Running title: Vascular risk, inflammation, and depressive symptoms

Mediation of the Association Between Vascular Risk Factors and Depressive Symptoms by C-Reactive Protein: Longitudinal Evidence from the UK Biobank

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Word count:

Word count abstract: 240

Word count introduction: 622

Word count paper: 3084

Number of references: 70

Number of tables: 3

Number of figures: 1

ABSTRACT

People with vascular risk factors (VRFs) are at higher risk for depressive symptoms. Given recent findings implicating low-grade systemic inflammation in both vascular and mental health, this study examined the extent to which the VRF–depressive symptom association might be mediated by low-grade systemic inflammation. To this end, we analysed longitudinal data of 9,034 participants from the UK Biobank (mean age = 56.54 years), who took part in three consecutive assessments over the course of about 8 years. Cumulative VRF burden at baseline was defined as the presence of 5 VRFs (hypertension, obesity, hypercholesterolemia, diabetes, and smoking). Low-grade systemic inflammation was assessed using serum-derived C-reactive protein (CRP) and depressive symptoms were measured using the Patient Health Questionnaire-9 (PHQ-9). We performed mediation models using longitudinal data and a path analytic framework, while controlling for age, gender, racial-ethnic background, socioeconomic status, and baseline mood. VRFs at baseline showed a small association with higher depressive symptoms at follow-up (total effect = 0.014, 95% CI [0.007; 0.021]). CRP mediated this association (indirect effect = 0.003, 95% CI [0.001; 0.005]) and accounted for 20.10% of the total effect of VRF burden on depressive symptoms. Exploratory analyses taking a symptom-based approach revealed that mediating pathways pertained to specific depressive symptoms: tiredness and changes in appetite. These results suggest that the small association between VRF burden and depressive symptoms may be partly explained by the inflammation-promoting effects of VRFs, which might promote a specific symptom-profile of depression.

Keywords: vascular risk factors, depressive symptoms, inflammation, longitudinal, UK Biobank

INTRODUCTION

Hypertension, overweight and obesity, hypercholesterolemia, diabetes, and smoking are important modifiable risk factors for vascular diseases and major contributors to global disease burden [1]. Vascular risk factors (VRFs) have also been implicated in the aetiology of mood disorders, particularly in later life depression [2–4]. Although findings have not always been consistent [5–7], a number of prospective population-based studies support that people with VRFs are at higher risk for developing depression and depressive symptoms [8–12]. This association is particularly strong for burden from multiple VRFs [9], which often tend to accumulate [13]. However, mechanistic explanations as to why VRFs burden and depressive symptoms are linked remain debated [6, 14, 15].

In recent years, low-grade systemic inflammation gained considerable attention as a potential link between vascular and mental health [14, 16–18]. Low-grade systemic inflammation reflects a chronic manifestation of the body's natural inflammatory response to physical injury or infection [18]. While an acute inflammatory response – as a temporally and spatially restricted activation of immune cells – is typically adaptive and resolves once the threat has passed [19, 20], low-grade systemic inflammation reflects a prolonged, unresolved activation of the immune system. Low-grade inflammation is thus characterized by the systemic presence of inflammatory markers and has been connected to a broad range of chronic diseases [18, 20, 21].

Increasing evidence supports that inflammatory processes are involved in the pathophysiology of depression [22–24]. Earlier experimental evidence has shown that acute inflammation is associated with protective behavioural responses ("sickness behaviour"), such as sadness, anhedonia, fatigue or social withdrawal [25, 26], that mimic depressive symptoms. In turn, low-grade systemic inflammation is thought to be linked to a chronification of these symptoms, which can lead to depression [19, 23, 24]. Support for this hypothesis comes from studies in patients with depression showing that elevated levels of C-reactive protein (CRP), a serum-derived marker of low-grade systemic inflammation, is present in about 25% of patients [27]. Moreover, an association between CRP and depressive symptoms has repeatedly been found in cross-sectional and longitudinal cohort studies [28–31]. Recent findings have

furthermore highlighted that these processes might not be general, but specific to certain symptoms of depression [30–34]. For example, a recent pooled analysis of 15 cohort studies [30] demonstrated that CRP levels are linked with four physical symptoms (e.g. changes in appetite, sleep problems) and one cognitive symptom (little interest in doing things).

