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The cardiometabolic depression subtype and its association with clinical characteristics: The Maastricht Study

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ABSTRACT

Background: Individuals with depression often show an adverse cardiometabolic risk profile and might represent a distinct depression subtype. The aim of this study was to investigate whether a cardiometabolic depression subtype could be identified and to investigate its association with demographics and clinical characteristics (severity, symptomatology, anti-depressant use, persistence and cognitive functioning).
Methods: We used data from The Maastricht Study, a population-based cohort in the southern part of The Netherlands. A total of 248 participants with major depressive disorder were included (mean [SD] age, 58.8 ± 8.5 years; 121 [48.8 %] were men). Major depressive disorder was assessed at baseline by the Mini-International Neuropsychiatric Interview. Cardiometabolic risk factors were defined as indicators of the metabolic syndrome according to the National Cholesterol Education Program Adult Treatment Panel III guidelines. We measured severity and persistence of depressive symptoms by use of the 9-item Patient Health Questionnaire.
Results: Latent class analysis resulted in two subtypes, one with cardiometabolic depression (n = 145) and another with non-cardiometabolic depression (n = 103). The cardiometabolic depression subtype was characterized by being male, low education, more severe depressive symptoms, less symptoms of depressed mood and more symptoms of loss of energy, more use of antidepressant medication and lower cognitive functioning.
Limitations: No conclusions can be made about causality.
Conclusions: Latent class analysis suggested a distinct cardiometabolic depression subtype. Participants with cardiometabolic depression differed from participants with non-cardiometabolic depression in terms of demographics and clinical characteristics. The existence of a cardiometabolic depression subtype may indicate the need for prevention and treatment targeting cardiometabolic risk management.

1. Introduction

Depression is the leading cause of disability worldwide and the largest contributor to disease burden, affecting almost 350 million people worldwide (WHO, 2017). The aetiology underlying depression is incompletely understood and likely heterogeneous, including differences across age groups (Disabato and Sheline, 2012). Older age is a risk factor for treatment failure (Schaakxs et al., 2018), and the antidepressant response rate is lower for patients aged 65 years or older (Tedeschini et al., 2011). Age-related physiological changes may

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contribute to these differences.

Previous studies have shown a bidirectional association between depression and cardiometabolic risk (Pan et al., 2012), which suggests that factors like central obesity, dyslipidaemia, hypertension and hyperglycaemia explain part of the heterogeneity in symptomatology and treatment response. Cardiometabolic risk factors have also been related to the symptomatology and persistence of depression, with high cardiometabolic risk being associated with an atypical depression subtype with symptoms of increased in appetite and weight gain (Lamers et al., 2010; Lamers et al., 2013; Veltman et al., 2017). Furthermore, high cardiometabolic risk has been related to chronic or persistent depression (Marijnissen et al., 2017; Vogelzangs et al., 2011). Such findings suggest that depression characterized by high cardiometabolic risk has a distinct clinical profile and a worse response to treatment compared to depression without this risk. Identification of a distinct cardiometabolic depression subtype and studying its clinical profile might help in developing targeted prevention and intervention strategies.

Two previous studies that have identified subtypes of depression based on cardiometabolic risk factors (Beijers et al., 2019; Kokkeler et al., 2020), have shown inconsistent findings. One study found three subtypes based on thirty-six biomarkers and cardiometabolic risk factors (Beijers et al., 2019), a 'healthy' subtype characterized by a healthy weight and a low cardiometabolic risk profile, an 'average' subtype without extreme scores, and an 'overweight' subtype with a high cardiometabolic risk profile. The 'overweight' subtype was associated with highest levels of psychopathology, severity and medication use. In another study, Kokkeler et al. (2020) found a 'healthy' depression subtype (49.7 %) and five subtypes characterized by different profiles of metabolic-inflammatory dysregulation. Compared to the healthy subtype, the subtype with mild 'metabolic and inflammatory dysregulation' (37.6 %) had higher depressive symptom scores, a lower rate of improvement in the first year, and were less likely to be remitted after 2-years, while the four smaller subgroups characterized by a more specific immune-inflammatory dysregulation profile did not differ from the two main subgroups regarding the course of depression.

The aim of this study was to test for a cardiometabolic depression subtype based on cardiometabolic risk factors among participants with major depressive disorder (MDD) by means of latent class analysis. In addition, we investigated whether subtypes may differ in demographics and clinical characteristics (severity, symptomatology, anti-depressant use, persistence and cognitive functioning).

