Disentangling the relationship between depression, obesity and cardiometabolic disease

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Symptomatology of depression and onset of cardiometabolic diseases - A 7-year follow-up study

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ABSTRACT

Background
Depression is associated with an increased risk of developing cardiometabolic diseases (i.e., a composite of type 2 diabetes and cardiovascular disease). This association may vary for different depressive symptom profiles and individual cardiometabolic diseases. We examined the association between depression and specific depressive symptom profiles with individual and composite cardiometabolic diseases.

Method
In 6561 participants from the Netherlands Epidemiology of Obesity (NEO) study, depressive symptoms were measured with the Inventory of Depressive Symptomatology (IDS-SR30) and two dimensional profiles were created: atypical energy-related symptom (AES) and melancholic symptom profiles. Participants were followed for 41 896 person-years, and incidents of type 2 diabetes and cardiovascular disease were extracted from medical records at general practitioners. The Cox proportional-hazard model was used to examine the relationships of overall, atypical energy-related symptoms and melancholic depression scores with overall cardiometabolic diseases and individual components of type 2 diabetes, and cardiovascular disease.

Results
The median follow-up time for type 2 diabetes and cardiovascular disease was seven years (8% developed a cardiometabolic disease, 5% type 2 diabetes, 5% cardiovascular disease). A one SD increase of IDS-SR30 at baseline was associated with an increased risk of cardiometabolic diseases (HR:1.20 CI 95% (1.10-1.31)). For the specific symptom profiles, atypical energy-related symptoms profile was associated with an increased risk of type 2 diabetes (HR 1.26 (95 % CI (1.14-1.42)), while melancholic symptom profile was associated with an increased risk of cardiovascular disease (HR 1.15 CI 95% (1.03-1.28)).

Conclusion
Depressive symptoms were associated with the onset of type 2 diabetes and cardiovascular disease (median follow-up of seven years). This association varied for different depressive symptom profiles and cardiometabolic diseases. Considering a more personalized approach that takes into account differential depression symptomatology may be beneficial to prevent or delay the development of cardiometabolic diseases.

INTRODUCTION

The relation between depression and cardiometabolic diseases (i.e., type 2 diabetes and cardiovascular disease) is complex, multifactorial, and not fully understood. The two conditions negatively impact individual health and well-being and burden the healthcare system. Large meta-analyses of longitudinal studies [1-3] indicate that depression is associated with a 30-60% increased risk of cardiometabolic diseases (i.e., heart disease, myocardial infarction, type 2 diabetes, and stroke). Interestingly, for all these cardiometabolic outcomes, bidirectional associations with depression have also been suggested showing that heart disease [4], diabetes [1] and stroke [5] are associated with an increased risk of developing depression.

Depression's heterogeneity likely contributes to variability in its link with cardiometabolic diseases. Patients with depression report different symptom profiles that, in turn, may represent the expression of different underlying pathophysiological processes. It is, therefore, likely that the association with cardiometabolic diseases may be stronger in individuals with specific symptom profiles. Emerging evidence suggests that inflammatory and metabolic dysregulation, commonly accompanying cardiometabolic diseases, tend to cluster with "atypical" depressive symptoms characterized by altered energy intake and expenditure balance [6]. For instance, recent studies showed that an atypical energy-related symptom (AES) profile characterized by increased sleepiness, increased appetite, increased weight, low energy level and leaden paralysis was associated with altered inflammatory and metabolic markers (i.e., fasting glucose, HDL-cholesterol, triglycerides, blood pressure, waist circumference, CRP, and IL-6) and inflammation-related tryptophan catabolites (i.e., kynurenine and quinolinic acid) [7, 8]. In contrast, these markers were not associated with a melancholic symptom profile characterized by early morning awakening, worse mood in the morning, distinct quality of mood, decreased appetite, weight loss, negative self-outlook, psychomotor retardation, and psychomotor agitation [7]. Based on this evidence, it is hypothesized that individuals expressing atypical energy-related depressive symptoms have a higher risk of cardiometabolic diseases than those mainly reporting melancholic symptoms.

This hypothesis is partially in line with results from two recent follow-up studies. In the first one [9], among 2522 individuals with at least one cardiovascular risk factor, 506 had relevant depressive symptoms based on Beck's Depression Inventory (BDI) questionnaire then melancholic and non-melancholic depressive symptoms groups were created [10]. The participant is classified into the melancholic group if the score of adding the following symptoms: the feeling of sadness, failure, anhedonia, guilt, being punished, irritability, loss of interest, and changes in sleeping and appetite is equal or higher than the score of the rest of BDI

symptoms (if the score is lower than the score above then participant is classified into the non-melancholic group) [9]. In both groups, the incidence of cardiovascular disease extracted from national registers over 8 years of follow-up was higher than in controls, with the largest effect size for the non-melancholic group. In the second study [11], among 28,726 individuals from the general population, 4711 had a lifetime diagnosis of major depressive disorder and were classified as either atypical or non-atypical based only on the presence or absence of hyperphagia and hypersomnia symptoms extracted from Alcohol Use Disorder and Associated Disabilities Interview Schedule-IV (AUDADIS-IV). Again, as compared with individuals without depression, both these groups had a higher risk of incident cardiovascular disorders over 3 years, with the largest effect size for the atypical subgroup.

