Vital Exhaustion and Somatic Depression: The Same Underlying Construct in Patients With Myocardial Infarction?

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Objective: To test whether vital exhaustion overlaps more with somatic/affective depression than with cognitive/affective depressive symptoms and evaluate the risk of recurrent cardiovascular events associated with these constructs. **Methods:** The Beck Depression Inventory (BDI) and the Maastricht Questionnaire (MQ) were administered to 528 patients hospitalized with myocardial infarction (MI). Principal component analyses (PCAs) were performed to assess the structure of the BDI, the MQ, and both combined. Univariate and multivariate (adjusting for age, sex, left ventricular ejection fraction, Killip Class, and history of MI) Cox proportional hazard regression analyses were used to examine the risk of recurrent cardiovascular events associated with the subscales of the MQ and of both questionnaires together. **Results:** PCA on the MQ yielded only one dimension. Per-standard-deviation increase in total MQ score, the multivariate hazard ratio was 1.37 (confidence interval [CI] = 1.15–1.64, $p < .001$). PCA on the items of MQ and BDI together yielded two dimensions: a somatic/affective and a cognitive/affective dimension. All but two of the items of the MQ loaded on the somatic/affective dimension. The multivariate hazard ratio for recurrent events associated with a 1-standard deviation increase in the somatic/affective dimension was 1.39 (CI = 1.11–1.73, $p = .004$), which was higher than the risk associated with the cognitive/affective dimension (1.02, CI = 0.82–1.27, $p = .83$). **Conclusions:** Vital exhaustion and somatic/affective depression strongly overlap and may cover the same underlying construct that increased the risk of new cardiovascular events. **Key words:** depression, vital exhaustion, myocardial infarction, somatic/affective and cognitive/affective symptom dimension.

BDI = Beck Depression Inventory; **CI** = confidence interval; **HADS** = Hospital Anxiety and Depression Scale; **HR** = hazard ratio; **LVEF** = left ventricular ejection fraction; **MDD** = major depressive disorder; **MI** = myocardial infarction; **MQ** = Maastricht Questionnaire; **PCA** = principal component analysis; **SD** = standard deviation.

INTRODUCTION

The prevalence of depression in patients experiencing heart disease is much higher than that in the general population (1,2). Because heart disease and depression are predicted to be the number 1 and 2 diseases contributing to the global burden of disease by 2020 (3), it is essential that the relationship between the two is well understood.

Vital exhaustion has been developed as a construct describing symptoms of fatigue, irritability, and demoralization, both as a precursor and as a consequence of acute coronary syndrome (4,5). Like depression, vital exhaustion is a risk factor for the development and progression of cardiovascular disease (6–8), but it is unclear to what extent it reflects the same underlying mechanisms as depression. To date, studies evaluating the overlap between depression and vital exhaustion have generated inconsistent results. Three studies found evidence supporting a two-factor model in which depression and vital exhaustion are two different concepts (9–11). The first study by van Diest and Appels (11) in 1991 found the prevalence of

depressed mood to be very low in patients with vital exhaustion. The second by Kopp and colleagues (9) in 1998 found that depression related more to psychiatric factors, whereas vital exhaustion related more to cardiac disease factors. In 2004, the third study by Kudielka and colleagues (10) performed a factor analysis on a depression questionnaire and a short version of the Maastricht Questionnaire (MQ) that assesses vital exhaustion and found them to be representing different underlying constructs. However, one other study by Wojciechowski and colleagues (12) in 2000 found strong correlations between scores on depression questionnaires and the MQ.

A potential explanation for the discrepancies between findings from the first three studies and this last study may be the heterogeneity of depression. For instance, van Diest and Appels (11) found vital exhaustion not to be related to depressed mood but strongly related to the individual items "fatigability," "work inhibition," "sleep disturbances," and "loss of libido" of the Beck Depression Inventory (BDI). Previously, we described two different symptom dimensions of depression in patients with MI: a somatic/affective and a cognitive/affective dimension (13). Somatic/affective symptoms were found to be remarkably stronger associated with recurrent cardiovascular events than cognitive/affective symptoms, which was replicated in several other studies (13–15).