2. Methods

2.1. Population and design

The Maastricht Study is an observational prospective population-based cohort study. The rationale and methodology have been described previously (Schram et al., 2014). In brief, the study focuses on the aetiology, pathophysiology, complications and comorbidities of type 2 diabetes mellitus (T2DM), heart disease, and other chronic conditions, and is characterized by an extensive phenotyping approach. Eligible for participation were individuals aged between 40 and 75 years living in the southern part of the Netherlands. Participants were recruited through mass media campaigns and from the municipal registries and the regional Diabetes Patient Registry via mailings. Recruitment was stratified according to known T2DM status, with an oversampling of individuals with T2DM (and thus higher propensity for cardiometabolic risk factors), for reasons of efficiency.

Baseline data were collected between November 2010 and January 2018. Brain MRI measurements were implemented from December 2013 onwards until February 2017. The study has been approved by the institutional Medical Ethical Committee (NL31329.068.10) and the Minister of Health, Welfare and Sports of the Netherlands (Permit 131088-105,234-PG). All participants gave written informed consent.

Fig. 1 shows the flowchart of the study population. From the initial 7689 participants we excluded participants without data ($n = 315$) or without MDD ($n = 7126$) according to the Mini-International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998). Our analytical sample included participants with MDD at baseline ($n = 248$; 3.2 % of the total study population) according to the MINI) (Sheehan et al., 1998).

2.2. Demographics

Demographics were measured at baseline. Educational level (low/intermediate/high) was assessed by questionnaires (Schram et al., 2014).

2.3. Cardiometabolic risk factors

We measured waist circumference, triglyceride levels, HDL-cholesterol levels, fasting glucose levels, office blood pressure after 10 min of seated rest, and medication use as described elsewhere (Schram et al., 2014). Cardiometabolic risk factors were defined based on the definition of the metabolic syndrome according to the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III guidelines: (1) waist circumference $\geq$ 102 cm for men or $\geq$ 88 cm for women; (2) serum triglyceride level $\geq$ 1.7 mmol/l; (3) HDL-cholesterol level $<$ 1.03 mmol/l for men or $<$ 1.30 mmol/l for women; (4) fasting glucose level $\geq$ 5.6 mmol/l or use of glucose-lowering drug medication (insulin or oral agents); or (5) systolic blood pressure $\geq$ 130 mmHg and/or diastolic blood pressure $\geq$ 85 mmHg, and/or use of blood pressure-lowering medication (Alberti et al., 2009).

2.4. Major depressive disorder and symptomatology

MDD and symptomatology were assessed by the Mini-International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998). The MINI is a short diagnostic structured interview used to assess the presence of MDD in the preceding 2 weeks, in line with the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders. Fourth Edition). MDD was diagnosed if participants had (1) one core symptom (i.e., depressed mood or loss of interest) and at least four other symptoms of depression (i.e., significant weight change or change in appetite, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy, guilt or worthlessness, diminished ability to think or concentrate or indecisiveness and suicidal thoughts or plans), or (2) two core symptoms and at least three other symptoms, for a period of more than 2 weeks. The MINI was conducted by trained staff members.

2.5. Severity and persistence of depressive symptoms

Severity and persistence of depressive symptoms were assessed by a validated Dutch version of the PHQ-9 (Kroenke et al., 2001) both at baseline and during annual follow-up over 7 years. Follow-up data was available in 214 out of 248 participants with MDD (86.3 %). The PHQ-9 is a self-administered questionnaire that assesses the presence of the nine symptoms for the DSM-IV criteria for a major depressive disorder (Bell, 1994) on a 4-point Likert-scale ranging from 0 "not at all" to 4"nearly every day". When one or two items were missing, the total score was calculated as 9 $\times$ (total points/[9 $-$ number of missing items]) and rounded to the nearest integer. When more items were missing, the total score was scored as missing. The total PHQ-9 score at baseline was used to define severity of depressive symptoms. Persistence of depressive symptoms was defined as clinically relevant depressive symptoms on at least one follow-up moment (PHQ-9 $\geq$ 10) (Pettersson et al., 2015).