In the present study, we further expanded the examination of the association between depressive symptoms and incident cardiometabolic diseases, including both type 2 diabetes and cardiovascular disease recorded in general practitioner registries followed up for seven years. Furthermore, we refined the examination of different clinical manifestations of depression by using dimensional profilers for AES and melancholic symptoms rather than binary subtypes, as in previous studies [9, 11]. As a result, we were better able to capture the variability of a wider array of depressive symptomatology. We hypothesize that overall depressive symptoms are associated with cardiometabolic diseases. Furthermore, we expect this association to be driven by the AES profile, previously associated with markers of cardiometabolic risk.

METHODS

Study design and population

The Netherlands Epidemiology of Obesity (NEO) study is a population-based cohort study including 6671 men and women aged 45 to 65 years [12]. All inhabitants aged between 45 and 65 years with a self-reported body mass index (BMI) of 27 kg/m^2 or higher and living in the greater area of Leiden, the Netherlands, were eligible to participate in the NEO study. In addition, all inhabitants aged between 45 and 65 years from one adjacent municipality (Leiderdorp, the Netherlands) were invited to participate irrespective of their BMI. Prior to the study visit (2008-2012), participants completed questionnaires at home with respect to demographic, lifestyle, and clinical information. Participants visited the NEO study center after an overnight fast for an extensive physical examination.

Participants were followed over time (median = 6.7 years) for the occurrence of type 2 diabetes and cardiovascular disease via their electronic medical records at the general practitioners (see outcome and censoring). The present study is a

prospective analysis of the relationship between depressive symptoms (overall depression) and depressive symptom profiles measured by the Inventory of Depressive Symptomatology (self-report) IDS-SR30 at the baseline and 1) cardiometabolic diseases (i.e., merged type 2 diabetes and cardiovascular disease), 2) type 2 diabetes, and 3) cardiovascular disease. We excluded participants without IDS-SR30 total score data (n=16) or follow-up information (n=94), leaving 6561 participants for the main analyses. The NEO study was approved by the medical ethics committee of Leiden University Medical Center (LUMC) and all participants gave written informed consent.

Assessment of depressive symptoms and profiles

At baseline, we asked all participants to complete the Dutch version of the IDS-SR30 questionnaire [13], which assesses specific depressive symptoms during the past week and their severity. The IDS-SR30 rates (via a 4-level response system) the presence of a wide array of depressive symptoms, including core symptoms of major depressive episodes, melancholic (e.g., anhedonia, nonreactive mood, psychomotor retardation/agitation, appetite or weight decrease, early morning awakening, and self-outlook) and atypical energy-related (e.g., hypersomnia, increased appetite, weight gain, low energy level, and leaden paralysis (physical exhaustion)) features, and commonly associated symptoms (e.g., irritability, anxiety, somatic complaints). We used the total score ranges from 0 to 84, with higher scores indicating higher severity as a continuous variable. Furthermore, we categorized the total score in the secondary analyses. For that, we grouped the participant according to the clinically predefined severity cut-offs as follow: score ≤ 13 as "no depressive mood" status (n = 4625, reference), 14–25 as "mild depressive mood" (n = 1413), 26–84 as "severe depressive mood" (n = 523) [13].

We derived depressive profiles in line with previous studies [7, 14] using items from IDS-SR30. The AES profile was based on the sum score of the following items: increased sleepiness, increased appetite, weight gain, low energy level, and leaden paralysis. Then, we also used a melancholic depressive profile as another clinically established symptom profile for comparison with AES, as it also reflects severity [7, 15]. This symptom profile was created by summing the score of the following items: early morning awakening, mood worse in the morning, distinct quality of mood, decreased appetite, weight loss, self-outlook, psychomotor retardation, and psychomotor agitation. Additionally, in order to better illustrate the shape of the association between symptom profiles and cardiometabolic diseases, for each symptom profile, we grouped the participant into four severity score groups: no symptoms: 0 (reference), mild symptoms:1-2, moderate symptoms: 3-4 and severe symptoms: ≥5.

Ascertainment and definition of outcomes

Diagnoses of type 2 diabetes and cardiovascular disease incidence were extracted from electronic medical records of general practitioners (GPs). This record covers all medical information of the patients regarding prescriptions, GP consultations, and reports from laboratories and specialist visits available at the GP office. Data extraction was performed based on three criteria: (1) the diagnostic coding by the GPs to indicate the health problems or type of care, based on the International Classification of Primary Care (ICPC) [16], (2) finding of predefined type 2 diabetes and cardiovascular disease related keywords in the descriptions of the GP database, and (3) prescription of specific medication, registered according to the Anatomical Therapeutic Chemical (ATC) codes or by screening medication names [17]. The date of diagnosis was defined as the first date of an ICPC-coded diagnosis, a strong indication for the diagnosis based on keywords in the medical records, or prescription of relevant medication. In case only a keyword was found without a confirmed ICPC code, we confirmed the diagnoses using the laboratory values and reading the free text in the medical records. If it remained unclear whether a particular participant was diagnosed with type 2 diabetes or cardiovascular disease, the general practitioner was contacted. A participant was considered as having an incidence of type 2 diabetes or cardiovascular disease when the date of diagnosis occurred after the baseline visit date.

