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Research paper

Cardiovascular risk indicators among depressed persons: A special case?

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ABSTRACT

Background: Traditional cardiovascular risk indicators only partially explain cardiovascular risks in depressed persons. Depressed persons may exhibit a profile of cardiovascular risk indicators that goes beyond traditional cardiovascular risk indicators, such as symptom severity, insomnia, loneliness and neuroticism, yet research on the added value of these depression-related characteristics in predicting cardiovascular risks of depressed persons is scarce.

Methods: Data from $N = 1028$ depressed Dutch adults without prevalent CVD were derived from two longitudinal depression cohort studies. The outcome was medication-confirmed self-reported CVD. Fifteen depression-related clinical and psychological characteristics were included and tested against traditional cardiovascular risk indicators. Data were analysed using Cox regression models. Incremental values of these characteristics were calculated using c-statistics.

Results: After a median follow-up of 65.3 months, 12.7% of the participants developed CVD. Only anxiety and depressive symptom severity were associated with incident CVD beyond traditional cardiovascular risk indicators. The c-statistic of the model with traditional cardiovascular risk indicators was 85.47%. This increased with 0.56 or 0.33 percentage points after inclusion of anxiety or depression severity, respectively.

Limitations: Other relevant depression-related characteristics were not available in the datasets used.

Conclusion: Anxiety and depressive symptom severity were indicative of an increased cardiovascular risk. Including these as additional risk indicators barely improved the ability to assess cardiovascular risks in depressed persons. Although traditional cardiovascular risk indicators performed well in depressed persons, existing risk prediction algorithms need to be validated in depressed persons.

1. Introduction

Depressed persons have an up to 70% increased risk of cardiovascular disease (CVD) (Correll et al., 2017). The preventive measures to reduce this risk seem not successful enough in depressed persons (Gaye et al., 2016).

Prevention of and intervention on CVD requires adequate cardiovascular risk assessment. Cardiovascular risks are currently assessed using traditional cardiovascular risk indicators, including age, sex and lifestyle and metabolic factors. However, previous studies showed that cardiovascular risks in depressed persons cannot solely be explained by a higher prevalence of these traditional cardiovascular risk indicators (Penninx, 2017). This is also supported by studies showing that cardiovascular risk prediction algorithms used in clinical practice, such as the Framingham Risk Score, underestimate cardiovascular risks in persons with depression and other severe mental illnesses (Cunningham

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et al., 2019; Osborn et al., 2015). These algorithms consist of a subset of traditional cardiovascular risk indicators (age, sex, cholesterol levels, smoking and blood pressure). Cardiovascular risk assessment in persons with severe mental illnesses improved after external validation of the prediction algorithm and after inclusion of new predictors such as antidepressant use (Osborn et al., 2015). There seems to be a considerable scope of opportunity to improve cardiovascular risk assessment in depressed persons.

Risk indicators other than traditional cardiovascular risk indicators are needed to assess the full array of cardiovascular risks in depressed persons. Previous studies show a variety of indicators that are associated with both depression and CVD, including depression-specific features such as atypical depression and severity of depression and more generic features that are more prevalent in depressed persons, such as insomnia, loneliness and neuroticism (Lasserre et al., 2017; Syk et al., 2021; Wang et al., 2021). However, no study has examined whether these features contribute to cardiovascular risk predictions in depressed persons. Therefore, to what extent depressed persons exhibit a specific risk profile for cardiovascular disease remains unclear.

In the current study, we aimed to investigate whether depressed persons exhibit a profile of risk indicators for CVD that includes risk indicators complementary to the traditional cardiovascular risk indicators. We have selected fifteen clinical and psychological factors that have been associated with an increased cardiovascular risk previously and were available in both the Netherlands Study of Depression and Anxiety (NESDA) and the Netherlands Study of Depression in Older Persons (NESDO). Finding a depression-specific profile of cardiovascular risk indicators can improve the identification of depressed persons at increased cardiovascular risk. Targeting these persons can increase the success of cardiovascular risk reducing interventions and aid effective prevention efforts.

2. Methods

2.1. Sample description

We used data from two multi-site naturalistic longitudinal cohort studies: NESDA (Penninx et al., 2008) and NESDO (Comijs et al., 2011). Both studies were designed to investigate determinants, the course and consequences of depression.

NESDA participants, aged 18–65 years at inclusion, were recruited from the community, primary care and specialized mental health care settings in the Netherlands between 2004 and 2007. The sample (N = 2981) consists of adults with a six-month recency diagnosis of anxiety or depressive disorder (N = 1701; as determined with the DSM-IV-based Composite International Diagnostic Interview, lifetime version 2.1, CIDI), adults with a life-time diagnosis of depressive and/or anxiety disorder, a positive family history or subthreshold symptoms of depression and/or anxiety (N = 907), and healthy controls (N = 373). Exclusion criteria were 1) a primary clinical diagnosis of psychotic disorder, obsessive compulsive disorder, bipolar disorder or severe addiction disorder and 2) not being fluent in the Dutch language. New measurements were conducted about every two years. The NESDA study protocol was approved by the Ethical Review Board of all participating centres and all participants provided informed consent. The NESDA study is described in more detail by Penninx et al. (2008).