2.6. Cognitive functioning

Cognitive functioning was measured at baseline by a concise (30-

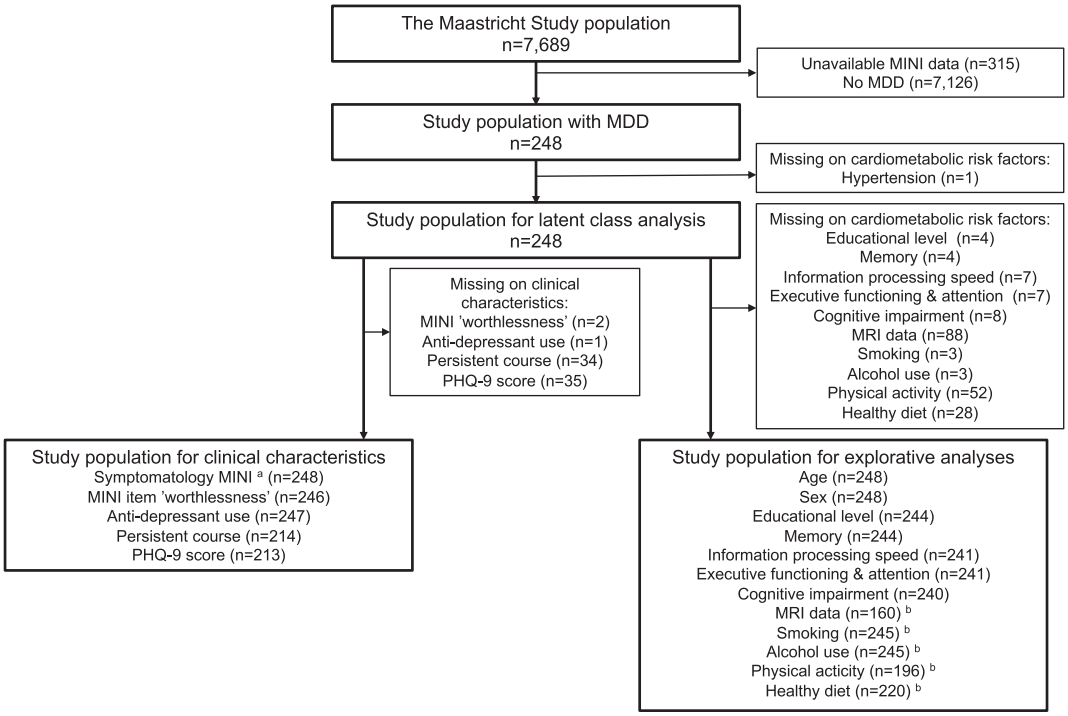

Fig. 1. Flowchart of study population.
MINI indicates Mini-International Neuropsychiatric Interview; MDD, major depressive disorder; PHQ-9, 9 item Patient Health Questionnaire; MRI, magnetic resonance imaging. [a] Except for MINI item 'worthlessness'. [b] Analyses with demographic, brain volumetrics and lifestyle data are performed in explorative analyses.

minute) test battery (Schram et al., 2014). For conceptual clarity, test scores were standardized and divided into three cognitive domains (i.e., memory function, information processing speed, and executive function & attention) (Martens et al., 2017). Individuals performing <-1.5 standard deviations below their norm-based expected score in one or more domain were categorized as having significant cognitive impairment (Van Der Elst et al., 2005, 2006a, 2006b, 2006c).

2.7. Additional analyses on lifestyle characteristics and brain volumetrics

Lifestyle characteristics and brain volumetrics were measured at baseline. Because lifestyle factors contribute to the development of cardiometabolic risk factors (Barbaresko et al., 2018), we investigated the associations of lifestyle factors with the depression subtypes in additional analyses. Smoking status (never/current/former), alcohol consumption (none/low/high), physical activity (Harada et al., 2001) and healthy diet (Looman et al., 2017; van Dongen et al., 2019) were assessed by questionnaires (Schram et al., 2014). Brain volumetric (3 T MRI) data were available in a smaller subsample of the study population because of logistic reasons (Figs. 1, 64.5 %, $n = 160$) and therefore analyzed in additional analyses. White matter hyperintensity volume as an in vivo measure of cerebral small vessel disease pathology and brain tissue volumes (white matter, grey matter and cerebral spinal fluid) as a measure of brain atrophy were assessed as previously described (Li et al., 2020).