In the present analysis, we used the preliminary follow-up data, as the extraction of information from the GP medical records is still ongoing. Our analyses were focused on the development of three outcomes: (1) cardiometabolic diseases (i.e., having either type 2 diabetes or/and cardiovascular disease), (2) type 2 diabetes, and (3) cardiovascular disease. For each outcome of interest, we excluded participants who had the prevalent condition of interest at baseline based on information extracted from the GP medical records (Figure 1). For this reason, the sample sizes for our analyses differ based on the studied outcome of interest (i.e., type 2 diabetes, cardiovascular disease, both type 2 diabetes and cardiovascular disease). Participants were coded as having type 2 diabetes when the extracted data from GP registration in 2018 indicated 1) the diagnosis of type 2 diabetes (i.e., ICPC codes T90 or T90.02). In addition, the medication list of participants was checked for the use of insulin, metformin and sulfonylurea derivative, and participants using these medications were considered to have type 2 diabetes (n of participants who developed the outcome=276). Similarly, participants were coded as having cardiovascular disease if the extracted data from GP registration in 2018 indicated any of the following diagnoses of 1) myocardial infarction (ICPC Code: K75 or K76.02), 2) transient ischemic attack (K89), or 3) stroke/cerebrovascular accident (K90 or its subtypes: K90.01, subarachnoid haemorrhage; K90.02, intracerebellar haemorrhage; or K90.03, cerebral infarction.

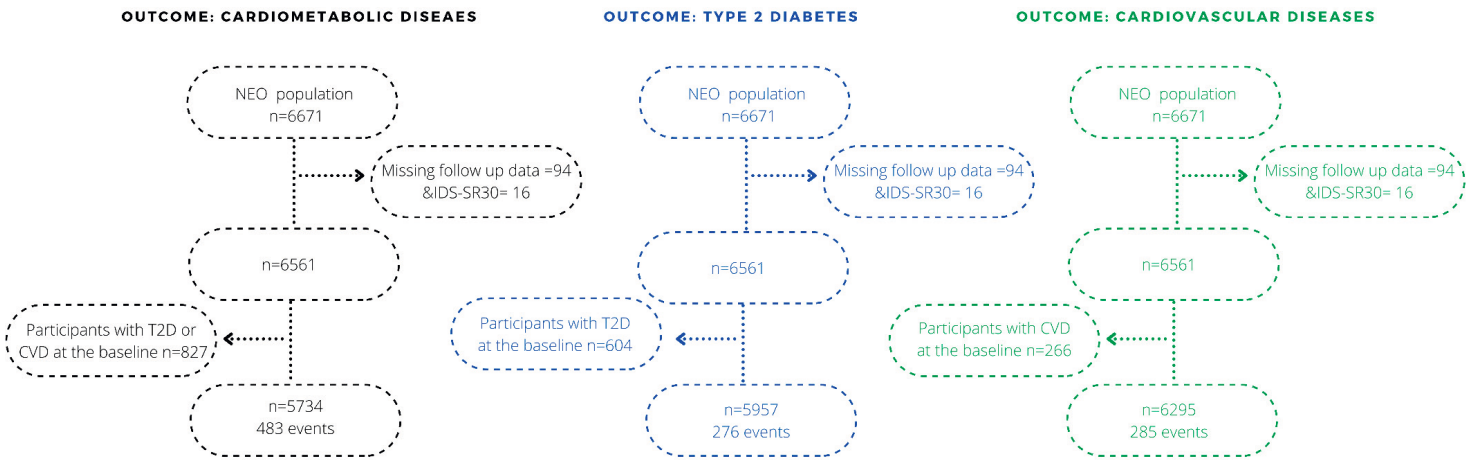


Figure 1. Study population

Keywords included synonyms of myocardial infarction, chest pain, cardiovascular surgery procedures such as coronary artery bypass grafting (CABG) or angioplasty, and synonyms of cerebrovascular accident or haemorrhage. The medication list of participants was checked for the use of specific anticoagulants. In this preliminary data, other types of cardiovascular disease were not yet included (n of participants who developed the outcome=285). We merged the two outcomes (i.e., type 2 diabetes and cardiovascular disease) into a new outcome called cardiometabolic diseases if the participants had either or both diseases (n of participants who developed the outcome=483).

Time of follow-up was defined as the number of days between the baseline of the study and the date of diagnosis or censoring due to death, loss to follow-up (move to another GP or outside of the Netherlands), or the end of the follow-up (extraction date at the GP in 2018), whichever comes first. However, not all participants were followed from start to finish.

Statistical analysis

Characteristics of the study population were expressed as a mean with standard deviation (SD), a median (25th, 75th percentiles) or percentages (%). The incidence rates per 1000 person-years for each outcome were estimated as: (new cases of outcome/ person-years of the population at risk) x 1000.