Also, vital exhaustion was found to be a heterogeneous concept. In 3877 healthy men, Appels et al. (16) evaluated vital exhaustion using the MQ, on which data they performed factor analysis. The factor analysis yielded a fatigue, a depressive affect, and an irritability subscale. Of these, the fatigue subscale was the strongest predictor of incident MI, and the depression and irritability subscales lost their predictive value after adjusting for fatigue. Studies appearing later, which performed a factor analysis on the MQ, found the MQ to consist of at least two dimensions (fatigue and depression) (17–19).

The heterogeneity of vital exhaustion and particularly depression could explain the inconsistent results of studies investigating the overlap between depression and vital exhaustion. Evaluating the overlap between specific subscales of depression

and subscales of vital exhaustion might give considerable understanding in the cardiotoxic components of psychosocial risk factors for cardiovascular disease. In addition, this would help to translate findings from both separate lines of research. To date, no study evaluated the overlap between (dimensions of) vital exhaustion and specific depressive symptom dimensions in patients with MI.

In this study, we therefore evaluated potential overlap between different subscales of the BDI and MQ in a sample of patients with MI by performing factor analysis on all items of both questionnaires together. We hypothesized that the items of the MQ would overlap substantially more with somatic/affective items of the BDI than cognitive/affective items. In addition, we evaluated the risk of recurrent cardiovascular events associated with subscales of the BDI and the MQ obtained by factor analysis. A previous publication, based on this sample, showed that somatic/affective, but not cognitive/affective depressive symptoms of the BDI, predicted new cardiovascular events (13). In the present analysis, we evaluated the risk of new cardiovascular events associated with symptom dimensions of the MQ and symptom dimensions yielded by factor analysis on the 42 items of the BDI and MQ together. In addition, we evaluated the risk of new cardiovascular events associated with individual items from the BDI and the MQ.

METHODS

Data from the Depression after Myocardial Infarction (DepreMI) study were used. The methods of this study have been described in detail elsewhere (20–22) and are briefly described in the next paragraphs.

Design and Patients

The DepreMI was a naturalistic follow-up study on the impact of depression on cardiac prognosis in patients with MI. Subjects were recruited from four hospitals in the north of the Netherlands. From September 1997 and October 2000, all consecutive patients admitted for MI were assessed for eligibility. Inclusion criteria, of which at least two had to be met, were a) chest pain for at least 20 minutes, b) creatinine phosphokinase levels 100% greater than normal or creatinine phosphokinase MB levels greater than 10%, and c) presence of new pathological Q waves on the electrocardiogram in at least two leads. Exclusion criteria were life expectancy of less than a year because of noncardiac condition, too poor physical condition according to hospital staff, cognitive dysfunction, inability to speak or read Dutch, occurrence of an MI in patients admitted for another reason, and follow-up visits scheduled in a nonparticipating hospital. All participating patients in the study signed an informed consent form, and the ethics committee review board at all the participating hospitals approved the study protocol.

Assessment of Depressive Symptoms and Vital Exhaustion

Depressive symptoms were measured using the BDI (23). The BDI is a widely used 21-item self-report measure assessing the presence and severity of depressive symptoms. Participants were instructed to rate each symptom on a scale from 0 to 3, with a score of 0 representing absence and scores 1 to 3 representing increasing levels of severity. Total scores can range from 0 to 63, with a score of 10 or more indicating at least mild depressive symptoms.

Vital exhaustion was assessed using the MQ (4). The MQ is a 21-item questionnaire, originally developed to identify future cases of coronary heart disease (24). Each statement may be answered Yes, No, or Do Not Know, resulting in a score from 0 to 2. Total scores range from 0 to 42, with a score of 14 or more suggesting significant symptoms of vital exhaustion.

The MQ and the BDI were administered as a combined questionnaire (first MQ, then BDI) during hospitalization for index MI. Patients answered questions about the presence and severity of symptoms since the MI.

Assessment of Covariates

Age, sex, history of MI, Killip Class, left ventricular ejection fraction (LVEF), site of the MI, body mass index, procedures during hospitalization for index MI, history of peripheral and cerebral vascular disease, hypertension, hypercholesterolemia, and the presence of diabetes mellitus were assessed from hospital charts during hospital admission for index MI. Killip Class was assessed with a standardized 4-point clinical assessment, based on pulmonary rales and radiograph. LVEF was assessed by echocardiography, radionuclide ventriculography, gated single photon emission computed tomography, magnetic resonance imaging, angiography, or clinical assessment. Smoking status, living alone, and education were evaluated in a face-to-face interview at 3 months after the MI. Smoking was defined as current smoker or quit smoking less than 3 months before hospital admission.