NESDO participants, aged ≥60 years at inclusion, were recruited from general practitioners and specialized mental health care settings in the Netherlands between 2007 and 2010. The sample (N = 510) consists of older adults with a six-month recency diagnosis of major depressive disorder or a 1-month recency diagnosis of minor depression (as determined with the CIDI) (N = 378) and of non-depressed controls (no lifetime diagnosis of depression, N = 132). Exclusion criteria were 1) a primary clinical diagnosis of psychotic disorder, obsessive compulsive disorder or severe addiction disorder; 2) suspicion of dementia according to the clinician or a Mini Mental State Examination-score <18/30 points; and 3) not being fluent in the Dutch language. Written questionnaires were sent every six months during six years and a second and third face-to-face interview were conducted two and six years after the first measurement, respectively. The NESDO study protocol was approved by the Ethical Review Board of all participating centres and all participants provided written informed consent. The NESDO study is described in more detail by Comijs et al. (2011).

For the current study, we used data from NESDA measurement waves one, three, four and five and data from NESDO measurement waves one, five and thirteen, i.e. the face-to-face interviews, resulting in a follow-up of approximately six years (Fig. 1). We chose these measurement waves because the maximum available follow-up for NESDO is six years and only the face-to-face interviews contain data on CVD. We selected participants with a current depression (i.e. a one-year recency diagnosis of major depressive disorder as determined with the CIDI and an Inventory for Depressive Symptomatology – Self Rated (IDS) score >13 at the first measurement) (N = 1470). We excluded participants with medication-confirmed self-reported CVD at baseline (N = 220), with missing data on depressive symptom severity at baseline (N = 29) or with missing data on CVD at all follow-up waves (N = 193). The final sample consists of N = 1028 participants, N = 876 from NESDA and N = 152 from NESDO.

2.2. Cardiovascular disease

The outcome was medication-confirmed self-reported CVD with an atherosclerotic aetiology. Self-reported CVD was based on self-report of diseases, symptoms and surgery. Diseases included coronary artery disease, peripheral artery disease and stroke (Have you ever had… a heart attack/angina pectoris/abnormalities or diseases of arteries or vessels in the abdomen or in the legs/stroke). Self-reported symptoms included a question on chest pain at exertion disappearing within 10 min of rest or after taking medication and a question on pain in the calves during walking disappearing when standing still. Self-reported surgery included coronary artery bypass graft, coronary angioplasty and stent insertion (Did you have heart or coronary vessel surgery? If yes, what type of surgery: artificial valve/coronary bypass/angioplasty treatment or stent/pacemaker/other).

Self-reported medication use was supported by showing the packaging of the medication to the interviewer. Medication were retrospectively classified according to the ATC classification system. ATC codes starting with B01 (antithrombotic agents), C01D (vasodilators used in cardiac diseases), C02 (antihypertensives), C03 (diuretics), C04 (peripheral vasodilators), C07 (betablocking agents), C08 (calciumchannel blockers), C09 (agents acting on renin-angiotensin system) were included as cardiovascular medication, as were ATC codes N02BA01 (acetylsalicylic acid) and N02BA15 (carbasalate calcium) if the dosage was <100 mg. Only participants reporting disease, symptoms or surgery that also took cardiovascular medication were categorized as having CVD. Time to CVD was calculated as the number of months between the first measurement wave (baseline) and the midpoint between the last measurement wave where the participant reported not having CVD and the first measurement wave where the participant reported having CVD.

2.3. Depression-related characteristics

We selected clinical and psychological characteristics that tend to be more prevalent in depression, were associated with incident CVD in previous studies and were available at baseline in both NESDA and NESDO (Biffi et al., 2017; Javaheri and Redline, 2017; Jokela et al., 2014; Karlsen et al., 2021; Rantanen et al., 2020; Roepke and Grant, 2011; Seldenrijk et al., 2015; Valtorta et al., 2016). We consider these characteristics putative risk indicators that do not necessarily have a causal relation with CVD (Offord and Kraemer, 2000).

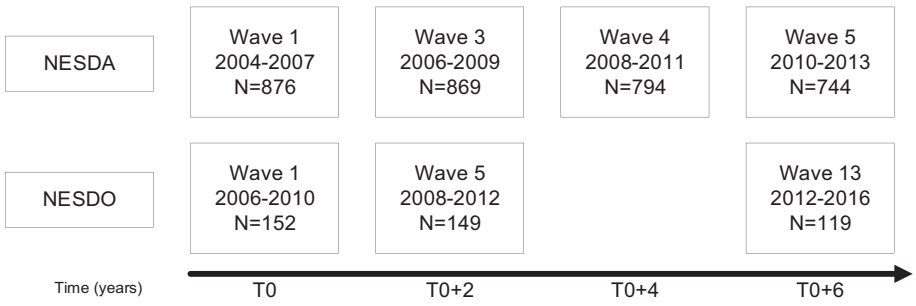

Fig. 1. Data used in the analyses.