Cox regression analyses

We performed Cox proportional-hazard models to investigate the relationship between the depressive symptoms at the baseline and the outcomes using 3 steps. In step 1, we performed adjusted Cox proportional-hazard models to investigate the relationships between depressive symptoms and cardiometabolic outcome. In step 2, we explored the relationship between the baseline depressive symptoms and (1) type 2 diabetes and (2) cardiovascular disease as individual outcomes. In step 3, to take the heterogeneity of depressive symptomatology into account, we conducted adjusted Cox proportional-hazard models to investigate the relationships between two depressive symptom profiles (atypical energy-related and melancholic) with type 2 diabetes and cardiovascular disease.

Analyses of the three steps were adjusted for age, sex (model 1) and further BMI adjustment (model 2). Model 2 is important because BMI is a strong risk factor for type 2 diabetes and is related to depression. Finally, in model 3 we further adjusted for type 2 diabetes at baseline when applicable (i.e., in analyses with cardiovascular disease as outcome). All analyses were done using R version 4.0.5, and for the Cox proportional-hazard model analysis "survival" package was used.

RESULTS

For cardiometabolic diseases as the outcome, some participants were lost to follow-up (n=45), died (n= 58), or only had data from an intermediate data extraction in 2012-2013 (n=306). For type 2 diabetes and cardiovascular disease as the outcomes of interest, 46 and 50 were lost to follow-up, 60 and 75 participants died, and 321 and 342 participants only had data from intermediate extraction in 2012-2013, respectively. For participants who did not develop the outcome of interest, data were censored at the known follow-up time or date of death or the last known follow-up time before death.

Table 1 shows the characteristics of the NEO population (mean age 56.0), men and women (52.0% women). For the cardiometabolic diseases as the outcome, the population at risk was 5734, the median (25th, 75th percentiles) follow-up time was 6.7 years (5.9, 7.9), and the incidence rate (IR) was 13/1000 person-years. For type 2 diabetes as the outcome, the population at risk was 5957, and the median (25th, 75th percentiles) follow-up time was 6.8 (6.0, 7.9). 5% developed the outcome, IR 7/1000 person-years. For cardiovascular disease, the population at risk was 6295, the median (25th, 75th percentiles) follow-up time was 6.7 (5.9,7.8). 5% developed the outcome, IR 7/1000 person-years. The Pearson's correlation between the two symptom profiles was 0.4, indicating that they are capturing partially different dimensions of depressive symptomatology.

Table 1. Baseline characteristics for 6561 men and women aged 45 to 65 years included in the analysis from Netherlands Epidemiology of Obesity study

Characteristic	N=6561
Age (years) Mean (sd)	56.0 (6.0)
Sex (women) (n(%))	3443 (52.0)
BMI Mean (sd)	30.1 (4.8)
Ethnicity (White) (n(%))	6227 (95.0)
Education (High) (n(%))	2452 (38.0)
Smoking (n(%))	
No	2274 (35.0)
Former	3217 (49.0)
Current	1067 (16.0)
Alcohol consumption (g/day) Median (25th, 75th percentiles).	9.0 (2.0, 22.0)
Type 2 diabetes incidence (outcome) (n(%))	276 (4.2%)
Type 2 diabetes prevalence (baseline) (n(%))	604 (9.2%)
Cardiovascular diseases incidence (outcome) (n(%))	285 (4.3%)

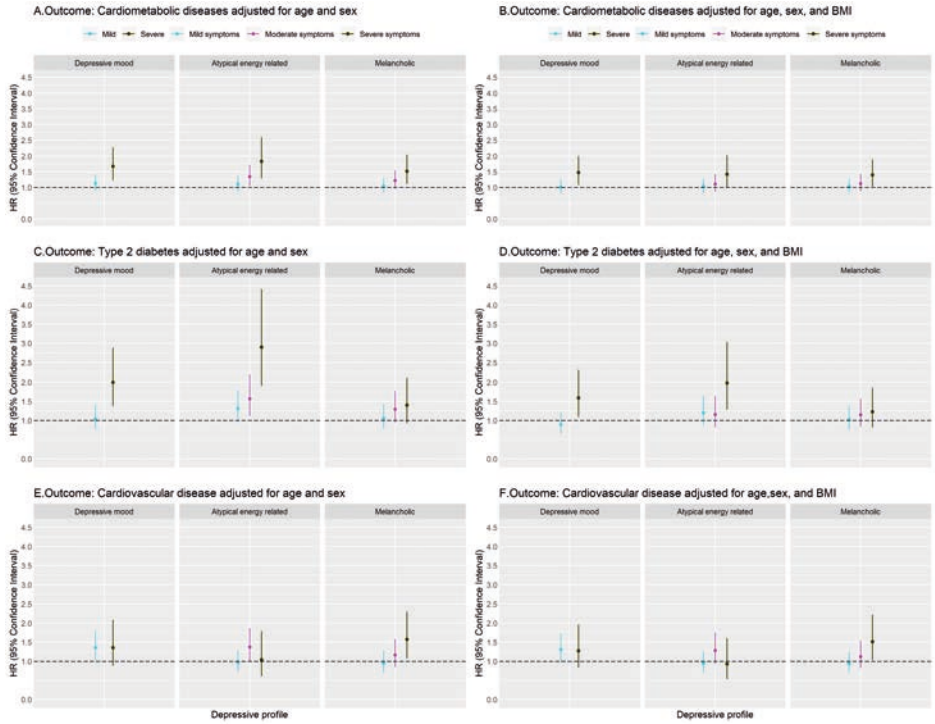
Table 1. Continued.