VRFs have been discussed as one of the main sources of low-grade systemic inflammation [35, 36]. Especially smoking, diabetes, and obesity have been linked to elevated plasma levels of inflammatory proteins [37–40]. For example, compounds consumed from smoking tobacco increase pro-inflammatory cytokines and proteins due to the burden of free radicals and inducing local inflammation in the lung parenchyma [36, 41]. These inflammatory processes might in turn contribute to the development of depressive symptoms [14, 16, 17]. Previous studies found that once the influence of individual VRFs is controlled for, the association between inflammation and depressive symptoms weakens substantially [42–44], pointing to the possibility that VRFs may precede inflammatory processes in depression. However, most of these previous studies were cross-sectional and could not establish the temporal order between VRFs, inflammation, and depressive symptoms. Moreover, previous research typically only focused on single VRFs, albeit their associations are likely exacerbated with the presence of multiple accumulated VRFs [35].

In the current study, we analysed longitudinal data in a large sample of middle-aged and older adults to examine the longitudinal association between VRF burden, inflammation, and depressive symptoms. Our main aim was to test to what extent serum CRP mediates the association between VRF burden and depressive symptoms. The analyses benefit from a clear temporal ordering with VRFs measured at the baseline assessment, serum CRP at the first follow up about 4 years later, and depressive symptoms at the second follow up about 8 years after baseline. Given studies suggesting symptom-specific associations with VRFs as well as inflammation [30–34, 45], we also explored whether these associations pertain to certain depressive symptoms.

METHODS

Participants

The UK Biobank is a large, ongoing cohort study that initially recruited about 500,000 community-dwelling adults aged 37 to 73 years from across the United Kingdom [46]. All participants included in the present study participated in three consecutive assessments: First, participants underwent a baseline assessment (T1), which comprised a wide range of demographic and health factors (including VRFs) and was conducted between 2006 and 2010. A subset of these participants took part in a second assessment between 2012 and 2013, which included a measure of CRP levels (T2). Participants' depressive symptoms were assessed at a third online mental health assessment, which was conducted between 2016 and 2017 (T3). We only included participants, who attended all three assessments (baseline assessment (T1), blood sampling (T2) and online follow-up (T3)). We excluded participants with manifest vascular disease (stroke, heart attack, heart failure), autoimmune diseases (multiple sclerosis, myasthenia gravis), neurodegenerative or severe neuropsychiatric disorders (motor neuron disease, Parkinson‘s disease, dementia, epilepsy, schizophrenia, bipolar disorder, mania, alcohol or substance abuse, post-traumatic stress disorder, eating disorders), or a prior diagnosis of depression (see **Table S1** in the Supplementary Material for further details on variables used). To avoid confounding due to possible acute infections, we also excluded participants whose CRP levels exceeded 10 mg/L [e.g. 27, 34]. **Figure S1** in the Supplementary Material shows a flow chart of participant inclusion and exclusion.

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. Further information on the consent procedure can be found in the UK Biobank Documentation.

Measures

In the following, we will describe the measures used in this study. Further details on the variables used can be found in **Table S2** in the Supplementary Material.

Vascular Risk Factor Burden

VRF burden was based on five VRFs that are associated with an increased risk of vascular diseases: hypertension, overweight or obesity, hypercholesterolemia, diabetes, and smoking [47]. Hypertension was defined as either reporting the presence of diagnosed hypertension or having systolic blood pressure ≥ 130mmHg and diastolic blood pressure ≥ 80 mmHg [48]. Overweight/obesity was defined as having a Body Mass Index (BMI) ≥ 25kg/m² [49]. Hypercholesterolemia and diabetes were defined as reporting the presence of diagnosed high cholesterol and diabetes, respectively. Smoking was defined as reporting (occasional) current smoking of tobacco. All five VRFs were coded as either present ("1") or absent ("0") and summed into a composite score with a higher score indicating higher VRF burden (total score range 0 to 5).