2.8. Statistical analyses

Statistical analyses were performed in Mplus version 8.4 (Muthén and Muthén, 2012, Los Angeles, CA, USA) and the Statistical Package for Social Sciences (version 25.0; IBM, Chicago, Illinois, USA). We performed latent class analysis to investigate whether depression subtypes based on differential clustering of cardiometabolic risk factors could be identified. First, different models were fitted (Muthén and Muthén, 2012), starting with a 1-class model and stepwise increasing the number of classes. The sample-size adjusted Bayesian Information Criterion (BIC) was used as a measure of absolute fit (smaller number suggests a better model). The Vuong-Lo-Mendell-Rubin likelihood ratio test and the bootstrapped likelihood ratio tests were applied to examine k-1 model vs k-class model, using a value of <0.05 indicating rejection of k-1 model (Asparouhov and Muthén, 2012). In addition, we used entropy as a measure of uncertainty in class allocation (ideally >0.80) and class size (minimal 10 % of total study population to have stable subtypes) (Byrne, 2013; Nylund et al., 2007). For each k-class model, increasing random start values were applied to avoid occurrence of local optima (Asparouhov and Muthén, 2012). The last step comprised checking face validity of final class model, by visualizing the conditional probabilities of an individual in a given class endorsing a given indicator. These probabilities were defined as high (70 % to 100 %), moderate (40 % to 69 %), and low (<40 %) (Ryan et al., 2007).

Next, we tested whether the identified subtypes differ in demographics and clinical characteristics (severity [PHQ-9 score], symptomatology, antidepressant use, persistence and cognitive functioning). Demographics were added as auxiliary predictors to the LCA model in univariate regression analyses using the R3step command (Asparouhov and Muthén, 2014; Vermunt, 2010). Chi-square tests were performed by adding the clinical characteristics as auxiliary outcomes to the LCA model using the DCAT (binary outcomes) and DCON (continuous outcomes) command (Asparouhov and Muthén, 2014).

In additional analyses, we performed univariate regression analyses by adding the lifestyle characteristics and brain volumetrics as auxiliary predictors to the LCA model using the R3step command (Asparouhov and Muthén, 2014; Vermunt, 2010). Because our study population is oversampled with participants with T2DM, who have a higher cardiometabolic risk, we repeated the latent class analysis in participants without T2DM. For all analysis, a *P*-value of 0.05 was considered statistically significant in two-sided test.

3. Results

3.1. General characteristics of the study population

Characteristics of the study population with MDD (n = 248) are shown in Table 1. Participants had a mean age of 58.8 ± 8.5 years and 48.8 % were men. Cardiometabolic risk factors were present in 29.4 % (low HDL cholesterol) up to 78.6 % (hypertension) of the participants, resulting in sufficient variation in cardiometabolic risk factors.

3.2. Latent class analysis to identify subtypes of depression

To identify subtypes of depression based on differential clustering of cardiometabolic risk factors, models with 1 to 3 classes were fit. The 2-class model was considered superior based on model fit criteria (Table 2). Entropy score was 0.665, indicating some degree of classification uncertainty, but still superior to models 1 and 3. Fig. 2 shows the conditional probabilities of the two subtypes. Participants of class 1 (cardiometabolic depression subtype, n = 145) had a high probability of having central obesity (80.6 %), hypertension (94.1 %) and/or hyperglycaemia (75.6 %), while having a moderate probability of having hypertriglyceridemia (59.3 %) and low HDL cholesterol (46.4 %). Participants of class 2 (non-cardiometabolic depression subtype, n = 103) had a moderate probability of having hypertension (57.4 %), while the probability for other cardiometabolic risk factors was low (30.8 % for central obesity, 8.3 % for hypertriglyceridemia, 5.2 % for low HDL cholesterol, and 12.5 % for hyperglycaemia).

Table 1
Characteristics of participants with major depressive disorder (n = 248).

Characteristic	
Demographics	
Age (years), mean (SD)	58.8 ± 8.5
Sex, *n* (% female)	121 (48.8)
Educational level, low/medium/high, *n* (%)	128/72/44 (51.6/29.0/17.7)
Cardiometabolic risk factors	
Central obesity, *n* (%)	149 (60.1)
Hypertension, *n* (%)	195 (78.6)
Hypertriglyceridemia, *n* (%)	95 (38.3)
Low high-density lipoprotein (HDL) cholesterol, *n* (%)	73 (29.4)
Hyperglycemia, *n* (%)	123 (49.6)
Depression	
Depressive symptoms (PHQ-9 score), median (interquartile range)	10 [6.5–16]
Persistent depressive symptoms, *n* (%)	130 (52.4)
Antidepressant medication, *n* (%)	73 (29.4)
Cognitive functioning	
Memory score, mean (SD)	−0.21 ± 0.94
Information processing speed score, mean (SD)	−0.30 ± 0.85
Executive functioning & attention score, mean (SD)	−0.31 ± 0.90
Cognitive impairment, *n* (%)	80 (32.3)
Markers of structural brain damage	
WMH volume (ml), median (interquartile range)	0.26 [0.08–0.80]
White matter volume (ml), mean (SD)	463.3 ± 62.8
Grey matter volume (ml), mean (SD)	648.5 ± 68.9
Cerebrospinal fluid volume (ml), mean (SD)	245.3 ± 48.3
Life style factors	
Smoking, never/former/current, *n* (%)	77/11/57 (31.0/44.8/23.0)
Alcohol use, none/low/high, *n* (%)	87/117/41 (35.1/47.2/16.5)
Physical activity (hours/week), mean (SD)	12.3 ± 8.3
Dutch healthy diet score, mean (SD)	78.7 ± 15.5