Assessment of Recurrent Cardiovascular Events

Cardiovascular mortality and cardiovascular-related readmissions to the hospital were obtained from hospital records and the participant's primary care physician. Cardiovascular-related readmissions included those for recurrent MI, (un)stable angina, heart failure, arrhythmia, peripheral cardiovascular disease, or cerebrovascular accident. An independent end point committee consisting of two cardiologists evaluated whether potential end points were cardiovascular or not. Discrepancies were discussed until consensus was achieved. Follow-up time started at the index MI and lasted up until a) the occurrence of cardiovascular complication and b) the end of follow-up time. Mean (standard deviation [SD]) follow-up time was 2.5 (0.9) years. Patients without an event were censored at the end of follow-up date or the date of death (in case of noncardiac death).

Data Analyses

First, principal component analysis (PCA) with oblimin rotation was performed on all 21 items of the BDI to obtain the symptom dimensions of depression. Previously, we reported that this resulted in a somatic/affective, a cognitive/affective, and an appetitive dimension (based on PCA on the BDI in this patient sample combined with another sample of patients with MI) (13). Next, PCA with oblimin rotation was performed on the 21 items of the MQ. Finally, to evaluate potential overlap between dimensions of vital exhaustion and dimensions of the BDI, PCA was performed on the 42 items from the BDI and MQ together. The optimal number of dimensions was determined based on a scree-plot. Standardized total factor scores were calculated using the regression method.

Univariate and multivariate Cox proportional hazard regression analyses were used to examine the risk of recurrent cardiovascular events associated with a) the factor scores obtained from the PCA on the BDI an MQ separately, b) the dimensions obtained from the PCA on the BDI and MQ together, and c) the dichotomized scores on the individual items of the MQ (items scoring "do not know" where classified as absent) and the BDI (items scoring 1, 2, or 3 were classified as present; items scoring 0 were classified as absent). In multivariate analyses, adjustments were made for age, sex, and LVEF less than 40% (Y/N), Killip Class (range = 1–4), history of MI (Y/N), and the score on other dimension(s).

RESULTS
Sample

A total of 528 patients with MI gave informed consent. BDI scores and MQ scores were present for 509 and 520 patients, respectively. For 464 patients, data on whether they had recurrent cardiovascular events were present. Of these, 110 (23.7%) had a recurrent cardiovascular event during a M (SD) follow-up time of 2.03 (1.02) years (median = 2.15 years, range = 8 days to 4.23 years). Table 1 shows the baseline characteristics for the total group and for those with and without recurrent cardiovascular events separately. Compared with those who remained

event-free, those with a recurrent cardiovascular event were significantly older, more often had anterior site MI, Killip Class higher than 1, LVEF less than 40%, history of MI, peripheral vascular disease, hypercholesterolemia, diabetes, less often had CABG during hospitalization for index MI, and had higher total scores on the BDI and MQ.

Structure of the BDI and MQ

PCA on the BDI yielded two dimensions, representing somatic/affective and cognitive/affective symptoms, which is comparable to what was previously reported on PCA based on this patient sample combined with another sample of patients with MI (13). In contrast to this previous analysis, which resulted in a three-factor solution, the third (appetitive) dimension explained less of the variance, resulting in a two-factor solution. The correlation between the somatic/affective and cognitive/affective dimension was 0.42.

PCA on the 21 items of the MQ yielded only one dimension, which explained 35% of the variance.

PCA on the 42 items from both scales together yielded two dimensions, which explained 34% of the variance together. The first was a somatic/affective dimension including the somatic/affective items from the BDI and all items from the MQ, except items 13 (giving up) and 16 (wish to be dead). The second was a cognitive/affective dimension (including the cognitive/affective items from the BDI and items 13 and 16 of the MQ).

Factor loadings of the PCA on the 42 items of both questionnaires together are shown in Table 2.