C-Reactive protein

Serum concentrations of high-sensitivity CRP were used as a marker of low-grade systemic inflammation. Serum CRP levels were determined using an immuno-turbidimetric method (Beckman Coulter AU5800) with a reportable range of high sensitivity serum CRP from 0.08–80 mg/L. Detailed information on the blood sampling and the serum CRP measurement can be found in the UK Biobank documentation [50–52]. CRP values were log-transformed due to their skewed distribution.

Depressive Symptoms

Depressive symptoms were assessed using the Patient Health Questionnaire-9 (PHQ-9). The PHQ-9 is a well-established screening instrument for diagnosing and monitoring the severity of depression [53]. Participants answered nine items following the nine DSM criteria for Major Depressive Disorder: (1) feelings of depression, (2) feelings of inadequacy, (3) feelings of tiredness or low energy, (4) lack of interest or pleasure in doing things, (5) poor appetite or overeating, (6) thought of suicide or self-harm, (7) concentration problems, (8) sleep problems, (9) changes in speed/amount of moving or speaking). Answers were given on a Likert-scale ranging from 0 ("not at all") to 3 ("nearly every day"). The scale showed good internal consistency (Cronbach's $\alpha = .81$). For our analyses of overall depressive symptom severity, we calculated an average score with higher values indicating more severe depressive symptoms.

Covariates

Age, gender, racial-ethnic background, educational attainment, household income, Townsend deprivation index (TDI), and baseline depressed affect were included as covariates. Age (in years) was assessed at baseline. Gender was defined as a dichotomous variable due to its binary assessment (women / men). We defined racial-ethnic background 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 most of the sample 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"). The TDI reflects material deprivation within a population and was assessed as a continuous variable with higher values indicating greater deprivation [54, 55]. 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") (see **Table S2** in the Supplementary Material for variable details).

Statistical Analyses

To investigate whether serum CRP mediates the relationship between VRF burden and overall or single depressive symptoms, we performed longitudinal mediation analyses (**Figure 1**). VRF burden at baseline was defined as the exposure (X), serum CRP as the mediator (M), and depressive symptoms 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 [56].

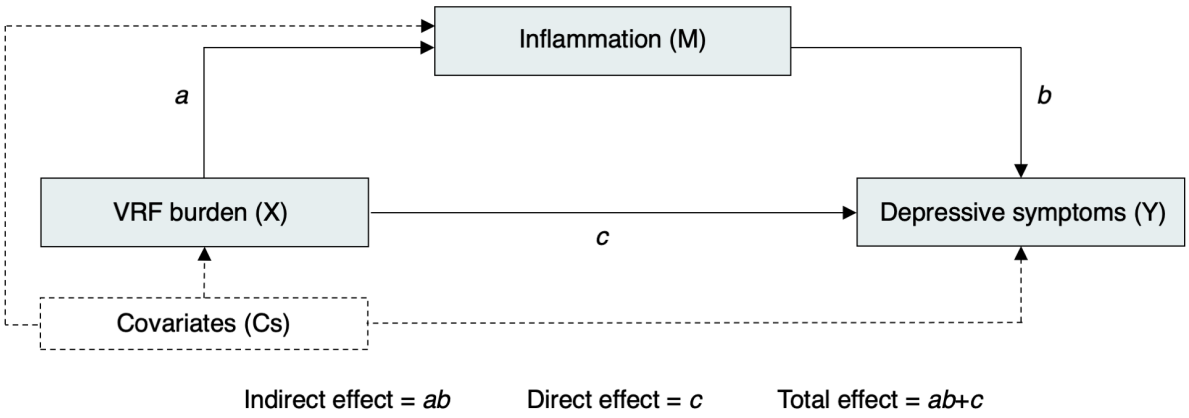

Figure 1. Illustration of the longitudinal mediation model. VRF burden was measured at T1, inflammation at T2, and depressive symptoms at T3. Covariates included age, gender, racial-ethnic background, educational attainment, household income, Townsend deprivation index, and baseline depressed mood.