SD indicates standard deviation; PHQ-9, 9 item Patient Health Questionnaire; MINI, Mini-International Neuropsychiatric Interview; HbA1c, glycated hemoglobin A1c; BP, blood pressure; HDL, high-density lipoprotein; eGFR, estimated glomerular filtration rate; CVD, cardiovascular disease; CVA, cerebral vascular accident; WMH, white matter hyperintensities; MRI, magnetic resonance imaging.

Table 2
Fit statistics for different latent class models to identify subtypes of depression.

	1 Class	2 Class	3 Class
Log likelihood	−781.181	−716.052	−709.615
Adjusted BIC	1574.080	1457.881	1459.068
Entropy	n/a	0.665	0.611
LMR test	n/a	<0.001	0.699
BLR test	n/a	<0.001	0.375

Log likelihood (smaller number suggests a better model fit); Adjusted BIC indicates adjusted Bayesian Information Criterion (smaller number suggests a better model fit); Entropy, an overall measure of how well a model predicts class membership, ranging from 0 (no predictive power) to 1 (perfect prediction); LMR test, Lo-Mendell-Rubin likelihood ratio test (test to compare n with n – 1 classes (significant LMR indicates the n-class solution is better than an (n−1)-class solution); BLR test, bootstrap likelihood ratio test (test to compare n with n - 1 classes (significant BLR indicates the n-class solution is better than an (n – 1)-class solution); n/a, not applicable.

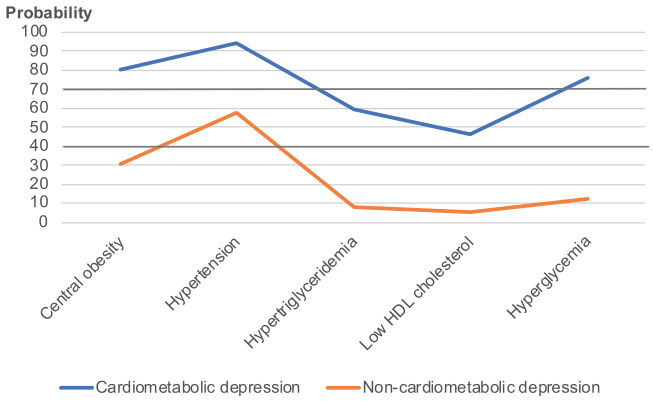

Fig. 2. Conditional probabilities.
Conditional probabilities of an individual in the cardiometabolic depression subtypes and the non-cardiometabolic depression subtype endorsing cardiometabolic risk factors. Probabilities are defined as high (70–100 %), moderate (40 %–69 %) and low (<40 %). HDL indicates high-density lipoprotein.

3.3. Characteristics of cardiometabolic depression

Table 3 shows the demographics, severity, symptomatology, antidepressant use, persistence and cognitive functioning of participants with compared to without cardiometabolic depression. Participants with cardiometabolic depression were more often men (odds ratio [OR] = 5.56[2.70;12.5], $P < 0.001$) and lower educated (OR = 2.22[1.04;4.76], P = 0.039) compared to non-cardiometabolic depression. Cardiometabolic depression was associated with a higher depression severity (mean PHQ-9 score [SE] = 11.91[0.62] vs 10.08[0.59], P = 0.033), but presented less often with depressed mood (χ^2[1] = 4.351, P = 0.036), and more often with loss of energy (χ^2[1] = 5.651, P = 0.017), and more antidepressant use (χ^2[1] = 8.607, P = 0.003), compared to the non-cardiometabolic subtype. No difference was observed with regard to persistence of depressive symptoms (χ^2[1] = 2.045, P = 0.153).