2.4. Clinical characteristics

We included current depressive symptom severity, age of onset, recurrent depression, atypical features, melancholic features, use of antidepressant medication, insomnia, anxiety symptom severity and loneliness as clinical characteristics. Depressive symptom severity was determined with the 30-item IDS (Rush et al., 1996; Trivedi et al., 2004). Age of onset and recurrence of disease (single vs. >1 episode) were obtained by the CIDI. Presence of atypical features (no/yes), which include mood reactivity and ≥2 of hyperphagia, hypersomnia, leaden paralysis and interpersonal rejection sensitivity, was determined using an IDS-based algorithm (Novick et al., 2005). Presence of melancholic features (no/yes), which include lack of mood reactivity or loss of pleasure and ≥3 of distinct mood quality, mood worse in morning, early morning awakening, psychomotor retardation or agitation, anorexia/weight loss and guilt feelings, was determined using an IDS-based algorithm (Khan et al., 2006). Antidepressant medication use was categorized as none/tricyclic antidepressants (TCA, ATC codes starting with N06AA: non-selective monoamine reuptake inhibitors)/selective serotonin reuptake inhibitors (SSRI, ATC codes starting with N06AB: selective serotonin reuptake inhibitors)/other (ATC codes starting with N06AF: monoamine oxidase inhibitors, non-selective; N06AG: monoamine oxidase A inhibitors; N06AX: other antidepressants). Insomnia was measured with the Insomnia Rating Scale (IRS) (Levine et al., 2005; Levine et al., 2003a; Levine et al., 2003b). Anxiety symptom severity was measured with the Beck Anxiety Index (BAI) (Beck et al., 1988; Steer et al., 1993). Loneliness was measured with the De Jong Gierveld loneliness scale (de Jong Gierveld and van Tilburg, 1999).

2.5. Psychological characteristics

We included mastery and personality traits as psychological characteristics. Mastery was measured with the 5-item Pearlin Mastery scale (Pearlin and Schooler, 1978). Personality traits neuroticism, extraversion, openness, agreeableness and conscientiousness were measured with the NEO Five-Factor Inventory (NEO-FFI) (Costa and McCrae, 1995).

2.6. Traditional cardiovascular risk indicators

We included age at inclusion (continuous, range 18–90) and biological sex (male/female) as non-modifiable traditional risk indicators. We included smoking, body mass index (BMI), physical activity, alcohol use, blood pressure, LDL cholesterol and diabetes mellitus as modifiable traditional cardiovascular risk indicators. Smoking (not currently/currently) was based on self-report. BMI was calculated using height and weight as measured during the interview. Physical activity was measured with the International Physical Activity Questionnaire (IPAQ) (Craig et al., 2003; IPAQ group, n.d.). The number of alcoholic drinks per week was determined with questions from the Alcohol Use Disorders Identification Test (Babor et al., 2001). Blood pressure was measured during the interview. Cholesterol levels were determined after an overnight fast. Diabetes mellitus (no/yes) was defined as medication use (ATC codes starting with A10: drugs used in diabetes), fasting blood glucose levels >7.7 mmol/l or self-reported disease.

We additionally included education as a proxy for socio-economic status, which is an important underlying determinant of aforementioned modifiable risk indicators. Education was based on the highest degree earned and converted into the nominal number of years of education needed for that degree (range 5–18 years).

2.7. Missing data

There was missing data in 21.3% of the participants on at least one of the following variables: BMI ($N = 1$), smoking (N = 1), alcohol use ($N = 3$), blood pressure ($N = 5$), melancholic features ($N = 7$), age of onset ($N = 8$), anxiety symptom severity (N = 8), neuroticism ($N = 10$), extraversion (N = 10), atypical features (N = 10), conscientiousness ($N = 11$), openness ($N = 12$), agreeableness (N = 12), LDL cholesterol levels ($N = 23$), physical activity ($N = 60$), loneliness ($N = 108$), sleep ($N = 109$), mastery ($N = 118$). We handled missing data using multiple imputation (predictive mean matching, 100 iterations, 22 imputations). We checked convergence with iteration plots.