In these models, the direct effect *c* reflects the association between the exposure VRF burden at T1 (X) and the outcome depressive symptoms at T3 (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 serum CRP measured at T2 (M). It is the product of two path coefficients: the coefficient from regressing X on M (*a*), and the coefficient from regressing M on Y while accounting for X and all covariates (*b*). The total effect is the sum of the direct (*c*) and the indirect effect (*a*b*) and reflects the association between X and Y that is direct and mediated via M.

For our main analyses, we estimated a longitudinal mediation model with mean depressive symptoms at T3 as the outcome (Y) to test whether inflammation mediates the effect of VRFs on overall depressive symptoms. In addition, we estimated longitudinal mediation models with single depressive symptoms as outcomes to explore the symptom-specificity of potential mediating effects.

In all models, 95%-confidence intervals (CI) were computed using bootstrapping (with 5,000 bootstrapping samples) to test the direct, the total, and the indirect effect. Effects were declared significant when the 95% CI did not contain zero. The ratio of the indirect effect to the total effect was used to quantify the proportion of the total effect mediated by the indirect effect, which is a useful metric when evaluating the size of the mediating

effect [57]. However, this effect size is technically speaking not a proportion since it can reach values above one or below zero and can only be calculated sensibly when both the total and indirect effect have the same direction [58].

All data analyses were conducted using R version 4.1.1. Mediation models were fitted using the structural equation modelling (SEM) package lavaan [59].

Robustness Analyses

To ensure that results of the main analysis were robust against plausible analysis decisions, we conducted several robustness analyses. First, we estimated the model with the CRP variable as mediator before log-transformation. Second, we ensured our results were robust against bias due to missing data in the outcome or covariates by estimating a further model using the robust Full Information Maximum Likelihood (FIML) estimation, which assumes that data is missing at random (MAR) [60]. Finally, we conducted a sensitivity analysis by examining how the size of the indirect effect changes when we include an (unobserved) confounder of the mediator-outcome relation of a small, a moderate, and a large size [61].

RESULTS

Sample Characteristics

Our sample included 9,034 participants with longitudinal data for VRF burden, CRP, and depressive symptoms. The baseline characteristics of participants included in the study are shown in **Table 1**. On average, participants were 56.54 years old at baseline (*SD* = 7.27, range 40–70) and 4,480 participants (49.59%) were women. **Table S3** in the Supplementary Material shows zero-order correlations between all variables.

Table 1

Baseline characteristics of study participants (N = 9,034)

Variable	*n* (%) or *M* ± *SD*
Age (in years)	56.54 ± 7.27
Gender	
Women	4,480 (49.59)
Men	4,554 (50.41)
Racial-ethnic background	
White	8,882 (98.32)
People of Colour[a]	152 (1.68)
Education attainment	
University degree	4,497 (49.78)
No university degree	4,537 (50.22)
Baseline depressive symptoms	0.26 ± 0.38
Household income	
Less than 18,000	1,178 (13.1)
18,000 to 30,999	2,320 (25.68)
31,000 to 51,999	2,787 (30.85)
52,000 to 100,000	2,236 (24.75)
Greater than 100,000	513 (5.68)
TDI	-2.22 ± 2.55
VRF burden	1.33 ± 0.94
Time T1 → T2 (in days)	1,526.42 ± 312.79
Time T2 → T3 (in days)	1,342.12 ± 93.71

Note. SD = standard derivation, TDI = Townsend deprivation index, VRF = vascular risk factor, CRP = C-reactive protein, FU = follow-up.

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

VRF burden, CRP, and overall depressive symptoms

We first examined whether VRF burden at T1 was associated with overall depressive symptom severity at T3. Our longitudinal mediation analysis revealed a positive total effect (estimate = 0.014, 95% CI [0.007; 0.021]), suggesting that higher VRF burden at T1 was associated with higher depressive symptoms at T3 (**Table 2**). With respect to our second hypothesis, the model yielded a significant indirect effect (estimate = 0.003, 95% CI [0.001; 0.005]), indicating a mediating effect of serum CRP on the association between VRF burden and depressive symptoms. The proportion mediated

was 20.10% (95% CI [7.4%; 46.5%]). Accordingly, higher VRF burden was associated with higher levels of log CRP at T2 (estimate (a) = 0.237, 95% CI [0.217; 0.257]), and higher log CRP levels were associated with higher depression scores at follow-up (estimate (b) = 0.012, 95% CI [0.004; 0.020]).

