

Cardiometabolic dysregulation and cognitive decline: potential role of depressive symptoms

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Background

Previous studies have examined associations of cardiometabolic factors with depression and cognition separately.

Aims

To determine if depressive symptoms mediate the association between cardiometabolic factors and cognitive decline in two community studies.

Method

Data for the analyses were drawn from the Rotterdam Study, the Netherlands ($n = 2940$) and the Whitehall II study, UK ($n = 4469$).

Results

Mediation analyses suggested a direct association between cardiometabolic factors and cognitive decline and an indirect association through depression: poorer cardiometabolic status

at time 1 was associated with a higher level of depressive symptoms at time 2 (standardised regression coefficient 0.07 and 0.06, respectively), which, in turn, was associated with greater cognitive decline between time 2 and time 3 (standardised regression coefficient of -0.15 and -0.41 , respectively).

Conclusions

Evidence from two independent cohort studies suggest an association between cardiometabolic dysregulation and cognitive decline and that depressive symptoms tend to precede this decline.

Declaration of interest

None.

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Cognitive decline is an important public health issue.¹ Progressive deterioration of cognitive function can affect an individual's overall health and well-being, including daily self-care activities (for example dressing, bathing and housework), as well as the ability to effectively manage existing medical conditions and to participate actively in society. Increasing evidence suggests that cardiometabolic factors, including central obesity,² dyslipidemia,³ hypertension,⁴ insulin resistance or diabetes⁵ and inflammation⁶ might accelerate cognitive decline in midlife and at older ages. Similarly, the metabolic syndrome, a cluster of metabolic abnormalities that increase cardiovascular risk, has been associated with cognitive decline in prospective cohort studies.⁷

Emerging evidence suggests that the association between cardiometabolic dysregulation and cognitive decline may include indirect pathways via depressive symptoms.⁸ Specifically, a meta-analysis by Pan *et al*⁹ found evidence for a bidirectional association between metabolic syndrome and depression. There is also considerable evidence linking depression with cognitive impairment. Meta-analyses suggest that depression at older ages may be a risk factor for Alzheimer's disease¹⁰ and have found moderate impairment in executive function, memory and attention in individuals with depression relative to controls.¹¹ However, recurrent or increasing levels of depressive symptoms may also be a prodrome of dementia.¹² We hypothesise that depressive symptoms are one pathway that links cardiometabolic factors to cognitive decline. Given that previous studies have examined associations of cardiometabolic factors with depression and cognitive functioning separately, the temporal relationships between these factors are unknown. Using data from two longitudinal community-based samples of adults in the Netherlands (Rotterdam Study) and the UK (Whitehall II study), this study evaluated if depressive symptoms mediate the association between cardiometabolic factors and cognitive decline while controlling for other risk factors.

Method

Design/setting and participants

Rotterdam study

The Rotterdam Study is a prospective population-based cohort study of adults in Rotterdam, the Netherlands. More details are provided elsewhere.¹³ Briefly, in 1990 all inhabitants aged 55 years and older living in a catchment area in Rotterdam were invited to participate. A total of 7983 (78%) individuals agreed to participate. The initial cohort was expanded by 3011 individuals aged 55 years and older in 2000. This study used the third data wave of the first cohort (1997–99) and the first wave of the expanded cohort (2000–01) as baseline. All participants underwent home interviews and an extensive set of examinations in a research centre at baseline and after approximately 5 and 12 years (2002–04 and 2009–11; original cohort) and after approximately 4 and 11 years (2004–05 and 2011–12; extension cohort). The Rotterdam Study has been approved by a medical ethics committee, in accordance with the Population Screening Act: Rotterdam Study, executed by the Netherlands Ministry of Health, Welfare and Sports. All participants in the present analysis provided written informed consent.

Depression was assessed using a validated Dutch 20-item version of the Center for Epidemiologic Studies Depression (CES-D) scale,¹⁴ which measures self-reported frequency of depressive symptoms experienced during the past week. The CES-D is scored on a four-point Likert scale, ranging from 'rarely or none of the time' to 'most or all of the time'. Cognitive function was assessed twice (second and third wave) at separate centre visits.¹⁵ The test battery included the Stroop test,¹⁶ letter-digit substitution task (LDST),¹⁵ verbal fluency test (VF),¹⁷ 15-word verbal learning test (15-WLT)¹⁸ and the Purdue pegboard test.¹⁹ Higher scores on each test indicate a better performance, except for the Stroop test in which a higher score indicates a worse performance. Scores for the Stroop test were therefore inverted. All

tests were scored so that higher scores indicated better cognitive function.