2.8. Analyses

We used Cox regression to analyse the data. Linearity assumptions (checked with quartiles) were violated. We aimed to transform the variables to achieve linearity and avoid loss of power. However, this only worked for a minority of the variables. Therefore we decided to apply a uniform approach and dichotomized continuous independent variables when linearity assumptions were violated. We used recommended cut-offs for categorization of current depressive symptom severity, age of onset, insomnia, anxiety symptom severity, loneliness, BMI, physical activity, alcohol use, blood pressure and LDL cholesterol. For depressive symptom severity, we categorized IDS sum scores into mild (14–25)/moderate (26–38)/severe (39–48)/very severe (49–84) depression (UT Southwestern Medical Center, 2021). For late-onset depression, various criteria are used in the literature. Following the findings of Kendler et al. (2009) and Seldenrijk et al. (2011), we used a cut-off of 40 years for early (≤40 years) vs. late (>40 years) onset of depression. For insomnia, we used a cut-off of 9 on the IRS sum score as indicator of clinically significant insomnia (no/yes) (Levine et al., 2003b). For anxiety symptom severity, we categorized BAI sum scores as normal (0−10)/mild (10–19)/moderate (19–30)/severe (>30) (Beck et al., 1988; Steer et al., 1993). Because cardiovascular risks in persons with mild or moderate anxiety symptoms were quite similar (HR = 1.83 and HR = 1.95, respectively), we merged these categories into none/mild to moderate/severe anxiety symptoms. For loneliness, we categorized sum scores as not lonely (score 0–3) vs. lonely (score ≥3) (de Jong Gierveld and van Tilburg, 1999). As there are no recommended cut-offs available for mastery and personality traits, we used the median as cut-off. Median scores were fifteen for mastery, 32 for neuroticism, 23 for extraversion, 26 for openness, 32 for agreeableness and 29 for

conscientiousness.

We categorized BMI as obesity (no/yes) using a cut-off of ≥30. We categorized IPAQ scores as low, moderate or high level of physical activity, based on the intensity and duration of activities (Craig et al., 2003; IPAQ group, n.d.). Because cardiovascular risks in persons with moderate (HR = 0.64) or high levels (HR = 0.54) of physical activity were quite similar, we merged these categories into low vs. moderate-high levels of physical activity. We categorized alcohol use as excessive (>14 units/week for women and >21 units/week for men) vs. not excessive (Babor et al., 2001; Volksgezondheidenzorg.info, 2021). We defined hypertension (no/yes) as either a systolic blood pressure ≥140 mmHg, a diastolic blood pressure ≥90 mmHg or use of antihypertensive medication (ATC codes starting with C02 (antihypertensives), C03 (diuretics), C07 (beta blocking agents), C08 (calcium channel blockers) or C09 (agents acting on renin-angiotensin system). We defined high LDL cholesterol (no/yes) as either LDL cholesterol levels ≥2.6 mmol/l or use of lipid-lowering medication (ATC codes starting with C10: lipid modifying agents) (Visseren et al., 2021). All variables fulfilled the proportionality of hazards assumption, which we tested with interactions with time.

We continued our analyses by determining the crude associations between depression-related characteristics and incident CVD (model 1). Next, we determined the associations between depression-related characteristics and incident CVD after taking the effects of traditional cardiovascular risk indicators and education into account. We adjusted for those traditional cardiovascular risk indicators that are often included in clinical cardiovascular prediction algorithms (model 2; age, sex, hypertension, hypercholesterolemia, diabetes mellitus and smoking (Damen et al., 2016)) and subsequently we adjusted for all traditional cardiovascular risk indicators included in this study (model 3). The set of traditional cardiovascular risk indicators added in model 3 is referred to as behavioural indicators. Finally, to determine the incremental value of depression-related characteristics over the set of traditional cardiovascular risk indicators, we calculated concordance statistics (c-statistics, also known as area under the curve) (Steyerberg et al., 2012). The c-statistic is a measure of discrimination that gives the probability of a randomly selected participant with a shorter time-to-CVD having a higher risk score than a participant with a longer time-to-CVD. The c-statistic ranges from 0 to 1, with higher values indicating better discrimination. A c-statistic of 0.8 is considered to indicate good discrimination (Steyerberg et al., 2010). We determined the incremental value by calculating the difference in c-statistics of a model consisting of the set of traditional cardiovascular risk indicators and education (reference model) and a model consisting of the set of traditional cardiovascular risk indicators, education and a depression-related characteristic. We did not use one of the existing risk scores, such as the Framingham Risk Score, as reference model because these have not been validated in depressed persons. Nguyen and Kattan (2011) suggested that an incremental value of <0.005 indicates that "the marker does not contribute any independent prognostic information and is therefore not useful", yet others argue that this cut-off is not statistically justified (Caetano et al., 2018). Therefore, there is currently no accepted cut-off to determine whether or not a new marker actually improves the accuracy of a model. We also calculated the difference in pseudo-R^2, showing insight into the extent to which the model fit improves by adding depression-related characteristics, as readers may be more familiar with this measure.

We considered using *p*-values adjusted for multiple testing. However, we had plausible independent hypotheses for each test because included depression-related characteristics were found to be associated with CVD in previous studies. Furthermore, adjustment for multiple testing increases type-2-error rates (Perneger, 1998). Therefore, we decided to consider a p-value of <0.05 as statistically significant. Data were analysed in STATA version 14.1, except for c-statistics which were calculated in R version 4.0.3 using the psfmi package.