Characteristic	N=6561
Cardiovascular diseases prevalence (baseline) (n(%))	266 (4.1%)
Atypical energy-related symptom profile Median (25th, 75th percentiles)	1.0 (0.0, 3.0)
Atypical energy-related symptom profile (Categorized) (n(%))	
None (≤0)	1994 (30.0)
Mild (>0 and <3)	2560 (39.0)
Moderate (≥3 and <5)	1553 (24.0)
Severe (≥5)	454 (6.9)
Melancholic symptom profile Median (25th, 75th percentiles)	1.0 (0.0, 3.0)
Melancholic symptom profile (Categorized) (n(%))	
None (≤0)	2597 (40.0)
Mild (>0 and <3)	1940 (30.0)
Moderate (≥3 and <5)	1394 (21.0)
Severe (≥5)	630 (9.6)
IDS-SR30 total score Median (25th, 75th percentiles)	9 (5, 15)
Depressive mood (Categorized) (n(%))	
None (≤ 13)	4625 (70.0)
Mild (14–25)	1413 (22.0)
Moderate to severe (26–84)	523 (8.0)

Step 1: Overall depressive symptoms and cardiometabolic diseases

Table 2 shows the results of the Cox proportional-hazard model of the continuous and categorized total score of IDS-SR30 and cardiometabolic diseases. We found that a one SD increase of IDS-SR30 in the baseline was associated with an increased risk of cardiometabolic diseases (HR:1.20 CI 95% (1.10-1.31)) for model 1 (adjusted for age and sex). In particular, compared to those without depressive mood, individuals in the severe depressive mood group had the highest risk of cardiometabolic diseases (HR:1.67 CI 95% (1.23-2.27) (Figure 2A). Additional adjustment for BMI (model 2) slightly reduced the strength of the associations; the HR of cardiometabolic diseases in individuals with severe depressive mood, as compared to those without depressive mood, was 1.47 CI (95% 1.08-2.00) (Figure 2B).

Figure 2. Cox proportional-hazard regressions for the depressive mood, atypical energy-related and melancholic symptoms profile and all three outcomes



Depressive mood: we grouped the participant according to the clinically predefined severity cut-offs as follow: score ≤ 13 as "no depressive mood" status (n = 4625, reference), 14–25 as "mild depressive mood" (n = 1413), 26–84 as "severe depressive mood" (n = 523). Atypical energy-related symptom profile (a sum score of the five symptoms, increased sleepiness, increased appetite, increased weight, low energy level, leaden paralysis). Melancholic symptoms profile: a sum score of the symptoms, decreased appetite, decreased weight, early morning awakening, mood variation in relation to the time of the day, distinct quality of mood, excessive guilt, psychomotor agitation, psychomotor retardation. For each symptom profile, we grouped the participant in four severity score groups: no symptoms: 0 (reference), mild symptoms:1-2, moderate symptoms: 3-4 and severe symptoms: ≥5.

Table 2. Cox proportional-hazard regressions for IDS-SR30 total score, atypical energy-related and melancholic symptoms profiles with cardiometabolic diseases.

		Model 1 HR (95% CI)	Model 2 HR (95% CI)
Cardiometabolic diseases (n= 5734, 483 events)	**IDS-SR30 total score (continuous)**	1.20 (1.10-1.31)	1.14 (1.04-1.25)
	Depressive mood (categorical)		
	None	*Reference*	*Reference*
	Mild	1.12 (0.89-1.41)	1.01 (0.81-1.27)
	Severe	1.67 (1.23-2.27)	1.47 (1.08-2.00)
Cardiometabolic diseases (n= 5734, 483 events)	**AES (continuous)**	1.15 (1.06-1.26)	1.07 (0.97-1.17)
	AES (categorical)		
	None	*Reference*	*Reference*
	Mild	1.10 (0.88-1.37)	1.03 (0.82-1.29)
	Moderate	1.34 (1.05-1.71)	1.11 (0.86-1.42)
	Severe	1.83 (1.29-2.59)	1.41 (0.99-2.02)
Cardiometabolic diseases (n= 5734, 483 events)	**Melancholic (continuous)**	1.14 (1.05-1.24)	1.11 (1.02-1.21)
	Melancholic (categorical)		
	None	*Reference*	*Reference*
	Mild	1.04 (0.84-1.30)	1.03 (0.82-1.28)
	Moderate	1.22 (0.96-1.54)	1.12 (0.88-1.43)
	Severe	1.51 (1.11-2.04)	1.39 (1.03-1.89)

Model 1: Adjusted for age and sex. Model 2: Adjusted for age, sex, and BMI. IDS-SR30: Inventory of depressive symptomatology-self report (standardized). None group was set as the reference group throughout the analyses. AES: Atypical energy-related symptom profile (a sum score of the five symptoms, increased sleepiness, increased appetite, increased weight, low energy level, leaden paralysis) (standardized). Melancholic symptoms profile: a sum score of the symptoms, decreased appetite, decreased weight, early morning awakening, mood variation in relation to the time of the day, distinct quality of mood, excessive guilt, psychomotor agitation, psychomotor retardation (standardized). For each symptom profile, we grouped the participant in four severity score groups: no symptoms: 0 (reference), mild symptoms:1-2, moderate symptoms: 3-4 and severe symptoms: ≥5.