Cardiometabolic dysregulation was defined using the facets of the metabolic syndrome:²⁰ elevated blood pressure (BP >130/85 mmHg or use of antihypertensive medication), impaired glycaemic control (fasting blood glucose concentration greater than 5.6 mmol/L (38 mmol/mol) or diagnosed type 2 diabetes), low high-density lipoprotein cholesterol (<1.03 mmol/L in men and <1.30 mmol/L in women), elevated triglycerides (>1.7 mmol/L) and central obesity (waist circumference \geq 102 cm (men), \geq 88 cm (women)). Systemic inflammation was added as an additional risk factor (C-reactive protein >3 mg/L). These measures were collected during research centre visits.

Level of education was categorised into low (primary education), medium (intermediate general education) and high (higher vocational education or university) levels. Smoking status was assessed by interview and categorised as smoker (current smoker) and non-smoker (never or former smoker). Physical activity levels were assessed with an adapted version of the Zutphen Physical Activity Questionnaire, which assigns a metabolic equivalent of task (MET) to all activities.²¹ Participants were classified into three groups of physical activity as low physical activity (<10 Met-hours per week); medium physical activity (between 10 and 50 Met-hours per week) and high physical activity (>50 Met-hours per week).

The Whitehall II study

The Whitehall II study is a prospective cohort study of London-based office staff working in 20 civil service departments. More details are provided elsewhere.²² Briefly, a total of 10 308 individuals (73% response rate) aged 35–55 years were recruited between 1985 and 1988. Ten follow-up assessments were conducted; participants were assessed approximately every 2 to 3 years. A clinical assessment was conducted every second phase. Informed consent was obtained from all participants, and the University College London Medical School Committee on the Ethics of Human Research approved the protocol.

Wave five (1997–1999) was used as the baseline for our analyses where the age range was between 45 and 69 years. Cardiometabolic factors were categorised as in the Rotterdam Study. Missing waist circumference was substituted with body mass index (BMI >30 kg/m² for obesity). Depression was assessed using the 20-item CES-D scale,¹⁴ which was administered at wave seven for the first time. Therefore, we have used the four-item depression subscale of the 30-item General Health Questionnaire (GHQ)²³ to control for depressive symptoms at baseline.

Educational attainment was grouped into three levels (no formal education or lower secondary education, intermediate education and higher degree). Ethnicity was drawn from wave one and categorised as White/Black minority ethnic. Smoking status was assessed by interview and coded as never, former and current. Intensity of physical activity was assessed via questionnaires. Participants were asked about the frequency and duration of their participation in 'mildly energetic', 'moderately energetic' and 'vigorous' physical activity. The measures were combined and categorised high, medium and low activity.

Cognitive function was assessed by four standard tasks at waves five, seven and nine. Short-term verbal memory was assessed with a 20-word free recall test. The Alice Heim 4-I (AH4-I)²⁴ was used to assess inductive reasoning. Phonemic and semantic verbal fluency was assessed via 'S' words for phonemic fluency and via 'animal' words for the semantic fluency.²⁵ More details can be found elsewhere.²⁶ The most recent waves (i.e. seven and nine) were used in the present study.

Statistical analyses

Structural equation modelling was used to examine a potential mediating role of depression in the association between cardiometabolic dysregulation and cognitive decline. Mediation analysis requires a temporal relationship between exposure (cardiometabolic dysregulation, wave one), mediator (depressive symptoms, wave two) and outcome (cognitive decline, wave three). Therefore, longitudinal data from three waves was used for each cohort.²⁷ Structural equation models are an extension of regression analysis that can handle measurement error, latent variables and relationships among latent and observed variables. Latent variables summarise the information from observed variables and account for measurement error and the individual contribution of each measure.²⁸ Elevated blood pressure, impaired glycaemic control, low high-density lipoprotein cholesterol, elevated triglycerides, central obesity and systemic inflammation were used as indicators for the baseline latent cardiometabolic dysregulation measure. The cognitive tests in each study were used as indicators for a general cognitive function (g-factor).

Change in cognitive function between two assessments was modelled using a latent change score approach.²⁹ In these models, a latent difference score is created by a distinct latent construct representing the difference between the two cognitive g-factors. Briefly, the model constrains the association between the first latent score and the second latent score to 1 such that any variance in the second latent score that was not explained by the first latent score would be accounted for by the latent change score for a given participant.

