participants. Compared to the 491,037 participants from the full UK Biobank sample who were excluded in this study, included participants with longitudinal data had a similar age ($d = 0.03$) and a comparable gender composition ($d = 0.07$), but were less racially-ethnically diverse ($d = 0.17$) and had higher levels of educational attainment ($d = 0.33$).

Table S2

Variables Relevant for Analyses with Descriptions and Hyperlinks to the UK Biobank Showcase

Data ID	Data descriptor	Item formulation / assessment method
Vascular risk factors		
4080	Systolic blood pressure, automated reading (mmHg)	Blood pressure, automated reading, systolic. Two measures of blood pressure were taken a few moments apart.
93	Systolic blood pressure, manual reading (mmHg)	Blood pressure, manual reading, systolic. Two measures of blood pressure were taken a few moments apart. A manual sphygmometer was used if the standard automated device could not be employed.
4079	Diastolic blood pressure, automated reading (mmHg)	Blood pressure, automated reading, diastolic. Two measures of blood pressure were taken a few moments apart.
94	Diastolic blood pressure, manual reading (mmHg)	Blood pressure, manual reading, diastolic. Two measures of blood pressure were taken a few moments apart. A manual sphygmometer was used if the standard automated device could not be employed.
21001	Body mass index (kg/m^2)	BMI value here is constructed from height and weight measured during the initial Assessment Centre visit. Value is not present if either of these readings were omitted.
20002	Non-cancer illness code, self-reported [high cholesterol] [hypertension] / [essential hypertension] / [gestational hypertension / pre-eclampsia]	Tree-structured list used by clinic nurses to code non-cancer illness
2443	Diabetes diagnosed by doctor	Has a doctor ever told you that you have diabetes? (Yes / No / Do not know / Prefer not to answer)
1239	Current tobacco smoking	Do you smoke tobacco now? (yes, on most or all days / only occasionally / no)
Inflammatory marker		
30710	C-reactive protein	Measured by immunoturbidimetric - high sensitivity analysis on a Beckman Coulter AU5800

Depressive symptoms

20510	Recent feelings of depression	Over the last 2 weeks, how often have you been bothered by any of the following problems? [depressive symptoms] Feeling down, depressed, or hopeless (Prefer not to answer / Not at all / Several days / More than half the days / Nearly every day)
20507	Recent feelings of inadequacy	Over the last 2 weeks, how often have you been bothered by any of the following problems? [depressive symptoms] Feeling bad about yourself or that you are a failure or have let yourself or your family down (Prefer not to answer / Not at all / Several days / More than half the days / Nearly every day)
20519	Recent feelings of tiredness or low energy	Over the last 2 weeks, how often have you been bothered by any of the following problems? [depressive symptoms] Feeling tired or having little energy (Prefer not to answer / Not at all / Several days / More than half the days / Nearly every day)
20514	Recent lack of interest or pleasure in doing things	Over the last 2 weeks, how often have you been bothered by any of the following problems? [depressive symptoms] Little interest or pleasure in doing things (Prefer not to answer / Not at all / Several days / More than half the days / Nearly every day)
20511	Recent poor appetite or overeating	Over the last 2 weeks, how often have you been bothered by any of the following problems? [depressive symptoms] Poor appetite or overeating (Prefer not to answer / Not at all / Several days / More than half the days / Nearly every day)
20513	Recent thought of suicide or self-harm	Over the last 2 weeks, how often have you been bothered by any of the following problems? [depressive symptoms] Thoughts that you would be better off dead or of hurting yourself in some way

		(Prefer not to answer / Not at all / Several days / More than half the days / Nearly every day)
20508	Recent trouble concentrating on things	Over the last 2 weeks, how often have you been bothered by any of the following problems? [depressive symptoms] Trouble concentrating on things, such as reading the newspaper or watching television (Prefer not to answer / Not at all / Several days / More than half the days / Nearly every day)
20517	Trouble falling asleep, or sleeping too much	Over the last 2 weeks, how often have you been bothered by any of the following problems? [depressive symptoms] Trouble falling or staying asleep, or sleeping too much (Prefer not to answer / Not at all / Several days / More than half the days / Nearly every day)
20518	Recent changes in speed / amount of moving or speaking	Over the last 2 weeks, how often have you been bothered by any of the following problems? [depressive symptoms] Moving or speaking so slowly that other people could have noticed? Or the opposite - being so fidgety or restless that you have been moving around a lot more than usual (Prefer not to answer / Not at all / Several days / More than half the days / Nearly every day)
Covariates		
21003	Age (in years)	This is a derived variable based on date of birth and date of attending assessment centre and refers to the age of the participant on the day they attended an Assessment Centre, truncated to whole year part.
31	Gender (male/female)	Sex of participant. Acquired from central registry at recruitment, but in some cases updated by the participant. Hence this field may contain a mixture of the sex the NHS had recorded for the participant and self-reported sex.