Symptom Dimensions of the BDI and MQ and Recurrent Cardiovascular Events

The somatic/affective factor score of the BDI was a stronger predictor for recurrent cardiovascular events than the cognitive/affective factor score (unadjusted hazard ratio [HR] = 1.39 [95% confidence interval {CI} = 1.17–1.65, $p < .001$] per SD increase, multivariate HR = 1.35 [95% CI = 1.07–1.72, $p = .01$], which was 1.18 [95% CI = 0.98–1.42, $p = .09$] and 1.00 [95% CI = 0.77–1.28, $p = .98$], respectively, for the cognitive/affective factor score). This is comparable to what we reported previously for somatic/affective and cognitive/affective depressive symptoms obtained by PCA on the BDI of this patient sample combined with another sample of MI patients (13). Because PCA on the MQ yielded only one dimension, Cox regression was performed on the total score of the MQ. Per SD increase on the MQ, the risk of recurrent cardiovascular events was 1.37 (95% CI = 1.15–1.64, $p < .001$) in the univariate analysis and 1.33 (95% CI = 1.11–1.60, $p = .002$) in the multivariate analysis.

The HR for recurrent events associated with 1 SD increase in the somatic/affective factor score from the PCA on all 42 items together was 1.45 (95% CI = 1.21–1.75, $p < .001$), which was 1.18 (95% CI = 0.98–1.42, $p = .08$) for the cognitive/affective factor score in the univariate analyses. In multivariate analyses,

TABLE 1. Baseline Characteristics for the Total Sample and for Those With and Without New Events

	Total Sample ($n = 464$)	New Event ($n = 110$)	No New Event ($n = 354$)	p^a
Age, M (SD), y	60.5 (11.7)	62.8 (11.2)	59.8 (11.7)	.02
Female, n (%)	86 (18.5)	22 (20.0)	64 (18.1)	.65
Living alone, n (%)	70 (15.1)	19 (17.3)	51 (14.4)	.46
Primary school only, n (%)	90 (19.4)	23 (20.9)	67 (18.9)	.65
Anterior site of MI, n (%)	148 (31.9)	45 (40.9)	103 (29.1)	.02
Killip Class^b > 1, n (%)	64 (13.9)	24 (22.0)	40 (11.3)	.005
LVEF < 40%,^{b} n (%)	107 (23.1)	33 (30.3)	74 (20.9)	.04
Thrombolysis during hospitalization for index MI,^{b} n (%)	204 (44.2)	51 (46.4)	153 (43.5)	.59
PTCA during hospitalization for index MI,^{b} n (%)	103 (25.4)	21 (21.6)	82 (26.5)	.33
CABG during hospitalization for index MI, n (%)	14 (3.4)	0 (0.0)	14 (4.5)	.03
History of MI, n (%)	64 (13.8)	25 (22.7)	39 (11.0)	.002
History of cerebrovascular disease, n (%)	21 (4.5)	7 (6.4)	14 (4.0)	.29
History of peripheral vascular disease, n (%)	31 (6.7)	16 (14.5)	15 (4.2)	<.001
History of hypertension, n (%)	128 (27.6)	30 (27.3)	98 (27.7)	.93
History of hypercholesterolemia, n (%)	161 (34.7)	47 (42.7)	114 (32.2)	.04
History of diabetes, n (%)	47 (10.1)	18 (16.4)	29 (8.2)	.01
Family history of coronary artery disease, n (%)	174 (37.5)	47 (42.7)	127 (35.9)	.20
Smoking at the time of index MI, n (%)	222 (52.6)	56 (54.9)	166 (51.9)	.59
BMI,^{b} M (SD), kg/m^2	26.8 (4.0)	26.9 (4.3)	26.4 (3.2)	.25
BDI at hospitalization, IQR	3, 5, 9	3, 6, 13	2, 5, 9	<.001
MQ at hospitalization, IQR	5, 12, 22	9, 16, 25	5, 11, 20	.004

M = mean; SD = standard deviation; MI = myocardial infarction; LVEF = left ventricular ejection fraction; PTCA = percutaneous transluminal coronary intervention; CABG = coronary artery bypass grafting; BMI = body mass index; BDI = Beck Depression Inventory; IQR = interquartile range; MQ = Maastricht Questionnaire.
^{a} The p value was based on χ^2 for dichotomous variables, independent-sample t test for age and BMI, and Mann-Whitney U for the BDI and MQ scores.
^{b} Killip Class, $n = 462$; LVEF, $n = 463$; thrombolysis, $n = 462$; PTCA, $n = 406$; CABG, $n = 406$; smoking, $n = 422$; BMI, $n = 383$.