The conceptual framework is shown in Fig. 1: first, two latent constructs representing the cognitive g-factors at time 2 (T_2) and time 3 (T_3) were created. Second, a latent change score (cognitive decline) was constructed so that the cognitive g-factor at T_3 is considered to be the sum of the cognitive g-factor at T_2 plus the latent change score. Regression coefficients between the T_2 and T_3 cognitive functioning g-factors were constrained to 1, and regression coefficients between the T_3 cognitive functioning g-factor and the latent change score was also constrained to 1 so that the latent change score represented the nature of the change in cognitive functioning g-factors from T_2 to T_3 . The cognitive g-factor at T_2 was standardised to a mean of 1 and a s.d. of 1 so that higher scores indicate better cognitive functioning. Third, the latent change score was correlated with the cognitive functioning g-factors from T_2 to account for individual changes over time that are associated with the initial cognitive functioning score at T_2 . A negative change score indicates a cognitive decline.

Depressive symptoms at baseline were included in all models to account for previous depression symptoms. In a final step, associations between cardiometabolic risk factor at time 1 (T_1) (latent variable), depression at T_2 (manifest variable) and cognitive change (latent variable) are modelled using a regression framework. We controlled for gender, age, education, ethnicity, smoking and physical activity in our analyses. Depressive symptoms at baseline were included in all models to account for previous depression symptoms. In the Rotterdam Study, the cohort source was also controlled for.

Depression was modelled as a mediator between cardiometabolic dysregulation and cognitive decline. A direct association between the metabolic risk factor at T_1 and cognitive decline (T_2 – T_3) was estimated, as well as an indirect association through depression at T_2 (for example metabolic risk factor at T_1 predicts depression at T_2 , which in turn predicts cognitive decline from T_2 to T_3). Indirect association coefficients were calculated by multiplying the standardised coefficients for the paths from the predictor to the mediator (for example metabolic risk factor to depression) and from the mediator (depression) to the outcome (cognitive decline).³⁰