Step 2: Overall depressive symptoms and (1) type 2 diabetes and (2) cardiovascular disease)

Table 3 shows the results of the Cox proportional-hazard models of the continuous and categorized total score of IDS-SR30, atypical energy-related and melancholic symptom profiles and individual cardiometabolic diseases. We found that a one SD increase of IDS-SR30 in the baseline is associated with an increased risk of type 2 diabetes (HR:1.26 CI 95% (1.14-1.41)) for model 1. As compared to individuals without depressive mood, individuals in the severe depressive mood group had

the highest risk of type 2 diabetes (HR: 1.99 CI 95% (1.38-2.89) (Figure 2C), also after adjusting for BMI (HR: 1.59 CI 95% (1.09-2.31) (Figure 2D). Furthermore, a one SD increase of IDS-SR30 in the baseline is associated with an increased risk of developing cardiovascular disease (HR:1.15 CI 95% (1.03-1.29)) in model 1. Individuals in the severe depressive mood group, compared to those without depressive mood, had the highest risk of cardiovascular disease (HR: 1.36 CI 95% (0.88-2.08) for model 1 (Figure 2E). Additionally, adjusting for BMI or type 2 diabetes at baseline did not change the hazard ratios.

Table 3. Cox proportional-hazard regressions for IDS-SR30 total score, atypical energy-related and melancholic symptoms profiles with type 2 diabetes and cardiovascular disease.

		Model 1 HR (95% CI)	Model 2 HR (95% CI)
Type 2 diabetes (n= 5957, 276 events)	**IDS-SR30 total score (continuous)**	1.26 (1.14-1.41)	1.16 (1.04-1.30)
	Depressive mood (categorical)		
	Mild	1.04 (0.76-1.41)	0.89 (0.66-1.21)
	Severe	1.99 (1.38-2.89)	1.59 (1.09-2.31)
Type 2 diabetes (n= 5957, 276 events)	**AES (continuous)**	1.27 (1.14-1.42)	1.14 (1.02-1.27)
	AES (categorical)		
	Mild	1.31 (0.96-1.78)	1.20 (0.88-1.64)
	Moderate	1.57 (1.12-2.20)	1.16 (0.82-1.64)
	Severe	2.90 (1.90-4.41)	1.98 (1.29-3.04)
Type 2 diabetes (n= 5957, 276 events)	**Melancholic (continuous)**	1.13 (1.01-1.26)	1.07 (0.95-1.20)
	Melancholic (categorical)		
	Mild	1.06 (0.79-1.42)	1.02 (0.76-1.37)
	Moderate	1.29 (0.95-1.77)	1.15 (0.84-1.57)
	Severe	1.40 (0.93-2.11)	1.23 (0.82-1.86)
Cardiovascular disease (n=6295, 285 events)	**IDS-SR30 total score (continuous)**	1.15 (1.03-1.29)	1.13 (1.00-1.26)
	Depressive mood		
	Mild	1.35 (1.02-1.80)	1.30 (0.98-1.73)
	Severe	1.36 (0.88-2.08)	1.27 (0.83-1.96)
Cardiovascular disease (n=6295, 285 events)	**AES (continuous)**	1.08 (0.96-1.22)	1.05 (0.93-1.18)
	AES (categorical)		
	Mild	0.97 (0.73-1.29)	0.94 (0.71-1.25)
	Moderate	1.37 (1.01-1.86)	1.28 (0.93-1.75)
	Severe	1.04 (0.61-1.79)	0.93 (0.54-1.60)

Table 3. Continued.

		Model 1 HR (95% CI)	Model 2 HR (95% CI)
Cardiovascular disease (n=6295, 285 events)	**Melancholic (continuous)**	1.15 (1.03-1.28)	1.13 (1.01-1.26)
	Melancholic (categorical)		
	Mild	0.95 (0.71-1.27)	0.94 (0.70-1.26)
	Moderate	1.16 (0.85-1.58)	1.13 (0.82-1.54)
	Severe	1.57 (1.08-2.30)	1.51 (1.03-2.21)

Model 1: Adjusted for age and sex. Model 2: Adjusted for age, sex, and BMI. IDS-SR30: Inventory of depressive symptomatology-self report (standardized). None group was set as the reference group throughout the analyses. AES: Atypical energy-related symptom profile (a sum score of the five symptoms, increased sleepiness, increased appetite, increased weight, low energy level, leaden paralysis) (standardized). Melancholic symptoms profile: a sum score of the symptoms, decreased appetite, decreased weight, early morning awakening, mood variation in relation to the time of the day, distinct quality of mood, excessive guilt, psychomotor agitation, psychomotor retardation (standardized). For each symptom profile, we grouped the participant in four severity score groups: no symptoms: 0 (reference), mild symptoms:1-2, moderate symptoms: 3-4 and severe symptoms: ≥5.

