Cardiometabolic dysregulation and cognitive decline: potential role of depressive symptoms

Norbert Schmitz, Sonya S. Deschénes, Rachel J. Burns, Sofia M. Danna, Oscar H. Franco, M. Arfan Ikram, Mika Kivimäki, Archana Singh-Manouix and Henning Tiemeier

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 al9 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),17 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 ≥102 cm (men), ≥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 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).

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 (latent variable) are modelled using a regression framework. We constrained coefficients between the mediator (metabolic risk factor at time 1 (T1)) and the outcome (cognitive decline, wave three). Therefore, longitudinal data from three waves was used for each cohort.28 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 (T2) and time 3 (T3) were created. Second, a latent change score (cognitive decline) was constructed so that the cognitive g-factor at T3 is considered to be the sum of the cognitive g-factor at T2 plus the latent change score. Regression coefficients between the T2 and T3 cognitive functioning g-factors were constrained to 1, and regression coefficients between the T3 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 T2 to T3. The cognitive g-factor at T2 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 T2 to account for individual changes over time that are associated with the initial cognitive functioning score at T2. 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 (T1) (latent variable), depression at T2 (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 T1 and cognitive decline (T1–T3) was estimated, as well as an indirect association through depression at T2 (for example metabolic risk factor at T1 predicts depression at T2, which in turn predicts cognitive decline from T2 to T3). 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

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 analyses 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.28 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).

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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. Multiple imputed values 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 $\chi^2$ test statistic (WLSMV) and theta parameterisation were used for parameter estimation in MPlus.

**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%).

**Results**

**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%), more likely to have a high blood pressure (15.4 v. 9.6%), and 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...
functioning (g-factors controlled for age and gender). Individuals with no cardiometabolic risk factors had the highest cognitive functioning scores at T3 and T4 whereas individuals with three or more cardiometabolic risk factors had the lowest cognitive functioning scores at T1 and T2. 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 0.06, 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 (36.5% 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 T3 and T4 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 T3 (standardised regression coefficient of 0.07, P < 0.001) which in turn was associated with cognitive decline.

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

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

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

<table>
<thead>
<tr>
<th>Baseline cardiometabolic risk factors, n</th>
<th>Cognitive functioning g-factor</th>
<th>Cognitive functioning g-factor</th>
<th>Difference g-factor, mean (s.d.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rotterdam study</td>
<td>T3, mean (s.d.)</td>
<td>T4, mean (s.d.)</td>
<td>T3, mean (s.d.)</td>
</tr>
<tr>
<td>0</td>
<td>454</td>
<td>0.23 (0.83)</td>
<td>-0.30 (1.05)</td>
</tr>
<tr>
<td>1–2</td>
<td>1320</td>
<td>0.06 (0.89)</td>
<td>-0.52 (1.14)</td>
</tr>
<tr>
<td>3–6</td>
<td>1166</td>
<td>-0.16 (0.86)</td>
<td>-0.81 (1.09)</td>
</tr>
</tbody>
</table>

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(T3) and 3(T4) and a mean of 0 (T3) 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(3,2937) = 49.6, P < 0.001; Whitehall II study: F(3,4629) = 33.1, P < 0.001).
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.

**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 at baseline 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.

**Strengths and limitations**

The main strength of this study is the repeated measurement of cognitive function using validated cognitive batteries, 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. 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. Sullivan et al 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.

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.

Cardiometabolic dysregulation and depression also share common pathophysiological mechanisms, including dysregulation of the hypothalamic–pituitary–adrenocortical (HPA) axis. 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. Vogelzangs et al 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 physiological regulatory systems and increase allostatic load. Allostatic load has been associated with cognitive decline in population studies. Liu et al 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.

Norbert Schmitz, PhD, Department of Psychiatry, McGill University, Montreal, Douglas Mental Health University Institute, Montreal and Diabetes Research Centre Research, Montreal, Quebec, Canada; Sonya S. Deschenes, PhD, Rachael J. Burns, PhD, Department of Psychiatry, McGill University, Montreal, and Douglas Mental Health University Institute, Montreal Quebec, Canada; Sofia M. Danna, MSc, Department of Epidemiology and Biostatistics, McGill University, Montreal, Quebec, Canada; Oscar H. Franco, MD, PhD, M. Afriat Ikram, MD, PhD, Department of Epidemiology, Erasmus MC-University Medical Center Rotterdam, Rotterdam, the Netherlands; Milka Kvimski, PhD, Department of Epidemiology of Public Health, University College London (UCL), London, UK; Archana Singh-Manoux, PhD, Department of Epidemiology and Public Health, University College London, London, UK and INSERM U1018, Center for Research in Epidemiology and Population Health, Pôle Broussais Hôpital, Villejuif, France; Henning Tijmeler, MD, PhD, Department of Epidemiology, Department of Psychiatry and Department of Child and Adolescent Psychiatry, Erasmus MC-University Medical Center Rotterdam, Rotterdam, the Netherlands.

Correspondence: Norbert Schmitz, Douglas Mental Health University Institute, McGill University, 6875 LaSalle Boulevard, Montreal, Quebec, H4H 1R3, Canada. Email: norbert.schmitz@mcgill.ca

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Supplementary material
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