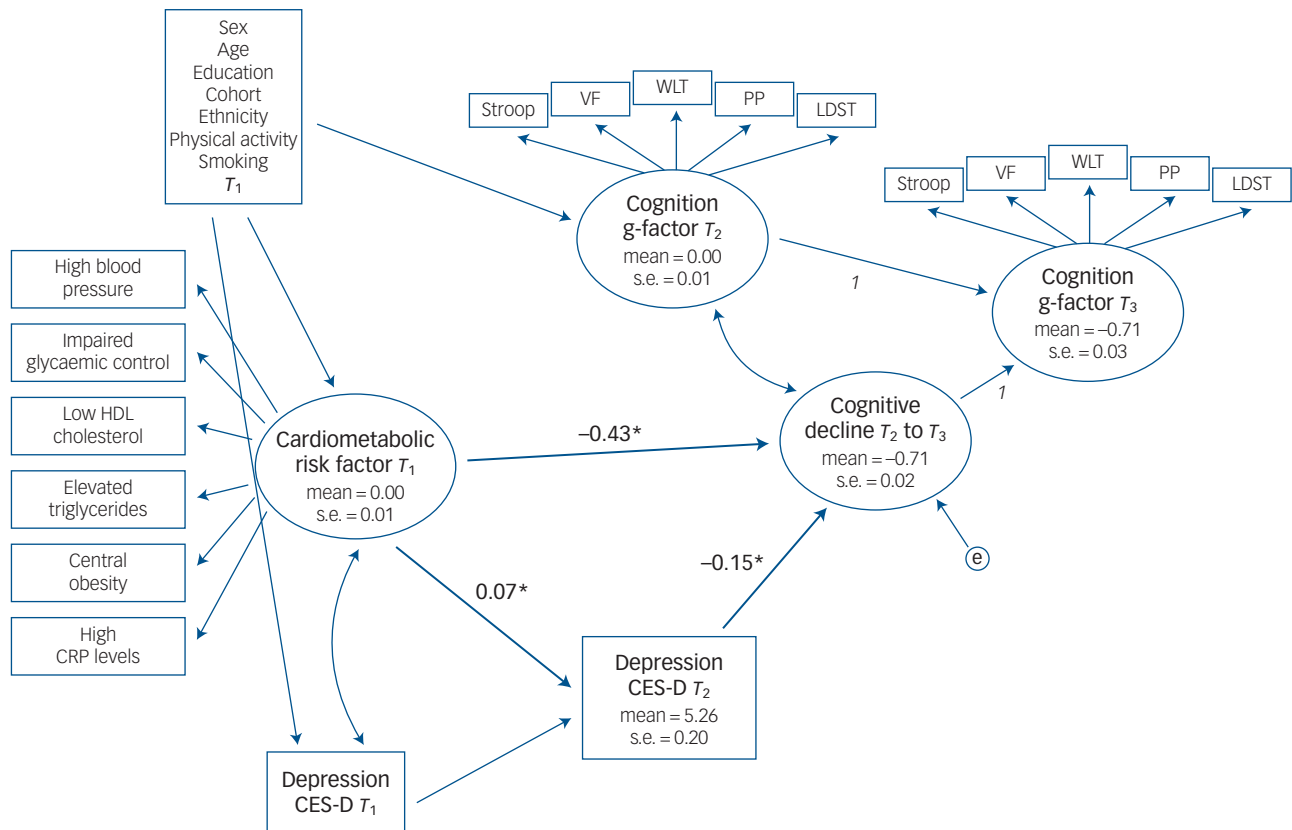


Fig. 1 Depressive symptoms as a potential mediator between cardiometabolic risk factors at baseline and cognitive decline at follow-ups in the Rotterdam Study cohort.

Rectangles represent measured variables, and circles represent latent constructs. Standardised regression coefficients are presented. Italicised path coefficients reflect constraints imposed on the model. The second assessment (time 2, T_2) was conducted approximately 4–5 years after baseline and the third assessment (time 3, T_3) was conducted approximately 10–11 years after baseline. The variable ‘cardiometabolic risk factors’ is standardised so that a positive score indicates higher risk. The variable ‘cognitive decline’ is standardised so that positive scores indicate cognitive improvement from T_2 to T_3 and negative scores indicate cognitive decline from T_2 to T_3 . T_1 , time 1; VF, verbal fluency test; WLT, word verbal learning test; PP, Purdue pegboard test; LDST, letter-digit substitution task; HDL, high-density lipoprotein; CRP, C-reactive protein; CES-D, Center for Epidemiologic Studies Depression scale. * $P < 0.05$.

The general goodness of fit of each model was evaluated using the comparative fit index (CFI) and the root mean square error of approximation (RMSEA). A CFI of 0.90 or more and RMSEA of 0.08 or lower indicates adequate fit.³¹ Multiple imputed values for the missing data from the variables used in the analysis were generated (PROC MI in SAS). In sensitivity analyses, analyses were rerun without imputed values for missing covariates. All analyses were conducted with SAS (version 9.4) and MPlus (version 7.4). Because observed cardiometabolic indicators were dichotomous, the weighted least squares estimator with a diagonal weight matrix, robust standard errors and a mean- and variance-adjusted χ^2 test statistic (WLSMV) and theta parameterisation³² were used for parameter estimation in MPlus.

Results

Findings from the Rotterdam study

A total of 2940 individuals participated in all three assessments of the Rotterdam Study and had data on cardiometabolic factors, depression and cognitive functioning (see flow chart for sample selection in supplementary Fig. 1; available at <http://dx.doi.org/10.1192/bjp.2017.26>). Mean ages at baseline, first and second follow-ups were 65.0 years (s.d. = 5.9), 69.3 years (s.d. = 6.1) and 75.8 years (s.d. = 6.1), respectively. There were more women than men in the sample (57%).

Table 1 presents baseline characteristics of participants. There were sociodemographic and health differences at baseline between those who participated in all three assessments and those who participated only in one or two assessments; individuals who participated at all assessments were younger (65 v. 73 years), more likely to have a high educational level (16.0 v. 10.6%), more likely to have a high physical activity level (74.6 v. 59.1%), less likely to have elevated depressive symptoms (5.8 v. 15.3%) and were more likely to have no metabolic risk factors (15.4 v. 9.6%). See supplementary Fig. 1 for a flow chart of the sample selection.

Mean depression scores increased between the first (mean 3.9, s.d. = 6.2) and second assessment (mean 5.3, s.d. = 6.9; $P < 0.001$). Individuals with no metabolic risk factor had lower mean depression scores at the second assessment (mean 4.5, s.d. = 5.7) than those with one or two metabolic risk factors (mean 5.2, s.d. = 6.8) and those with three or more metabolic risk factors (mean 5.7, s.d. = 7.5) (test for a linear trend across the cardiometabolic risk factors groups: $F(1,2937) = 13.4$, $P < 0.001$).