3. Results

3.1. Sample description and attrition

Characteristics of included participants are shown in Table 1. Participants were on average 44.6 (±15.5) years old, 68.2% were female and 90.5% were of Dutch nationality. Participants that were excluded because of missing data on depressive symptom severity or missing follow-up data on CVD (*N* = 222) did not differ from included participants in age or sex composition, but attained less years of education than included participants (*N* = 1028). The prevalence of smoking and physical inactivity was higher in excluded participants. The prevalence of the other traditional cardiovascular risk indicators was similar in excluded and included participants. Excluded participants had more severe depressive symptoms, a lower prevalence of recurrent depression, a higher prevalence of melancholic features, more severe anxiety symptoms, higher neuroticism and lower openness. Other depression-related characteristics did not differ between included and excluded participants.

3.2. Associations between depression-related characteristics and incident CVD

After a mean follow-up of 65.3 (±16.10) months (range: 23–84 months), 131 participants (12.7%) developed CVD. Crude and adjusted associations between depression-related characteristics and incident

Table 1
Sample characteristics at the first measurement (*N* = 1028).

	N	Observed		Imputed	
Traditional cardiovascular risk indicators					
Age *mean, SD*	1028	44.6	15.5		
Sex, female *%, N*	1028	68.2	701		
Years of education *mean, SD*	1028	11.6	3.2		
Currently smoking *%, N*	1027	40.0	411	40.1	412
Obesity *%, N*	1027	16.7	172	16.7	172
Low level of physical activity *%, N*	968	23.6	228	23.8	245
Excessive alcohol use *%, N*	1025	10.7	110	10.7	110
Hypertension *%, N*	1024	39.5	404	39.5	406
High LDL cholesterol *%, N*	1000	75.2	752	75.1	772
Diabetes mellitus *%, N*	1028	4.3	44		
Clinical characteristics					
Depressive symptom severity *%, N*	1028				
Mild		29.3	301		
Moderate		43.4	446		
Severe		18.8	193		
Very severe		8.6	88		
Late-onset depression *%, N*	1020	23.3	238	23.4	241
Recurrent depression *%, N*	1028	53.4	549		
Atypical features *%, N*	1018	19.7	201	19.8	204
Melancholic features *%, N*	1021	13.2	135	13.4	138
Use of antidepressants *%, N*	1028				
None		52.1	536		
TCA		5.9	61		
SSRI		30.3	311		
Other		11.7	120		
Insomnia *%, N*	919	64.7	595	64.6	664
Anxiety symptoms *%, N*	1020				
Normal		25.3	285	25.3	260
Mild to moderate		61.3	625	61.3	630
Severe		13.4	137	13.4	138
Lonely *%, N*	920	82.2	756	82.2	845
Psychological characteristics					
Mastery *mean, SD*	910	14.7	4.0	14.6	4.2
Neuroticism *mean, SD*	1018	32.0	7.0	32.0	7.0
Extraversion *mean, SD*	1018	23.0	7.9	23.0	7.9
Openness *mean, SD*	1016	26.6	6.2	26.6	6.2
Agreeableness *mean, SD*	1016	32.7	7.1	32.8	7.1
Conscientiousness *mean, SD*	1017	29.2	6.8	29.2	6.8

CVD are shown in Table 2. The majority of the depression-related characteristics were statistically significantly associated with a higher risk of incident CVD (Table 2, model 1). However, after taking the effects of traditional cardiovascular risk indicators into account, only depressive symptom severity and anxiety symptom severity remained significantly associated with incident CVD (Table 2, model 2 and model 3).

In comparison with participants with mild depressive symptoms, participants with moderate, severe or very severe depressive symptoms had on average a 1.40 (95% C.I.: 0.89–2.20), 2.12 (95% C.I.: 1.30–3.48) or 1.93 (95% C.I.: 1.01–3.67) times higher risk of incident CVD, respectively. Cardiovascular risks were not significantly different between participants with moderate, severe or very severe depressive symptoms (moderate vs. severe HR = 1.52 (95% C.I.: 0.97–2.37, p = 0.07), moderate vs. very severe HR = 1.38 (95% C.I.: 0.75–2.53, p = 0.30), severe vs. very severe HR = 0.91 (95% C.I.: 0.49–1.69, p = 0.77)).

In comparison with participants without anxiety symptoms, participants with mild to moderate or severe anxiety had on average a 1.99 (95% C.I.: 1.20–3.29) or 2.63 (95% C.I.: 1.42–4.87) times higher risk of incident CVD, respectively. Participants with severe anxiety did not have a significantly higher risk of incident CVD than participants with mild to moderate anxiety (HR = 1.32, 95% C.I.: 0.83–2.10, p = 0.23).