Robustness Analyses

This pattern of results remained unchanged when we used the untransformed serum CRP variable as a mediator (see **Table S4**) and when accounting for missing data using FIML estimation (see **Table S5**). However, sensitivity analyses indicated that the indirect effect is not significantly different from zero when controlling for an unobserved confounder of the mediator-outcome relation with a medium effect (estimate = 0.006, 95% CI = [-0.008, 0.004]).

Table 2

Results of longitudinal mediation analyses of VRF burden, log CRP, and overall depressive symptoms

	estimate	lower 95% CI	upper 95% CI
Total effect	0.014	0.007	0.021
Direct effect (*c*)	0.011	0.004	0.019
Indirect effect	0.003	0.001	0.005
VRFs → CRP (*a*)	0.237	0.217	0.257
CRP → depr. sympt. (*b*)	0.012	0.004	0.020
Proportion mediated	20.1%	7.4%	46.5%

Note. 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. CRP = C-reactive protein. VRFs = Vascular risk factors.

VRF burden, CRP, and single depressive symptoms

Additional analyses examined symptom-specific effects. We found significant total effects of VRF burden on feelings of tiredness (estimate = 0.050, 95% CI [0.034; 0.065]), changes in appetite (estimate = 0.045, 95% CI [0.033; 0.057]), and sleep problems (estimate = 0.025, 95% CI [0.006; 0.046]). However, log CRP only mediated the effect between VRF burden and feelings of tiredness (estimate = 0.010, 95% CI

[0.006; 0.014]) and changes in appetite (estimate = 0.006, 95% CI [0.003; 0.010]). The full results of all longitudinal mediation models for single symptoms are shown in **Table 3**.

Table 3

Results of longitudinal mediation analyses of VRF burden, log CRP, and single depressive symptoms

	Total effect (95% CI)	Direct effect (95% CI)	Indirect effect (95% CI)	Proportion mediated[a] (95% CI)
Feelings of depression	-0.001 (-0.012, 0.009)	-0.002 (-0.013, 0.008)	0.001 (-0.002, 0.003)	–
Inadequacy	-0.002 (-0.013, 0.009)	-0.003 (-0.014, 0.009)	0.001 (-0.002, 0.003)	–
Tiredness	**0.050** (0.034, 0.065)	**0.039** (0.023, 0.055)	**0.010** (0.006, 0.015)	21.0% (12.2%, 34.4%)
Lack of interest	0.003 (-0.008, 0.014)	-0.001 (-0.012, 0.010)	**0.004** (0.001, 0.007)	–
Changes in appetite	**0.045** (0.033, 0.057)	**0.039** (0.027, 0.050)	**0.006** (0.003, 0.010)	14.2% (6.9%, 23.0%)
Thoughts of suicide	0.004 (-0.001, 0.009)	0.004 (-0.001, 0.009)	0.001 (-0.001, 0.002)	–
Concentration problems	0.004 (-0.008, 0.015)	0.002 (-0.010, 0.013)	0.002 (-0.001, 0.005)	–
Sleep problems	**0.025** (0.006, 0.046)	**0.027** (0.008, 0.048)	-0.002 (-0.006, 0.003)	–
Changes in speed	-0.001 (-0.008, 0.005)	-0.004 (-0.011, 0.002)	**0.003** (0.001, 0.004)	–

Note. All associations are adjusted for covariates age, gender, racial-ethnic background, educational attainment, household income, Townsend deprivation index, and baseline depressed depressive symptoms. CI = confidence interval.

[a] Proportion mediated was only calculated when total and indirect effects were significantly different from zero.