Cognitive decline was observed between the second and third assessment on all cognitive functioning subtests: the effect sizes of change (difference between first and second cognitive functioning subtest score, divided by standard deviation of the first score) were 0.41, 0.18, 0.39, 0.12 and 0.50 for the letter-digit substitution task, verbal fluency test, Stroop test, 15-word verbal learning test and Purdue pegboard test, respectively.

Table 2 describes the associations between the number of cardiometabolic risk factors at baseline and change in cognitive

Table 1 Baseline characteristics of the Rotterdam Study cohort and the Whitehall II Study cohort

	Rotterdam Study (<i>n</i> = 2940)	Whitehall II Study (<i>n</i> = 4635)
Age, mean (s.d.)	65.0 (5.9)	55.2 (5.9)
Gender, %		
Women	57.0	26.1
Educational level, %		
Low	7.5	31.9
Intermediate	76.4	31.1
High	16.0	37.0
Ethnicity, %		
White	98.4	93.3
Smoking, %		
Current smoker	19.0	8.0
Physical activity, %		
Low	0.7	14.1
Medium	24.7	32.1
High	74.6	53.9
Cardiometabolic risk factors		
Hypertension, %	51.0	38.0
Impaired glycaemic control, %	43.5	15.9
Low high-density lipoprotein cholesterol, %	27.2	14.8
Elevated triglycerides, %	30.6	24.2
Elevated CRP levels, %	26.5	16.2
Central obesity, %	41.7	17.6
<i>Depression</i>		
CES-D summary score	3.9 (6.2)	
Elevated depressive symptoms, %	5.8	
GHQ depression subscale summary score		0.9 (1.8)
Elevated depressive symptoms %		16.5

CRP, C-reactive protein; CES-D, Center for Epidemiologic Studies – Depression; GHQ, General Health Questionnaire.

functioning (g-factors controlled for age and gender). Individuals with no cardiometabolic risk factors had the highest cognitive functioning scores at T_2 and T_3 whereas individuals with three or more cardiometabolic risk factors had the lowest cognitive functioning scores at T_2 and T_3 . The largest cognitive decline was observed for those with three or more cardiometabolic risk factors.

Results of the mediation analyses are presented in Fig. 1. The model fit was acceptable (CFI = 0.933, RMSEA = 0.041). Results show that a poorer cardiometabolic status at baseline was associated with greater cognitive decline, after controlling for age, gender, education, ethnicity, cohort, smoking and physical activity. There was a direct association from the latent variable cardiometabolic risk factor to cognitive decline (standardised regression coefficient of -0.43 , $P < 0.001$) and an indirect association through depression; poorer cardiometabolic status at baseline was associated with a higher level of depressive symptoms at T_2 (standardised regression coefficient of 0.07 , $P < 0.001$) which in turn was associated with

cognitive decline (standardised regression coefficient of -0.15 , $P < 0.001$).

The indirect association coefficients were small but significant: -0.011 (95% CI -0.002 to -0.020), suggesting that depression partially mediated the association between cardiometabolic status and cognitive decline.

Findings from the Whitehall II study

A total of 4469 individuals participated in waves five, seven and nine of the Whitehall II study and had data on cardiometabolic factors, depression and cognitive functioning. The mean age at baseline (wave five, mean 55.2, s.d. = 5.9) was almost 10 years lower compared with the Rotterdam Study and there were almost three times more men than women in this cohort. Mean ages at wave seven and nine were 61 (s.d. = 6.0) years and 66 (s.d. = 6.0) years, respectively.

Table 1 shows sociodemographic and clinical characteristics of participants at wave five (the baseline). Those who participated in all three assessments were more often male (73.9% v. 63.3%), more likely to be younger (55 v. 57 years), more likely to have a high educational level (38.6% v. 30.7%), more likely to have a high physical activity level (56.5% v. 47.8%), less likely to have elevated depressive symptoms (16.1 v. 20.5%), and were more likely to have no metabolic risk factors (31.7 v. 23.5%) than those who participated only in wave five. Individuals with no metabolic risk factor had lower mean depression scores at the second assessment (mean 7.7, s.d. = 7.5) then those with three or more metabolic risk factors (mean 8.4, s.d. = 7.8). See supplementary Fig. 1 for a flow chart of the sample selection.