3.3. Incremental value

The c-statistic of the model only consisting of traditional cardiovascular risk indicators that are included in clinical cardiovascular prediction algorithms was 0.8456 (95% C.I.: 0.81–0.87) and had an R^2 of 12.02 (model 2 in Table 3). This means that, when cardiovascular risks estimated from these traditional cardiovascular risk indicators are compared between two randomly selected participants of whom one developed CVD and one did not develop CVD, there is an 84.56% probability that the estimated cardiovascular risk of the participant who developed CVD is higher than the estimated cardiovascular risk of the participant who did not develop CVD. Adding the behavioural traditional cardiovascular risk indicators increased this probability to 85.47% (c-statistic = 0.8547; 95% C.I.: 0.82–0.88; model 3 in Table 3). Adding anxiety symptom severity or depressive symptom severity further increased the probability with 0.56 or 0.33 percentage points respectively. Adding both simultaneously increased the probability with 0.67 percentage points (c-statistic = 0.8614; 95% C.I.: 0.83–0.89), incremental value = +0.0067). The incremental value of the other depression-related characteristics was also very small (Table 3).

The R^2 values show similar results. Including the anxiety or

Table 3
Incremental value of depression-related characteristics.

	Model 2		Model 3	
	C-statistic: 0.8456 R^2: 12.02		C-statistic: 0.8547 R^2: 12.61	
	Incremental value		Incremental value	
	Δ C-statistic	Δ R2	Δ C-statistic	Δ R2
Model 2	na	na	−0.0091	−0.59
Model 3	+0.0091	0.59	na	na
Depressive symptom severity	+0.0063	+0.70	+0.0033	+0.55
Late-onset depression	+0.0001	+0.03	−0.0001	+0.02
Recurrent depression	+0.0021	+0.09	+0.0005	+0.06
Atypical features	+0.0002	+0.01	0.0000	0.00
Melancholic features	+0.0002	+0.02	0.0000	+0.02
Use of antidepressants	−0.0002	+0.25	+0.0001	+0.26
Insomnia	−0.0004	+0.08	+0.0007	+0.13
Anxiety symptom severity	+0.0085	+0.75	+0.0056	+0.67
Lonely	+0.0004	+0.02	+0.0003	+0.02
Low mastery	+0.0006	+0.07	+0.0004	+0.04
High neuroticism	+0.0016	+0.15	+0.0001	+0.13
High extraversion	+0.0004	+0.02	+0.0006	+0.02
Low openness	+0.0013	+0.05	−0.0001	+0.02
High agreeableness	+0.0002	+0.07	+0.0015	+0.11
High conscientiousness	+0.0004	+0.02	+0.0006	+0.02

Model 2: age, sex, hypertension, high LDL cholesterol, diabetes mellitus and smoking.
Model 3: model 2 + education, obesity, low physical activity and excessive alcohol use.

Table 2
Associations between depression-related characteristics and incident CVD.

	Model 1			Model 2			Model 3		
	HR	95% C.I.	p	HR	95% C.I.	p	HR	95% C.I.	p
Depressive symptom severity									
Mild	ref			ref			ref		
Moderate	1.03	0.66–1.61	0.90	1.35	0.86–2.12	0.19	1.40	0.89–2.20	0.15
Severe	1.83	1.13–2.94	0.01	2.25	1.38–3.67	0.001	2.12	1.30–3.48	0.003
Very severe	1.59	0.85–2.99	0.15	2.12	1.12–4.00	0.02	1.93	1.01–3.67	0.046
Late-onset depression	3.04	2.16–4.30	<0.001	1.16	0.79–1.70	0.44	1.13	0.77–1.66	0.53
Recurrent depression	0.82	0.59–1.16	0.27	0.80	0.56–1.12	0.20	0.84	0.59–1.19	0.33
Atypical features	0.76	0.48–1.21	0.25	1.14	0.70–1.86	0.61	1.06	0.65–1.73	0.83
Melancholic features	1.18	0.73–1.91	0.49	1.18	0.73–1.91	0.50	1.15	0.71–1.86	0.58
Use of antidepressants									
None	ref			ref			ref		
TCA	1.87	0.98–3.57	0.06	0.77	0.39–1.52	0.46	0.69	0.35–1.37	0.29
SSRI	1.12	0.74–1.72	0.59	1.08	0.70–1.66	0.73	1.05	0.68–1.62	0.83
Other	2.73	1.75–4.26	<0.001	1.50	0.94–2.39	0.09	1.42	0.89–2.27	0.15
Insomnia	1.69	1.12–2.54	0.01	1.23	0.80–1.86	0.33	1.29	0.85–1.96	0.23
Anxiety symptom severity									
None	ref			ref			ref		
Mild to moderate	1.88	1.14–3.09	0.01	2.08	1.26–3.44	0.004	1.99	1.20–3.29	0.007
Severe	2.79	1.54–5.05	0.001	2.71	1.48–4.98	0.001	2.63	1.42–4.87	0.002
Lonely	1.62	0.93–2.84	0.09	1.05	0.60–1.82	0.87	1.02	0.59–1.78	0.94
Low mastery	0.98	0.68–1.40	0.89	1.14	0.78–1.67	0.50	1.08	0.73–1.59	0.70
High neuroticism	1.76	1.24–2.51	0.002	1.34	0.93–1.95	0.12	1.31	0.90–1.90	0.16
High extraversion	1.85	1.30–2.63	0.001	1.03	0.69–1.54	0.88	1.05	0.70–1.57	0.82
Low openness	1.19	0.84–1.68	0.32	1.13	0.79–1.60	0.51	0.96	0.65–1.40	0.82
High agreeableness	2.38	1.65–3.43	<0.001	1.22	0.81–1.85	0.34	1.33	0.87–2.03	0.19
High conscientiousness	1.72	1.21–2.44	0.002	0.94	0.64–1.38	0.76	0.93	0.63–1.36	0.70