In addition, cardiometabolic depression was characterized by lower scores on memory (mean score [SE] = −0.40[0.08] vs 10.08[0.59], $P <$ 0.001), information processing speed (mean score [SE] = −0.48[0.07] vs 10.08[0.59], $P < 0.001$) and executive functioning & attention (mean score [SE] = −0.46[0.08] vs 10.08[0.59], P = 0.001), while the association with cognitive impairment was statistically non-significant (χ^2[1] = 3.033, P = 0.082).

Table 3
Characteristics of cardiometabolic depression.

	Cardiometabolic depression ($n = 145$) OR (95 % CI)		*P*-value
Demographics[a]			
Age (years)	1.04 (1.00;1.08)		0.052
Being male	**5.56 (2.70;12.5)**		**<0.001**
Education low[b]	**2.22 (1.04;4.76)**		**0.039**
Education high[c]	0.47 (0.19;1.14)		0.096
	Cardiometabolic depression (n = 145) OR	Overall test probabilities across subtypes Chi-Square	*P*-value
Depression symptoms based on MINI[d]			
Depressed mood	**0.42**	**4.351**	**0.037**
Apathy	1.53	1.052	0.305
Change of appetite	1.19	0.300	0.584
Sleeping problems	0.98	0.002	0.968
Psychomotor agitation or restlessness	1.10	0.041	0.840
Loss of energy	**3.68**	**5.651**	**0.017**
Feelings of worthless or guilty	1.36	0.949	0.330
Problems with concentration or decision making	0.96	0.008	0.930
Suicidal feelings	1.19	0.198	0.656
Antidepressant use[d]			
Antidepressant use	**2.70**	**8.607**	**0.003**
Persistence of depressive symptoms			
Depressive symptoms during follow-up	1.65	2.045	0.153
Cognitive functioning[d]			
Cognitive impairment	1.92	3.033	0.082
	Cardiometabolic depression (n = 145) Mean (SE)	Overall test means across subtypes Chi-Square	*P*-value
Severity[d]			
PHQ-9 score	11.91 (0.62)	4.551	0.033
Cognitive functioning[d]			
Memory score	−0.40 (0.08)	16.310	<0.001
Information processing speed score	−0.48 (0.07)	18.056	<0.001
Executive functioning & attention score	−0.46 (0.08)	10.442	0.001

Reference group is non-cardiometabolic depression (n = 103). OR indicates odds ratio; CI, confidence interval; SE, standard error; MINI, Mini-International Neuropsychiatric Interview; PHQ-9, 9 item Patient Health Questionnaire.
$p<.05$ are considered statistically significant and presented in bold.
[a] Added as auxiliary predictors in the model.
[b] Compared to medium education level.
[c] Compared to low education level.
[d] Added as auxiliary outcomes in the model.

3.4. Additional analyses

Additional analyses are shown in Table 4. There was an association between less physical activity and cardiometabolic depression (OR = 0.90[0.85;0.94], $P < 0.001$). No associations of smoking behaviour, alcohol consumption and adherence to healthy diet with cardiometabolic depression were observed (Table 4). Additional analyses in a subsample of the study population with MRI data showed that cardiometabolic depression was characterized by lower white matter brain volume (OR = 0.40[0.19;0.42] per SD, $P = 0.032$) compared to non-metabolic depression, while no differences were seen in WMH, grey matter and cerebrospinal fluid volume (Table 4). Repetition of the latent class analysis in participants without T2DM also resulted in a superior 2-class model, although the entropy was lower (0.569), indicating a higher classification uncertainty.

Table 4
Lifestyle characteristics and brain volumetrics of cardiometabolic depression.

	Cardiometabolic depression ($n = 145$) OR (95 % CI)	*P*-value
Lifestyle factors		
Smoker former[a]	1.92 (0.78;4.68)	0.154
Smoker current[a]	1.73 (0.82;3.65)	0.151
Alcohol consumption low[b]	0.49 (0.24;1.03)	0.059
Alcohol consumption high[b]	0.89 (0.33;2.42)	0.816
Physical activity (hours/week)	**0.90 (0.85;0.94)**	**<0.001**
Dutch healthy diet score	1.00 (1.00;1.00)	0.607
Brain volumetrics		
WMH volume (per SD)[c,d]	1.31 (0.86;1.99)	0.212
White matter volume (per SD)[d]	**0.40 (0.19;0.42)**	**0.032**
Grey matter volume (per SD)[d]	1.10 (0.57;2.14)	0.774
CSF volume (per SD)[d]	1.43 (0.85;2.39)	0.179

Reference group is non-cardiometabolic depression (n = 103). OR indicates odds ratio; CI, confidence interval; SD, standard deviation; WMH, white matter hyperintensity; CSF, cerebrospinal fluid.
$p<.05$ are considered statistically significant and presented in bold.
[a] Compared to never smoked.
[b] Compared to moderate alcohol consumption.
[c] log10 transformed.
[d] Adjusted for intracranial brain volume.