DISCUSSION

In the UK Biobank, we investigated the longitudinal association between VRF burden, low-grade inflammation, and depressive symptoms. We identified a small association between VRF burden and depressive symptoms at follow-up. Part of this association was mediated by serum CRP, a marker of low-grade systemic inflammation: Higher VRF burden was associated with increased serum CRP, which in turn was associated with higher depressive symptoms, after adjusting for sociodemographic variables and baseline depressed mood. Additional analyses exploring individual depressive symptoms revealed that this mediating effect was most prominent for two somatic symptoms: feelings of tiredness and changes in appetite.

Our findings are in line with several studies showing a small association between cumulative burden from multiple VRFs and depressive symptoms in mid- and later life [9, 11, 12]. Importantly, our results inform the debate on mechanisms underlying the VRF-depression relationship by suggesting that the small depressogenic effect of VRFs is, at least in part, due to their inflammation-promoting characteristics. Several authors have previously proposed inflammation as a possible mechanism linking vascular and mental health [14, 16–18]. However, studies disentangling the mediational effect of inflammation on the relationship between VRF burden and depressive symptoms are still scarce and mainly focused on cross-sectional data or on bivariate associations [43, 62, 63]. A strength of the present study was to directly quantify this mediating pathway in a large cohort study with temporal ordering of the variables under study.

Our results thus also add to the growing literature on the complex interconnections between inflammation, vascular health, and mental health. Specifically, our results support one hypothesised pathway that inflammation mediates the association between VRF burden and depressive symptoms [35, 43, 63]. Other research has shown that inflammation in turn also increases the risk of manifest cardiovascular diseases, independent of 'classical' VRFs used in this study [36, 64]. Inflammation directly affects the development of atherosclerotic lesions in the arterial tree and weakens endothelial reactivity and myocardial function [64]. Some studies have even suggested that inflammation might explain part of the increased risk of manifest vascular diseases (e.g. heart disease, stroke) in depression, although results have

been inconsistent [65–68]. VRF burden therefore might be a promising shared downstream target for preventing depressive symptoms and manifest vascular diseases by reducing inflammatory processes [69].

Thus, one particularly promising avenue for future research will be to investigate whether interventions or policies aimed at reducing VRF burden (and preventing vascular diseases) can also alleviate low-grade systemic inflammation and depressive symptoms. Large-scale RCTs with multiple components of interventions in middle-aged and older adults are underway and could aid to answer these research questions in the future [70, 71]. Moreover, it remains to be investigated if these findings could inform treatment stratification and whether inflammation-reducing treatments are an effective complementary treatment for depressed patients with high VRF burden [72].

The symptom-specific associations observed in our study are consistent with recent work suggesting that depression is not a homogeneous construct but an interplay of symptoms that can have different risk factors [73, 74]. Several previous reports have supported that VRFs as well as inflammation have distinct associations with specific depressive symptoms related to somatic or metabolic processes [30–32, 45, 63]. Our findings are in line with this research, supporting the notion that VRFs and low-grade inflammation might promote a specific symptom profile in depression. For example, the recently proposed immuno-metabolic subtype of depression has been suggested to be characterised by altered vascular and metabolic functions, disturbances in immune function, and specific behavioural symptoms [75]. Our findings support one specific pathway involving VRF burden, which may promote low-grade inflammation and specific depressive symptoms.

A limitation of our study is that our sample might be limited with respect to generalisability. While the UK Biobank offers a unique data source with extensive health data and longitudinal design, the sample has been shown to be selective and healthier than the general UK population [76]. Moreover, the UK Biobank is known to be less diverse with respect to racial-ethnic identity than the general population of the UK [77]. To understand mechanisms between VRFs, inflammation, and depression in more detail, future studies using large, representative, and more diverse samples are needed. Another limitation is that we were not able to include data before midlife. While middle-aged and older adults are at increased risk for VRFs and inflammation [78, 79],

the underlying pathological processes likely start much earlier in life. For example, recent studies demonstrate that VRFs are associated with depressive symptoms in the first 18 years of life [80, 81], and that inflammation is already linked to depressive symptoms in younger adults [82]. Future studies including assessments during childhood and adolescence would be needed to extend our findings and disentangle the associations between VRFs, inflammation, and depressive symptoms across the lifespan.