Step 3: Depressive profiles and type 2 diabetes and cardiovascular disease

Table 3 shows Cox proportional-hazard model results for the continuous and categorized depressive profiles (atypical energy-related and melancholic symptom profiles) and type 2 diabetes, and cardiovascular disease. We found that the atypical energy-related symptom profile and melancholic symptom profile had a different pattern of association with type 2 diabetes and cardiovascular disease. One SD increase in the atypical energy-related symptom profile was associated with an increased risk of type 2 diabetes HR 1.27 (95 % CI (1.14-1.42)) in model 1. As compared to those without AES, results showed an increased risk of type 2 diabetes for individuals with moderate ((HR: 1.57 CI 95% (1.12-2.20)) and severe depressive AES (HR: 2.90 CI 95% (1.90-4.41) (Figure 2C). In Model 2, further adjustment for BMI decreased the strength of the association: the HR of individuals with severe AES, when compared with those without AES, was 1.98 (CI 95% 1.29-3.04) (Figure 2D). The same symptom profile was not associated with cardiovascular disease in any of the adjusted Cox proportional-hazard models.

For melancholic symptom profile, one SD increase in the score was associated with an increased risk of type 2 diabetes (HR 1.13 CI 95% (1.01-1.26)) for model 1. Nevertheless, adding BMI to the model substantially decreased the hazard ratio (HR 1.07 CI 95% (0.95-1.20)). For cardiovascular disease, one SD increase in the melancholic symptom profile was associated with an increased risk of the outcome (HR 1.15 CI 95% (1.03-1.29)) for the model adjusted for age and sex. As compared to participants without melancholic symptoms, participants with the severe

melancholic symptoms have an increased risk of cardiovascular disease (HR: 1.57 CI 95% (1.08-2.30)) (Figure 2E). All further adjustments for type 2 diabetes at the baseline and BMI did not change the hazard ratio.

DISCUSSION

This study explored the association between depressive symptoms and the risk of developing cardiometabolic diseases in large population-based cohort with a median follow-up of seven years. We were able to disentangle the heterogeneity of the exposure (i.e., depressive symptoms) and the outcome (i.e., cardiometabolic diseases) by examining the association of two specific depressive symptom profiles, atypical energy-related symptom and melancholic profiles, with type 2 diabetes and cardiovascular disease. We found that having higher overall depressive symptoms at the baseline is associated with an increased risk of developing cardiometabolic diseases over time. When zooming in the atypical energy-related symptom profile, we found that it was specifically associated with a higher risk of developing type 2 diabetes, while the melancholic was associated with a higher risk of developing cardiovascular disease.

The incidence rate of type 2 diabetes was 2.5 times higher in cohort of this study compared to the general Dutch population [18]. This was expected because of the oversampling of obese and overweight individuals (i.e., higher BMI individuals are at higher risk of developing type 2 diabetes) in the NEO study. However, the incidence rate of cardiovascular disease was similar to the general Dutch population [19]. Moreover, our finding that depressive symptoms increased the risk of developing cardiometabolic diseases and its component (i.e., type 2 diabetes and cardiovascular disease) are in line with the previous knowledge. Meta-analyses of longitudinal studies showed that depression (both clinical depression and depressive symptoms) increased the risk of developing type 2 diabetes (relative risk= 1.37 -1.67) [1, 20-22]. Similarly, another recent meta-analysis that included twenty-one follow-up studies reported that depression (i.e., combined depressive scales and depression diagnosis) increased the risk of type 2 diabetes (risk ratio 1.18) [23]. Additionally, depression was also reported as a risk factor for developing cardiovascular disease (i.e., myocardial infarction (MI), stroke, or coronary death) in meta-analyses of longitudinal studies (hazard ratio= 1.31-2.6) [2, 3, 24, 25]. The direction of this association is in agreement with a Mendelian Randomization (MR) study that suggested that genetic predisposition to depression is associated with increased risk of cardiovascular disease (i.e., coronary artery disease (14%) and myocardial infarction (21%)) [26]. Additionally, data from another MR study [27] suggest that obesity, type 2 diabetes, smoking, and high lipid level mediate this causal relationship.

Many mechanisms were studied earlier and described as potential links between depressive symptoms with cardiometabolic diseases. These mechanisms are behavioral (i.e., physical inactivity, unbalanced diet, smoking, alcohol abuse, and low level of medical/lifestyle adherence), biological (i.e., HPA, immuno-metabolic, autonomic dysregulations), and iatrogenic (i.e., the pharmacological impact of depression medication on cardiometabolic diseases) [28]. Furthermore, possible common causes for the independent expression of both depression and cardiometabolic diseases include childhood trauma, personality, and genetic pleiotropy [28]. A recent study [29] identified 24 pleiotropic genes likely to be shared between depression and cardiometabolic diseases (i.e., defined in this study as type 2 diabetes, cardiovascular disease, and their risk factors such as obesity, hypertension, HDL and LDL cholesterol, triglycerides, and fasting glucose and insulin). Four of these genes were shared between depression with type 2 diabetes or cardiovascular disease and regulate neurogenesis, appetite, neurotransmitters, and melatonin receptor [29].