Cognitive decline was observed between the second and third assessment on all cognitive functioning subtests: the effect sizes were 0.07, 0.29, 0.16, and 0.14 for the Alice Heim 4-I task, short-term verbal memory task, phonemic and semantic verbal fluency tasks, respectively. Associations between the number of cardiometabolic risk factors at baseline and the change in cognitive functioning (g-factors controlled for age and gender) are presented in Table 2. Associations were similar as in the Rotterdam Study, although changes in cognitive functioning g-factors were smaller. Individuals with no cardiometabolic risk factors had the highest cognitive functioning scores at T_2 and T_3 compared with those with one or more cardiometabolic risk factors.

The mediation analyses (Fig. 2) also suggested a potential mediating effect of depression in the association between metabolic risk factors and cognitive decline. Model fit was acceptable (CFI = 0.917, RMSEA = 0.049). There was a direct association from the latent variable cardiometabolic risk factor to cognitive decline (standardised regression coefficient of -0.38 , $P < 0.001$) and an indirect association through depression: poorer cardiometabolic status at baseline was associated with a higher level of depressive symptoms at T_2 (standardised regression coefficient of 0.06 , $P = 0.003$) which,

Table 2 Association between cardiometabolic risk factors and depression and cognitive functioning in the Rotterdam Study and the Whitehall II study cohort^a

Baseline cardiometabolic risk factors, <i>n</i>	Rotterdam study				Whitehall II study			
	<i>n</i>	Cognitive functioning g-factor T_2 , mean (s.d.)	Cognitive functioning g-factor T_3 , mean (s.d.)	Difference g-factor, mean (s.d.)	<i>n</i>	Cognitive functioning g-factor T_2 , mean (s.d.)	Cognitive functioning g-factor T_3 , mean (s.d.)	Difference g-factor, mean (s.d.)
0	454	0.23 (0.83)	-0.30 (1.05)	-0.53 (0.29)	1579	0.18 (0.90)	0.01 (0.94)	-0.18 (0.10)
1–2	1320	0.06 (0.89)	-0.52 (1.14)	-0.58 (0.32)	2279	-0.08 (0.99)	-0.27 (1.03)	-0.19 (0.11)
3–6	1166	-0.16 (0.86)	-0.81 (1.09)	-0.65 (0.31)	777	-0.14 (1.02)	-0.34 (1.06)	-0.20 (0.11)

a. A g-factor for cognitive functioning was computed from the five cognitive function tests using confirmatory factor analyses as shown in Fig. 1. Scores were standardised to have a standard deviation of 1 (time 2 (T_2) and time 3 (T_3)) and a mean of 0 (T_2) so that negative scores indicate poorer cognitive function. A test for a linear trend of g-factor decline across the cardiometabolic risk factors groups indicated a statistically significant decrease of g-factor scores across groups (Rotterdam Study: $F(1,2937) = 49.6$, $P < 0.001$; Whitehall II study: $F(1,4632) = 31.1$, $P < 0.001$).