21000	Ethnic background	This is an amalgam of sequential branching questions asked during the initial Assessment Centre visit as part of the touchscreen questionnaire.
6138	Educational attainment	Which of the following qualifications do you have? (You can select more than one) (College or University degree / A levels/AS levels or equivalent / O levels/GCSEs or equivalent / CSEs or equivalent / NVQ or HND or HNC or equivalent / Other professional qualifications eg: nursing, teaching / None of the above / Prefer not to answer)
738	Household income	What is the average total income before tax received by your HOUSEHOLD? (Less than 18,000 / 18,000 to 30,999 / 31,000 to 51,999 / 52,000 to 100,000 / Greater than 100,000 / Do not know / Prefer not to answer)
189	Townsend deprivation index	Townsend deprivation index calculated immediately prior to participant joining UK Biobank. Based on the preceding national census output areas. Each participant is assigned a score corresponding to the output area in which their postcode is located.
20508	Frequency of depressed mood in last 2 weeks	Over the last 2 weeks, how often have you been bothered by any of the following problems? [depressive symptoms] Trouble concentrating on things, such as reading the newspaper or watching television
2060	Frequency of unenthusiasm / disinterest in last 2 weeks	Over the past two weeks, how often have you had little interest or pleasure in doing things? (Prefer not to answer / Not at all / Several days / More than half the days / Nearly every day)
2070	Frequency of tenseness / restlessness in last 2 weeks	Over the past two weeks, how often have you felt tense, fidgety or restless? (Prefer not to answer / Not at all / Several days / More than half the days / Nearly every day)

2080	Frequency of tiredness / lethargy in last 2 weeks	Over the past two weeks, how often have you felt tired or had little energy? (Prefer not to answer / Not at all / Several days / More than half the days / Nearly every day)
2090	History of mood disorder	Have you ever seen a general practitioner (GP) for nerves, anxiety, tension or depression? (Yes / No / Do not know / Prefer not to answer)
30710	C-reactive protein	Measured by immunoturbidimetric - high sensitivity analysis on a Beckman Coulter AU5800

Supplementary Methods: Mediation path analytic framework and causality

Although the path-analytic framework to mediation has not explicitly been developed to test causal effects, comparisons to the causal mediation framework based on counterfactual perspectives of mediation have shown that under specific assumptions, the estimated effects of mediation in a path-analytic framework may be interpreted as causal (1,2): Specifically, there should be (1) no uncontrolled exposure-outcome confounding, (2) no uncontrolled mediator-outcome confounding, (3) no uncontrolled exposure-mediator confounding, (4) no mediator-outcome confounder that is itself affected by the exposure. In addition, the model should be correctly specified and there should be no interaction between the treatment and the mediator (1,2). We aimed to address assumptions (1) to (4) by including relevant sociodemographic, socioeconomic covariates as well as baseline levels of the mediator and the outcome. To provide more detail on the role of confounding by previous levels of the mediator and the outcome on the association between VRF burden, CRP, and depressive symptoms, we estimated three models with consecutive inclusion of covariate sets. Model 1 included only sociodemographic and socioeconomic covariates, model 2 additionally included baseline depressive symptoms and potential history of mood disorder as covariates. Model 3 additionally included CRP at baseline as covariate; model 3 thus represents the final model with the full set of confounders (see Figure 1). Furthermore, we probed the effect of potential violations against assumption (4) via sensitivity analyses.

Table S3

Zero-order correlations among study variables

	1	2	3	4	5	6	7	8	9	10	11	12
1. Age	–											
2. Gender	−0.08	–										
3. Ethnicity	0.08	0.00	–									
4. Education	−0.09	−0.00	−0.05	–								
5. Income	−0.32	0.07	−0.02	0.25	–							
6. TDI	−0.13	−0.01	−0.09	−0.02	−0.15	–						
7. Dep (T1)	−0.14	0.07	−0.02	0.01	−0.01	0.07	–					
8. Hist. Dep.	−0.02	0.14	0.00	−0.01	−0.08	0.05	0.22	–				
9. CRP (T1)	0.05	0.04	0.01	−0.08	−0.06	0.03	0.03	0.01	–			
10. VRFs (T1)	0.18	−0.24	0.01	−0.10	−0.07	−0.03	0.02	0.01	0.20	–		
11. CRP (T2)	0.06	0.04	0.01	−0.08	−0.07	0.03	0.04	0.02	0.47	0.18	–	
12. Dep (T3)	-0.13	0.08	−0.01	−0.02	−0.05	0.09	0.41	0.21	0.06	0.03	0.07	–

Note. TDI = Townsend deprivation index, Dep = Depressive symptoms, Hist Dep = History of doctor visit for mood disorder, VRF = vascular risk factor, CRP = C-reactive protein, FU = follow-up.

Table S4

Results of sensitivity analyses using unwinsorized CRP data

	estimate	lower 95% CI	upper 95% CI
Total effect	0.112	0.051	0.173
Direct effect (*c*)	0.105	0.044	0.166
Indirect effect	0.008	0.002	0.015
Proportion mediated	6.7%	1.4%	17.5%

Note. All associations are based on model 3 of the main manuscript and are adjusted for covariates age, gender, ethnicity, educational attainment, household income, Townsend deprivation index, and baseline depressed affect, potential history of mood disorder, and CRP at baseline. CI = confidence interval. CRP = C-reactive protein. VRF = Vascular risk factor.

Table S5

Results of sensitivity analyses using log-transformed CRP data

	estimate	lower 95% CI	upper 95% CI
Total effect	0.085	0.023	0.146
Direct effect (*c*)	0.078	0.017	0.139
Indirect effect	0.006	0.001	0.012
Proportion mediated	7.3%	0.9%	26.1%

Note. All associations are based on model 3 of the main manuscript and are adjusted for covariates age, gender, ethnicity, educational attainment, household income, Townsend deprivation index, and baseline depressed affect, potential history of mood disorder, and CRP at baseline. CI = confidence interval. CRP = C-reactive protein. VRF = Vascular risk factor.

Supplementary References

1. Valeri L, Vanderweele TJ (2013): Mediation analysis allowing for exposure-mediator interactions and causal interpretation: theoretical assumptions and implementation with SAS and SPSS macros. *Psychol Methods* 18: 137–150.
2. VanderWeele TJ (2016): Mediation Analysis: A Practitioner's Guide. *Annual Review of Public Health* 37: 17–32.