To deepen our understanding, we investigated the association between specific depressive symptom profiles and individual cardiometabolic diseases. Our study suggests that atypical energy-related symptom profile was the main driver for the association between depression and increased risk of type 2 diabetes. This noted link could be explained by interconnected behavior factors and biological mechanisms such as surplus calorie intake and immuno-metabolic dysregulation (i.e., low-grade inflammation and adipokines over secretion), which may later manifest as type 2 diabetes [6, 30]. The hemostatic shift toward positive energy balance, which distinguishes AES, may lead to lipid accumulation in ectopic organs, a known risk factor for insulin resistance and type 2 diabetes [31, 32]. This positive energy balance also creates cellular nutrient stress, especially on the site of protein folding (i.e., endoplasmic reticulum) [33]. This cellular stress triggers the "metaflammation" response. The "metaflammation" describes the situation when the low-grade inflammation alters the function of insulin in metabolic tissues such as the liver and brain [33]. Accumulated white adipose tissue secrete adipokines (e.g., leptin) that play a significant role in inhibition of insulin secretion from pancreatic β cells [34]. This aligns with the previous work that confirmed the increased pro-inflammatory markers and metabolic dysregulation (e.g., CRP and IL-6, high BMI and total body fat, insulin resistance, leptin resistance, dyslipidemia, and hyperglycemia) in individuals with depression reporting AES profile [6, 7, 35-41]. Additionally, pro-inflammatory markers may trigger neuroinflammation associated with decreased tryptophan and increased catabolites associated with the atypical energy-related symptom profile and worse health outcomes such as type 2 diabetes [8, 42]. Furthermore, chronic low-grade inflammation, has been suggested to mediate the relationship between atypical energy-related symptoms and type 2 diabetes [43]. Several genetic studies converged in showing that MDD

patients reporting AES symptoms carried a higher number of genetic risk variants for the following metabolic traits such as increased obesity, CRP, triglycerides and leptin [44-46].

In contrast to that atypical energy-related symptoms, the melancholic symptoms profile was specifically associated with cardiovascular disorders. Different potentially shared risk factors or mechanisms may explain this association. For instance, depressed individuals expressing a melancholic symptom profiles have been shown to be more likely smokers as compared to other patients [44, 45]. Biologically, individuals with depression who reported insomnia, early morning awakening, and decreased appetite were also experiencing HPA and locus ceruleus-norepinephrine LC-NE systems hyperactivation [46]. Hyperactivation of both systems was also linked to an imbalance in the autonomic tone (i.e., sympathetic and parasympathetic nervous systems). Not only activation of the sympathetic system, but the withdrawal of vagal tone (i.e., decreased activity of parasympathetic nervous system) was also associated with the melancholic subtype [47]. Researchers found that decreased heart rate variability (HRV) accompanied by increased resting heart rate were associated with this subtype of MDD compared to control [47]. This hyperactivation of the sympathetic and decreased parasympathetic nervous systems was associated with pro-inflammatory factors and heart rate variability associated with cardiovascular disease [48-50]. It is plausible that the differential association between the two depressive profiles (i.e., AES and melancholic) with the incidence of the two cardiometabolic profiles is rooted in partially distinct complex network of the underlying biological pathways and behavioral lifestyles. In addition to the abovementioned evidence, this explanation is supported by the recent postulation of possible distinct symptoms specific psychopathological pathways that links depression with cardiac risk, one through BMI and inflammation and the other through dysregulation of HPA and the autonomic nervous system [51]. Nonetheless, the exact nature of this specific associations is still unknown and requires further investigation in future research including mechanistic studies.

Several methodological aspects of this study should be addressed. The large sample size, the detailed information of the depressive symptomatology, the follow-up and the detailed information about cardiometabolic outcomes allowed us to investigate the heterogeneity of depression and cardiometabolic diseases. However, there were some limitations. For example, depressive symptoms were evaluated via a self-report questionnaire. Nonetheless, IDS-SR30 is time and cost-efficient for research purposes and showed high concordance with clinical diagnosis of depression [52]. Second, depressive symptomatology data was only available at the baseline, so we were unable to evaluate the depressive symptoms at the time of the occurrence of the cardiometabolic diseases. However, a recent

study [53] showed a remarkable stability of depressive symptoms measured with IDS-SR30 over nine years follow-up in 1941 participants of the NESDA study. Third, we cannot rule out the possibility of reverse causality. We do however consider this highly unlikely, especially due to the fact that we excluded participants with cardiometabolic diseases at the baseline.

In conclusion, we confirmed the previous association between depressive symptoms and increased risk of developing cardiometabolic diseases. Additionally, disaggregating depressive symptoms in different profiles showed a specific trend of associations with cardiometabolic risk. Following up on patients with depression for developing cardiometabolic diseases and measuring depressive symptoms in individuals at risk for cardiometabolic diseases could be beneficial in primary and secondary preventive efforts. Our findings suggest that such preventive efforts may benefit from a more personalized approach taking into account differential symptom manifestations.

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