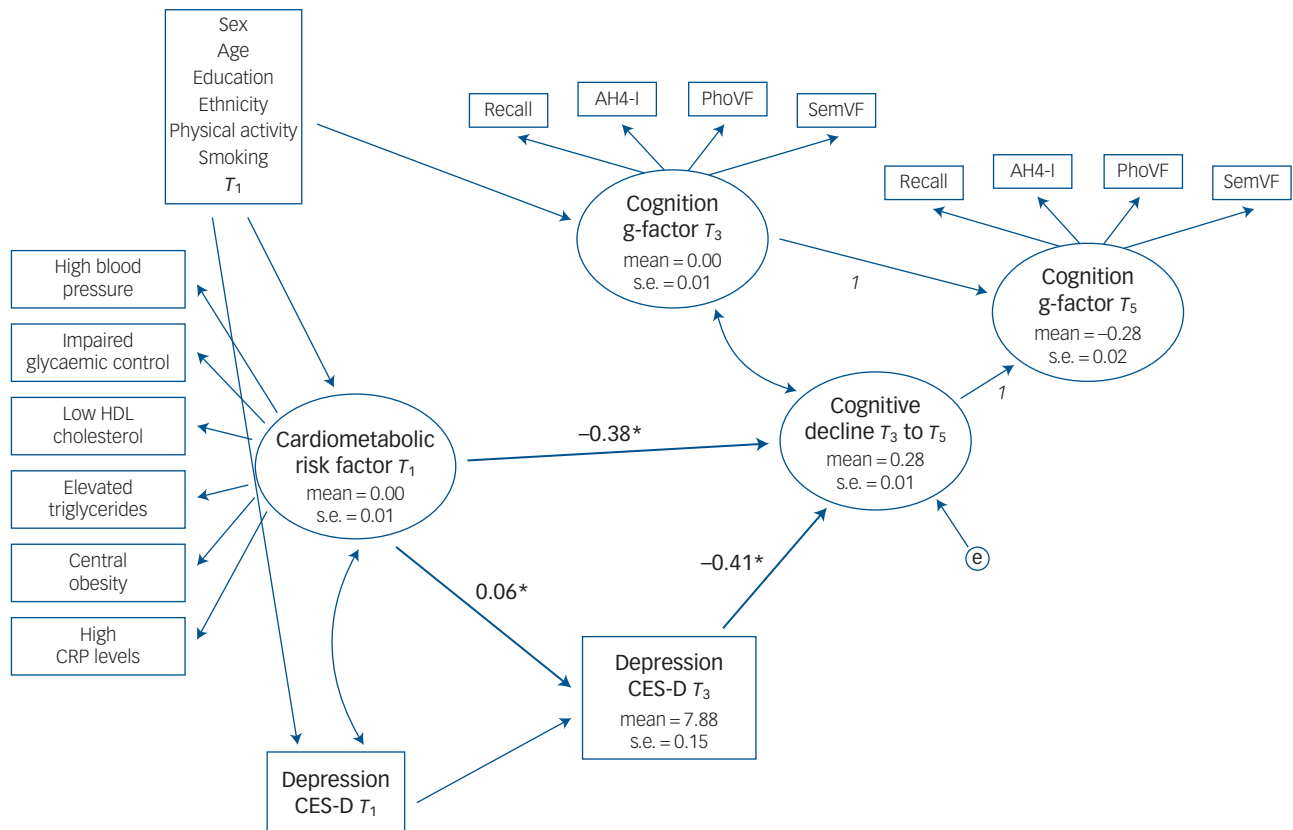


Fig. 2 Depressive symptoms as a potential mediator between cardiometabolic risk factors at baseline and cognitive decline at follow-ups in the Whitehall II study cohort.

Rectangles represent measured variables, and circles represent latent constructs. Standardised regression coefficients are presented (unstandardised estimates shown in parentheses). Italicised path coefficients reflect constraints imposed on the model. The third (time 3, T_3) and fifth (time 5, T_5) assessments were conducted approximately 4 and 8 years after baseline, respectively. The variable 'cardiometabolic risk factors' is standardised so that a positive score indicates higher risk. The variable 'cognitive decline' is standardised so that positive scores indicate cognitive improvement from T_3 to T_5 and negative scores indicate cognitive decline from T_3 to T_5 . T_1 , time 1; AH4-I, Alice Heim 4-I; PhoVF, phonemic verbal fluency; SemVF, semantic verbal fluency; HDL, high-density lipoprotein; CRP, C-reactive protein; CES-D, Center for Epidemiologic Studies Depression scale. * $P < 0.05$.

in turn, was associated with cognitive decline (standardised regression coefficient of -0.41 , $P < 0.001$). The indirect association coefficient was -0.023 (95% CI -0.005 to -0.041), which if anything, was higher than in the Rotterdam Study.

Discussion

Main findings

This study evaluated temporal associations between cardiometabolic risk factors, depressive symptoms and change in cognitive function in two community studies of individuals aged 45 years and above in the Netherlands and the UK. Evidence from both studies suggest a direct association between cardiometabolic risk factors and cognitive decline and an indirect association through depressive symptoms: cardiometabolic risk factors at T_1 predicted depressive symptoms at T_2 (4–5 years later), which, in turn, predicted cognitive decline from T_2 to T_3 (4–6 years later).

These results suggest that depression might be one potential pathway through which cardiometabolic dysfunction is associated with cognitive decline. To our knowledge, this is the first study that simultaneously estimated longitudinal associations between cardiometabolic functioning, depressive symptoms and change in cognitive functioning. The congruence of the results from the Rotterdam cohort with those from the Whitehall II cohort, which is comprised individuals 10-years younger, suggests that the

mediating role of depression apply to elderly populations as well as middle-aged adults who are not yet experiencing accelerated cognitive decline.