In this longitudinal study, we show that the association between VRFs and depressive symptoms in mid- and later life is partially mediated by low-grade systemic inflammation. Our results suggest that VRF burden is linked to increased low-grade systemic inflammation, which in turn is associated with more depressive symptoms. The present study therefore adds weight to the long-standing notion that inflammation plays a crucial role in linking vascular and mental health. Furthermore, our exploratory results, suggesting that this mediation is pertinent to certain symptoms of depression, highlight that vascular and inflammatory processes pertain to a certain (somatic) subgroup of depression.

Acknowledgements

No specific funding was received for this paper. We are extremely grateful to all participants in the UK Biobank and the UK Biobank team.

Conflict of Interest

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

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Supplementary Material for

Mediation of the Association between Vascular Risk Factors and Depressive Symptoms by C-Reactive Protein: Longitudinal Evidence from the UK Biobank

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Table S1

Variables for Exclusion Criteria with Hyperlinks to the UK Biobank Showcase

Data ID	Data descriptor	If one of the following was present, participant was excluded
6150	Vascular/heart problems diagnosed by doctor	[heart attack]
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)

Figure S1

Flowchart of UK Biobank participants included in the current study

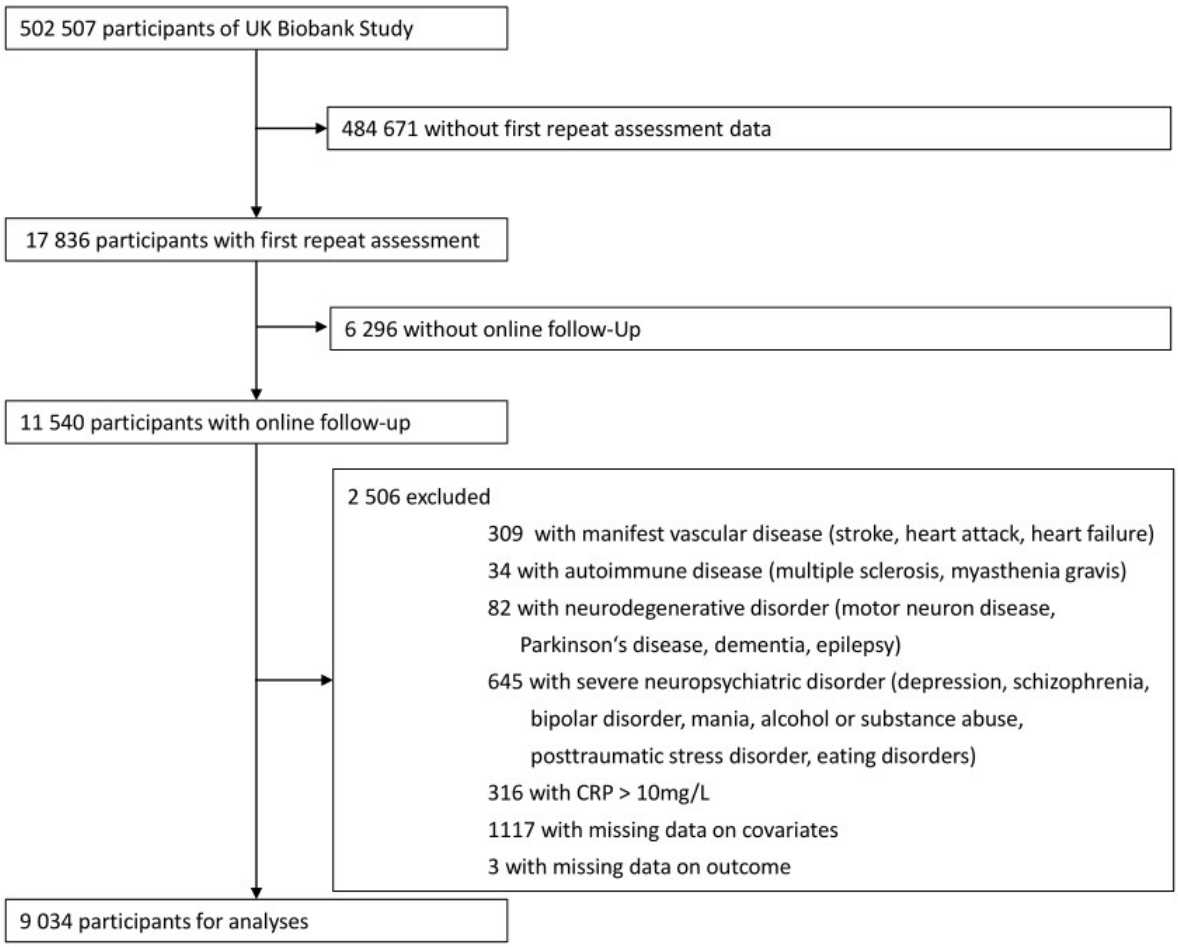

Table S2

Variables Relevant for Analyses with Hyperlinks to the UK Biobank Showcase

Data ID	Data descriptor
Vascular risk factors	
4080	Systolic blood pressure, automated reading (mmHg)
93	Systolic blood pressure, manual reading (mmHg)
4079	Diastolic blood pressure, automated reading (mmHg)
94	Diastolic blood pressure, manual reading (mmHg)
21001	Body mass index (kg/m^2)
20002	Non-cancer illness code, self-reported [high cholesterol] [hypertension] / [essential hypertension] / [gestational hypertension / pre-eclampsia]