Model 1: bivariable, crude.
Model 2: multivariable, adjusted for age, sex, hypertension, high LDL cholesterol, diabetes mellitus and smoking.
Model 3: model 2 + education, obesity, low physical activity, excessive alcohol use.

depressive symptom severity increases the R^2 with 0.67 and 0.55 percentage points, respectively, while including the other depression-related characteristics results in increases of 0.00–0.26 percentage points (Table 3).

4. Discussion

The aim of this study was to investigate whether depressed persons exhibit a profile of risk indicators for CVD that goes beyond the traditional cardiovascular risk indicators. Out of fifteen depression-related characteristics, only anxiety and depressive symptom severity were associated with incident CVD independent of traditional cardiovascular risk indicators. However, as the set of traditional cardiovascular risk indicators already had a c-statistic of 0.85, this left little room for further improvement. Accordingly, the incremental values of depression-related characteristics to the risk prediction model were negligible.

4.1. Comparison to previous studies

After taking the effects of traditional cardiovascular risk indicators into account, we found that anxiety and depressive symptom severity were statistically significantly associated with incident CVD, but other depression-related characteristics were not. Therefore, within a subgroup of depressed persons, the risk of incident CVD was higher in those with more severe symptoms of anxiety or depression than those with less severe symptomatology, independent of traditional cardiovascular risk indicators.

Findings from previous population-based studies also found that more severe symptoms of anxiety or depression were associated with an increased cardiovascular risk (Harshfield et al., 2020; Karlsen et al., 2021). For the other depression-related characteristics, some but not all previous studies found association with CVD (Coupland et al., 2016; Freak-Poli et al., 2021; Lee et al., 2014; Piano, 2017). Besides adjusting for the effects of traditional cardiovascular risk indicators, there are several other important differences between our study and previous studies that could explain why most depression-related characteristics were not associated with incident CVD in our study. The first is residual confounding by depression, as none of the previous studies was conducted in a sample consisting solely of depressed persons and only some studies adjusted for (severity of) depression. Consequently, the samples may be too different to allow a thorough comparison. The second is differences in the outcome measure. Some previous studies focused on specific types of CVD or cardiovascular mortality, while we used a composite of non-fatal coronary artery disease, peripheral artery disease and stroke to increase power and had no data on fatal new-onset CVD. A sensitivity analysis including medication-confirmed harder endpoints such as stroke and myocardial infarction was unfortunately not possible because this resulted in a number of events that was too low to perform our analyses. In addition, as the magnitude of the associations between depression-related characteristics and incident CVD may vary between types of CVD, our approach of combining types of CVD may have diluted the associations (Howell et al., 2019; Jokela et al., 2014; Ronksley et al., 2011). A final important difference is that, in contrast to some studies that use continuous predictors, we dichotomized scores on all depression-related characteristics because associations were not linear, thus violating basic assumptions of Cox regression analysis. This discretization lowered statistical power and c-statistics (Altman and Royston, 2006; Mbizvo and Larner, 2021). Nevertheless, since we were the first to test associations between a variety of depression-related characteristics and incident CVD in a sample of depressed adults, replication of our findings is needed.

Finally, it is notable that the severity of anxiety and depressive symptoms were significantly associated with CVD and both were also higher in excluded participants. However, as these differences were small and attrition in NESDA and NESDO was only to a limited extend associated with poor health, we believe that bias of the found effects is small (Comijs et al., 2015; Lamers et al., 2012).

4.2. Incremental value of depression-related characteristics

None of the previous studies examined the incremental value of depression-related characteristics over traditional cardiovascular risk indicators for the assessment of cardiovascular risks. However, it is important to do so, as a statistically significant risk increasing effect does not necessarily imply that the independent prognostic information of this variable notably improves the model's predictive ability (Kattan, 2003).

The incremental values we found appear to be small. Although consensus regarding cut-offs for incremental values is lacking, authors of a previous community-based study investigating the incremental value of newer cardiovascular risk markers such as ankle-brachial index and c-reactive protein found larger improvements in c-statistic (e.g. +0.01) than we did, but deemed these as negligible (Koller et al., 2012). Relative to the other included depression-related characteristics, adding anxiety symptom severity, followed by depressive symptom severity, showed the largest improvement in the model's ability to distinguish participants with incident CVD from those without incident CVD, yet this improvement is likely too small to be clinically relevant.