Strengths and limitations

The main strength of this study is the repeated measurement of cognitive function using validated cognitive batteries,³³ as well as the availability of depression assessments and cardiometabolic variables in two large population-based samples. Strengths of the analysis include a structural-equation modelling approach that permitted the modelling of the dynamic relationship between cardiometabolic factors, depressive symptoms and change in cognitive function. This approach accounted for measurement error by including latent variables for cardiometabolic functioning and cognitive functioning. A latent-change score approach for the evaluation of cognitive decline is a more flexible approach than a simple difference-score approach because latent-change score methods separate out the portion of change that is correlated with the initial measurement and thereby removing a source of unreliability of a simple change score.

There are also several study limitations. Depressive symptoms were assessed using a self-report scale, and not diagnostic interviews that assessed depressive symptoms experienced in the past week and does not account for treatment of depression and history of depression. The overall level of depression was low, given that we examined non-clinical cohorts. In addition, lifestyle-related behaviours were also assessed by self-report, and thus may be subject to some

bias. Cognitive functioning was only assessed at the second and third assessment. Therefore, we were not able to control for baseline cognitive functioning.

Attrition is an expected issue in large elderly population cohorts. Indeed, there were substantial sociodemographic and clinical differences between those who participated in all three assessments and those who did not, indicating that individuals with a better cardiometabolic functioning and a lower level of depressive symptoms were included in our cohort. This might have resulted in an underestimation of the underlying associations.

The time interval (4–5 years) between our single measurement of cardiometabolic functioning and the measurement of cognitive functioning could also be considered as a limitation. For example, Akbaraly *et al* have demonstrated that only persistent metabolic syndrome was associated with lower cognitive performance in late midlife.²⁶ Cardiometabolic functioning might have changed after the assessment because of clinical treatment or change of lifestyle-related behaviours. Finally, the applicability to other ethnic groups may be limited since the majority of the participants in the present study were White.

Comparison with findings from other studies

Our findings are consistent with previous prospective studies that have focused on comorbid depression as risk factor for cognitive decline or dementia in people with diabetes, a clinical form of cardiometabolic dysregulation. A recent systematic review on the association between depressive symptoms and cognitive functioning in people with diabetes found evidence that the presence of depressive symptoms in people with diabetes was associated with poorer cognitive outcomes.³⁴ Sullivan *et al*³⁵ described an interaction between depression and diabetes on cognitive outcomes in the Action to Control Cardiovascular Risk in Diabetes-Memory in Diabetes (ACCORD-MIND) trial; patients with type 2 diabetes and comorbid depression were at higher risk for cognitive decline than those with type 2 diabetes without depression. Similar results have been reported from two studies using administrative databases.^{36,37}

Our study adds to this evidence by considering temporality and suggesting that depression might explain some of the association between metabolic factors and cognitive decline (partial mediation). Management of cardiometabolic risk factors requires patient engagement. Depression is associated with poorer self-care behaviours (for example following a healthy diet, not smoking, engaging in exercise and medication adherence), which could worsen the management of the metabolic risk factors course and increase the risk of cognitive decline through a long-term exposure to metabolic risk factors.²⁶

Cardiometabolic dysregulations and depression also share common pathophysiological mechanisms, including dysregulation of the hypothalamic–pituitary–adrenocortical (HPA) axis.³⁸ The co-occurrence of both conditions might adversely have an impact on both conditions, which can in turn result in several metabolic dysregulations and might amplify the risk of cognitive decline.³⁹ Vogelzangs *et al*⁴⁰ have shown that metabolic dysregulations predicted a more chronic course of depressive disorders. Recurrent or chronic depressive symptoms are associated with prolonged exposure to psychosocial and other life stresses, which can cause wear and tear to different circulatory, inflammatory, immune and psychological regulatory systems^{41,42} and increase allostatic load.⁴¹ Allostatic load has been associated with cognitive decline in population studies.⁴³ Liu *et al*⁴⁴ concluded in a recent review that several other overlapping physiological mechanisms in addition to HPA-axis disturbances may explain the association of metabolic dysfunction with worse cognition in individuals with depression, including abnormalities in brain-derived neurotrophic factor signalling,

adipose-derived hormones, insulin signalling, inflammatory cytokines, and oxidative and nitrosative stress.

Implications

In conclusion, our findings show that people with metabolic dysregulation are at increased risk of cognitive decline and that depressive symptoms may partially mediate this decline. This has important implications for investigating the pathways that could link metabolic dysregulation and increased risk of cognitive decline. For adequate prevention of cognitive decline both cardiometabolic and mental health should play a key role.

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Supplementary material

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