2443	Diabetes diagnosed by doctor
1239	Current tobacco smoking (yes, on most or all days / only occasionally / no)
Inflammatory marker	
30710	C-reactive protein
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
20508	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

Zero-order correlations

	1	2	3	4	5	6	7	8	9	10
1. Age	-									
2. Gender	-0.08	-								
3. Ethnicity	0.08	0.00	-							
4. Education	-0.07	0.01	-0.05	-						
5. Baseline depressive symptoms	-0.15	0.07	-0.03	0.01	-					
6. Household income	-0.32	-0.07	-0.02	0.25	-0.02	-				
7. TDI	-0.13	0.02	-0.09	-0.02	0.07	-0.15	-			
8. VRF burden	0.19	-0.24	0.01	-0.10	0.03	-0.07	0.02	-		
9. Log CRP	0.10	0.02	0.01	-0.09	0.03	-0.007	0.03	0.25	-	
10. Depressive symptoms FU	-0.14	0.08	-0.01	-0.02	0.44	-0.0	0.09	0.03	0.05	-

Note. TDI = Townsend deprivation index, VRF = vascular risk factor, CRP = C-reactive protein, FU = follow-up.

Table S4

Results of longitudinal mediation analyses of VRF burden, raw CRP, and overall depressive symptoms

	estimate	lower 95% CI	upper 95% CI
Total effect	0.014	0.007	0.022
Direct effect (*c*)	0.012	0.005	0.019
Indirect effect	0.002	0.001	0.004
VRF → CRP (*a*)	0.355	0.316	0.394
CRP → depr. Sympt. (*b*)	0.006	0.002	0.011

Note. All associations are adjusted for covariates age, gender, ethnicity, educational attainment, household income, Townsend deprivation index, and baseline depressed affect. CI = confidence interval. CRP = C-reactive protein. VRF = Vascular risk factor.

Table S5

Results of longitudinal mediation analyses of VRF burden, log CRP, and overall depressive symptoms using FIML-estimator

	estimate	lower 95% CI	upper 95% CI
Total effect	0.014	0.008	0.021
Direct effect (*c*)	0.011	0.004	0.018
Indirect effect	0.003	0.002	0.005
VRF → CRP (*a*)	0.241	0.222	0.261
CRP → depr. Sympt. (*b*)	0.014	0.007	0.021

Note. All associations are adjusted for covariates age, gender, ethnicity, educational attainment, household income, Townsend deprivation index, and baseline depressed affect. CI = confidence interval. CRP = C-reactive protein. VRF = Vascular risk factor.