4. Discussion

This population-based study suggested the existence of a depression subtype based on clustering of cardiometabolic factors by use of LCA. It was characterized by being male, a lower educational level, higher depression severity, less symptoms of depressed mood, more symptoms of loss of energy, more often use of antidepressants, less physical activity, lower white matter brain volume, and lower scores on cognitive tests compared to the non-cardiometabolic subtype.

Although participants with cardiometabolic depression had higher conditional probabilities for all the cardiometabolic risk factors, the largest difference between the depression subtypes was found for central obesity and hyperglycaemia. The relation between hyperglyceamia and depression is well-established (Roy and Lloyd, 2012) and specific guidelines to identify and manage depression in diabetes care have been developed (Young-Hyman et al., 2016; Barents et al., 2018). Our results underscore the importance of the implementation of these integrated care approaches.

Two previous studies suggested the existence of a cardiometabolic depression subtype based on biomarkers and cardiometabolic risk factors by use of LCA, which was associated with a higher depression severity and more medication use (Beijers et al., 2019; Kokkeler et al., 2020). However, these studies included more biomarkers, including markers of inflammation to identify a cardiometabolic depression subtype. In addition, they found more depression subtypes. Nevertheless, the other subtypes they found did not differ from the 'healthy' depression subtype in terms of clinical characteristics. This may indicate that there is only one cardiometabolic depression subtype. However, replication is needed in future studies. Kokkeler et al. (2020) also found an association between the cardiometabolic depression subtype and a more persistent course of depression. The use of a clinical study population that is better monitored might explain the absent of this association in our study.

The characteristics of a putative cardiometabolic depression subtype are supported by previous studies that showed an association between cardiometabolic risk factors and depression (Lamers et al., 2010; Lamers et al., 2013; Pan et al., 2012; Veltman et al., 2017). Although we did find associations with a higher depression severity, no association between the cardiometabolic depression subtype and persistence of depression was found. This is in contrast to findings of the NESDO study (Marijnissen et al., 2017) and the InCHIANTI study (Vogelzangs et al., 2011). The NESDO study included older patients with MDD (age 60–93 years)

from mental health institutions and general practitioners. Our study population consisted of participants aged 40–75 years from the general population who were diagnosed with MDD according to the MINI diagnostic interview, with and without treatment, and probably lower depression severity. The InCHIANTI study used a higher than traditional cut-off score to define clinically relevant depressive symptoms in the general population (>20 versus 16). This could have resulted in a stronger discriminative power for this study than in our study.

We found that cardiometabolic depression was characterized by lower scores on memory, information processing speed and executive functioning & attention, and more cognitive impairment. Although the relation between depression and cognitive impairment is complex (Bennett and Thomas, 2014), it might be due to shared neurobiological mechanisms. Cardiometabolic risk factors may contribute to neurobiological changes (Wardlaw et al., 2013), which in turn may lead to both depression and cognitive impairments (Rensma et al., 2018). This is in line with the vascular depression hypothesis, which proposes that cerebrovascular diseases predispose or perpetuate depression (Alexopoulos et al., 1997). Although we did not observe an association of white matter hyperintensity volume with cardiometabolic depression, variation in white matter hyperintensity volume was low (median [IQR] 0.26[0.08–0.80] ml) in this relatively young study population. Possibly, cardiometabolic depression indicates an earlier stage of vascular depression (Sneed et al., 2008).

Several mechanisms linking cardiometabolic risk factors to depression exist. First, both share alterations of the stress system, including the hypothalamus–pituitary–adrenal axis, the autonomic nervous system and the immune system (Marazziti et al., 2014). Furthermore, recent neurobiological research suggested a role of peripheral hormones in mood regulation (Marazziti et al., 2014). Our finding that a lower white matter brain volume was associated with cardiometabolic depression, supports the role of atrophic changes of the neurological substrate and hints towards changes in connectivity between brain regions. Second, cardiometabolic risk factors can be the results of an unhealthy lifestyle of individuals with depression, which has been observed before (Payne et al., 2006). Our findings tentatively support this pathway by showing an association between the cardiometabolic depression subtype and physical inactivity, but not for smoking, alcohol consumption or diet. Third, use of antidepressant medication might increase the risk for cardiometabolic risk factors via weight gain. Prior evidence demonstrated a 5 % increased risk of weight gain in individuals on antidepressant treatment compared to those without (Gafoor et al., 2018). Fourth, alternative mechanisms that increase the risk of cardiometabolic risk factors and depression independently have been proposed, like childhood stressors, personality, and genetic vulnerability (Penninx, 2017).