TABLE 2. Factor Loadings of BDI and MQ Items Together

	Loading Somatic/Affective	Loading Cognitive/Affective
BDI	0.215	0.614
Sadness	0.127	0.631
Pessimism	0.112	0.738
Sense of failure	0.373	0.462
Dissatisfaction	0.173	0.701
Guilt	0.134	0.562
Punishment	0.032	0.636
Self-dislike	0.025	0.526
Self-accusations	0.049	0.546
Suicidal ideas	0.103	0.365
Crying	0.369	0.106
Irritability	0.124	0.488
Social withdrawal	0.467	0.174
Indecisiveness	0.093	0.217
Body image change	0.642	0.090
Work difficulty	0.443	0.159
Insomnia	0.615	0.012
Fatigability	0.482	0.134
Loss of appetite	0.323	0.141
Weight loss	0.314	0.331
Somatic preoccupation	0.378	0.202
Loss of libido	0.378	0.202
MQ	0.776	0.125
Often feel tired	0.324	0.118
Difficulties falling asleep	0.404	0.012
Often wake up at night	0.171	0.068
Feel altogether weak	0.696	0.193
Not accomplish much	0.617	0.063
Becomes all too much	0.460	0.294
Have come to a dead end	0.659	0.128
Lately feel listless	0.427	0.043
Loss of libido	0.413	0.330
Feelings of hopelessness	0.520	0.005
Difficulties comprehending	0.390	0.179
Little things irritate more	0.159	0.541
Want to give up	0.674	0.042
Feel fine (no)	0.625	0.010
Body like battery running out	0.095	0.598
Sometimes wish to be dead	0.562	0.089
Worthlessness	0.427	0.429
Feel dejected	0.329	0.258
Sometimes feel like crying	0.450	0.203
Ever wake up exhausted	0.611	0.013
Difficulties concentrating	0.611	0.013

BDI = Beck Depression Inventory; MQ = Maastricht Questionnaire.

this was 1.39 (95% CI = 1.11–1.73, p = .004) and 1.02 (95% CI = 0.82–1.27, p = .83), respectively. Figure 1 shows Kaplan-Meier curves showing the risk of recurrent cardiovascular events for the 20% of patients scoring highest on the somatic/affective and cognitive/affective dimensions from the BDI and MQ together.

Individual Items of the BDI and MQ and Recurrent Cardiovascular Events

Figure 2 shows the age- and sex-adjusted HRs (95% CI) for recurrent cardiovascular events associated with the presence of the individual items from the BDI and MQ. Most items posed an increased risk (HRs ranging from 0.68 to 1.88 for the BDI and from 1.05 to 2.02 for the MQ). The increased risk associated with the somatic/affective dimension could not be attributed to one or a few specific items. Furthermore, the difference between the somatic/affective and cognitive/affective dimension in cardiovascular risk was not clearly reflected in the individual items.

DISCUSSION

The present study examined the relationship between specific components of vital exhaustion and depression and their association with cardiovascular prognosis. Factor analysis on the MQ yielded only one dimension in patients with MI. Factor analysis on the items of the MQ and BDI together yielded two dimensions: a somatic/affective and a cognitive/affective dimension. All items but two from the MQ loaded on the somatic/affective dimension, which was more strongly associated with worse prognosis than the cognitive/affective dimension. These results suggest that vital exhaustion and somatic/affective depression reflect the same underlying construct that increases the risk of new cardiovascular events.

This study has several strengths. The large sample size and large number of patients with a recurrent cardiovascular event make it possible to perform factor analysis and multivariate Cox regression analysis respectively without creating bias. A limitation of the present findings is that it is not clear to what extent they can be generalized to other populations, such as healthy individuals or patients with other cardiovascular or noncardiovascular diseases. Furthermore, the interpretation of the present analysis may not be extended to other depression questionnaires than the BDI. The BDI includes a relatively large proportion of somatic/affective depressive symptoms, whereas other questionnaires, such as the Hospital Anxiety and Depression Scale (HADS), include relatively more cognitive/affective depressive symptoms.