Nonetheless, two remarks should be made. First, we did not expect the c-statistic of the reference model to be this high. Although we did not find studies validating cardiovascular risk prediction algorithms in depressed persons, external validation of cardiovascular risk prediction algorithms in persons without mental illness yielded c-statistics ranging from 0.55 to 0.82 (Damen et al., 2019). Traditional cardiovascular risk indicators thus performed unexpectedly well in our sample of depressed persons. The performance of a model is generally higher in the data set in which the model has been constructed, which may explain why the c-statistic of our reference model is larger than the c-statistics reported in external validation studies (Steyerberg and Vergouwe, 2014). In addition, simulation studies showed that the higher the c-statistic of the reference model, the smaller the incremental value of a new risk indicator (Austin and Steyerberg, 2013). The small incremental values we found are thus in line with the high c-statistic of our reference model. Altogether, the high c-statistics may be overestimated and the incremental values are underestimated.

4.3. Implications and suggestions for future research

Adequate assessment of cardiovascular risks in depressed persons is important, as this can help to identify individuals at increased risk of CVD, facilitating allocation of preventive measures. Our findings have several implications for the assessment of cardiovascular risks in depressed persons.

First, the set of traditional cardiovascular risk indicators included in existing cardiovascular risk prediction algorithms (model 2 in this study) contains a lot of predictive information that seems to assess cardiovascular risks quite well (good discriminative ability; c-statistic $>$ 0.8) (Steyerberg and Vergouwe, 2014). Additional information may not be needed to accurately assess cardiovascular risks in depressed persons.

Second, due to their small magnitude, the incremental values we found are unlikely to be clinically relevant. So, when information on the traditional cardiovascular risk indicators included in existing cardiovascular prediction algorithms is available, behavioural factors and depression-related characteristics are unlikely to further improve the assessment of cardiovascular risks in depressed persons.

Studies performing an external validation in depressed persons of the prediction algorithms that are used in clinical practice are necessary, as we were unable to find such studies. In addition, exploration of the generalizability of our findings to other ethnic groups is necessary. A final remark is that the reported associations may differ between men and women and between younger and older persons (Eid et al., 2019; Wagner et al., 2020). Although subgroup-analyses may uncover relevant

associations, we were unable to perform them because the number of cardiovascular events did not allow for stratification.

4.4. Strengths and limitations

Our study has several strengths. The large sample was recruited from different settings and covered an age span of 18–90 years. Our sample is therefore representative for routine mental healthcare. The two cohorts had a similar set-up, enabling combining of the data. Although clinical diagnoses of CVD were not available, we were able to confirm self-reported CVD by inspecting medication use, to reduce over-reporting of CVD. Finally, we quantified the incremental value of depression-related characteristics, which has not been done previously.

Our study also has several limitations. First, although we included many depression-related characteristics, baseline data on other depression-related characteristics that were of interest, such as duration of depression throughout life, type D personality and apathy, were not available. Second, to account for the non-linear associations between the continuous variables and CVD incidence, we categorized all depression-related characteristics using existing cut-offs or the median. These were not optimized for cardiovascular risk prediction. Third, we included a single measurement of depression-related characteristics and traditional cardiovascular risk indicators because not all characteristics were repeatedly measured. Although this could have biased the effect estimates, a single measurement of depression-related characteristics may reflect clinical practice more closely, where future changes in characteristics are also unknown. Fourth, we missed fatal events because data on causes of death were not available. Considering the age range in NESDO as compared to NESDA, the majority of fatal cardiovascular events likely occurred in the NESDO sample. In the NESDO sample, $N = 32$ participants died during follow-up. As approximately a quarter of mortality in depression is due to CVD, the approximate number of fatal events due to CVD missed in our study is approximately only eight (Prigge et al., 2022; St John and Tyas, 2016). We deem it unlikely that this has substantially affected our findings. Fifth, although we excluded participants with pre-existing CVD, there was no data on subclinical CVD to rule out reverse causation. Finally, we did not have data on diet and family history of CVD, which are important cardiovascular risk indicators.

5. Conclusion

Out of fifteen depression-related characteristics, only anxiety and depressive symptom severity were indicative of an increased cardiovascular risk in depressed persons, beyond traditional cardiovascular risk indicators. However, both improved the assessment of cardiovascular risks in depressed persons to a negligible extent. The set of traditional cardiovascular risk indicators that is included in existing cardiovascular risk prediction algorithms seemed to be a satisfactory set of predictors in our study of depressed persons.

CRediT authorship contribution statement

All authors contributed to conceptualization of the study. E.M. van Zutphen conducted the formal analysis and wrote the original draft. All co-authors provided critical review and editing. All authors have approved the final version of the manuscript.

Conflict of interest

None.

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