If replicated, the existence of a cardiometabolic depression subtype may indicate the need to routinely assess cardiometabolic risk factors in patients with depression. The NCEP criteria form a guideline in this, as they are commonly available in clinical practice. This might be especially important in men and patients with a low education level (Clark et al., 2009; Gerdts and Regitz-Zagrosek, 2019). Individuals with cardiometabolic depression should receive care from a multi-disciplinary coordinated team, in which modification of cardiometabolic risk factors by lifestyle changes is considered a therapeutic target on top of symptomatic treatment. A variety of lifestyle interventions have been developed to manage depression including physical activity, dietary modification, adequate relaxation/sleep and social interaction, the practice of mindfulness-based meditation, and the reduction of nicotine, drugs and alcohol use (Sarris et al., 2014). Furthermore, the cardiometabolic profile of a patient needs to be considered in antidepressant treatment, as medication can have detrimental cardiometabolic effects (Uzun and Kozumplik, 2009). Next to psychotherapy, alternative pharmacological targets should be considered for patients with cardiometabolic depression, including cytokines and their receptors, glucocorticoids receptors, inflammatory pathways, and peripheral mediators (Marazziti et al., 2014).

Strengths of our study include the use of LCA to gain a better understanding of subtypes (Scotto Rosato and Baer, 2012); its population-based design; the oversampling of individuals with T2DM, which provides a higher propensity for cardiometabolic risk factors; the definition of cardiometabolic risk factors according to the NCEP ATP III guidelines for metabolic syndrome; the use of the MINI diagnostic interview to assess prevalent MDD; and the annual follow-up measurement of the PHQ-9 to assess course of depressive symptoms.

This study also has some limitations. First, the two identified depression subtypes by LCA had an entropy score of 0.665, indicating significant degree of classification uncertainty. Because of this uncertainty, we investigated the characteristics of the depression subtypes by use of the 3-step method, which takes into account this class uncertainty when studying associations (Asparouhov and Muthén, 2014). Second, subtypes were identified based on cross-sectional data. Therefore, we cannot determine causality or predict depression subtype. Third, associations of the cardiometabolic depression subtype with clinical characteristics were descriptive in nature. These analyses provide insight in the relationship with other variables, but cannot draw any conclusions about the causality of the direct associations as extraneous variables might interfere. Fourth, brain volumetric data was only available in a subsample of our study population and were therefore analyzed in additional analyses. Although we found an association between a smaller white matter volume and less physical activity with cardiometabolic depression, the statistically non-significant association of white matter hyperintensity volume with cardiometabolic depression can be the result of the small variation in white matter hyperintensity volume as mentioned above. Alternatively, this could be the result of a specific role of white matter connections, which warrants more detailed investigations. Fifth, identification of depression subtypes by use of LCA does not directly define a distinct clinical depression subtype. The identified cardiometabolic depression subtype might also be the results of the increased risk for depression in individuals with cardiometabolic abnormalities.

5. Conclusion

This study suggested the existence of a depression subtype based on cardiometabolic risk factors by use of LCA. The cardiometabolic depression subtype was characterized by being male, low education, more severe depressive symptoms, less symptoms of depressed mood and more symptoms of loss of energy, more use of antidepressant medication and lower cognitive functioning. Future studies are needed to replicate our findings and contribute to a better understanding of the aetiological and clinical heterogeneity of depression.

CRediT authorship contribution statement

All authors were involved in the design or conduct of the study, the preparation of the manuscript, and the decision to submit it for publication. Anouk Geraets analyzed data and wrote the original draft of the manuscript, Jacobus Jansen, Walter Backes, Casper Schalkwijk, Coen Stehouwer, Martin van Boxtel, Simone Eussen, Jeroen Kooman, and Frans Verhey reviewed and edited the manuscript, and Sebastian Köhler analyzed data, and wrote the original draft of the manuscript. All authors read and approved the final manuscript.

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Declaration of competing interest

None of the authors has any competing interest to declare.

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