This was the first study that examined the overlap between depression and vital exhaustion while taking into account the heterogeneity of depression. We found that vital exhaustion overlaps with the somatic/affective dimension of depression rather than depression as a whole. Because there are differences between depression questionnaires in the proportion of somatic/affective depressive symptoms, the use of different depression questionnaires may explain the discrepant results between studies evaluating the overlap between vital exhaustion and depression. For instance, Kudielka et al. (10) evaluated the overlap between the HADS and a nine-item version of the MQ by performing factor analysis on the items of both questionnaires together. Because the HADS consists mainly of cognitive/affective depressive symptoms and the version of the MQ they used consists only of fatigue-related symptoms, it is not surprising
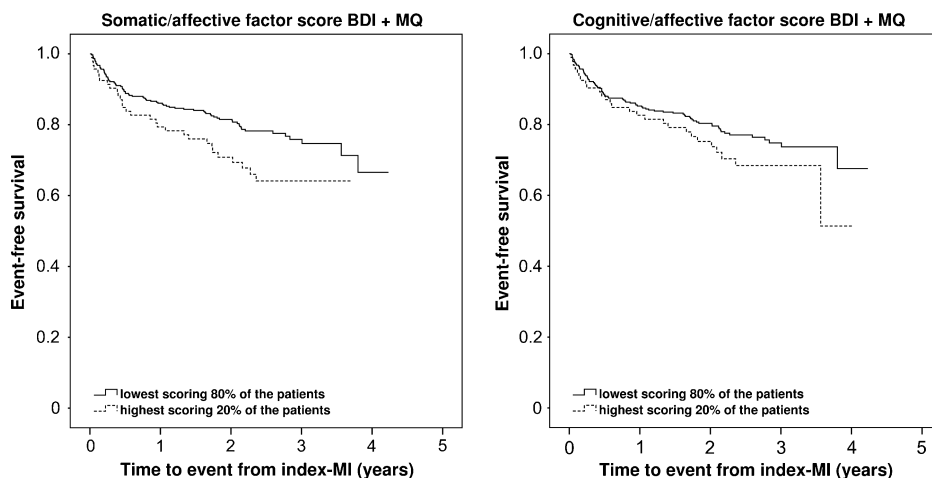
Figure 1. Event-free survival after MI and relationship to somatic/affective symptoms and cognitive/affective symptoms obtained by PCA on the 42 items of the BDI and MQ together.

that they found depression and vital exhaustion to represent two distinct dimensions.

In the present study, factor analysis on the MQ yielded only one dimension. In contrast, Appels et al. (16) found in a sample of healthy men three dimensions, comprising fatigue, depression, and irritability, respectively. McGowan et al. (17) found the following dimensions in a sample of 305 patients with MI: fatigue, depression, lack of concentration, and sleeping problems, explaining 18.2%, 17.9%, 9.5%, and 8.1% of the variance, respectively. Pedersen et al. (18) found in a sample of patients with unstable and stable angina a depression and a fatigue dimension. Contrary to the results from the present study, they found the depression dimension, but not fatigue, to be predictive of recurrent cardiovascular events, with hopelessness as the most cardiotoxic depressive symptom. The difference with the findings of the present study may be explained by relatively small number of patients with adverse outcome in their study (i.e., 31 in their study versus 110 in the present study).

Smith et al. (19) found in a sample patients with of chronic heart failure four dimensions representing fatigue, cognitive/affective depressive symptoms, sleep difficulties, and lack of concentration. It is worth mentioning that, in the present study, (cognitive) depression, sleeping problems, and irritability/lack of concentration dimensions explained most variance in the second (8%), third (6%), and fourth (5%) place. Therefore, the factor structure of the MQ in the present study is similar to those reported in other studies.

This was the first study that performed a factor analysis of the BDI and MQ together. Previously, Wojciechowski et al. (12) performed factor analysis on the Zung-SDS, the Depression Scale of the SCL-90 and the MQ, which yielded one dimension. This ldiscrepancy may be explained by the smaller sample size of Wojciechowski et al. (12).

The individual item analysis did not reveal specifically cardiotoxic items/symptoms. Instead, most symptoms posed an increased risk (Fig. 2). This finding is consistent with that of
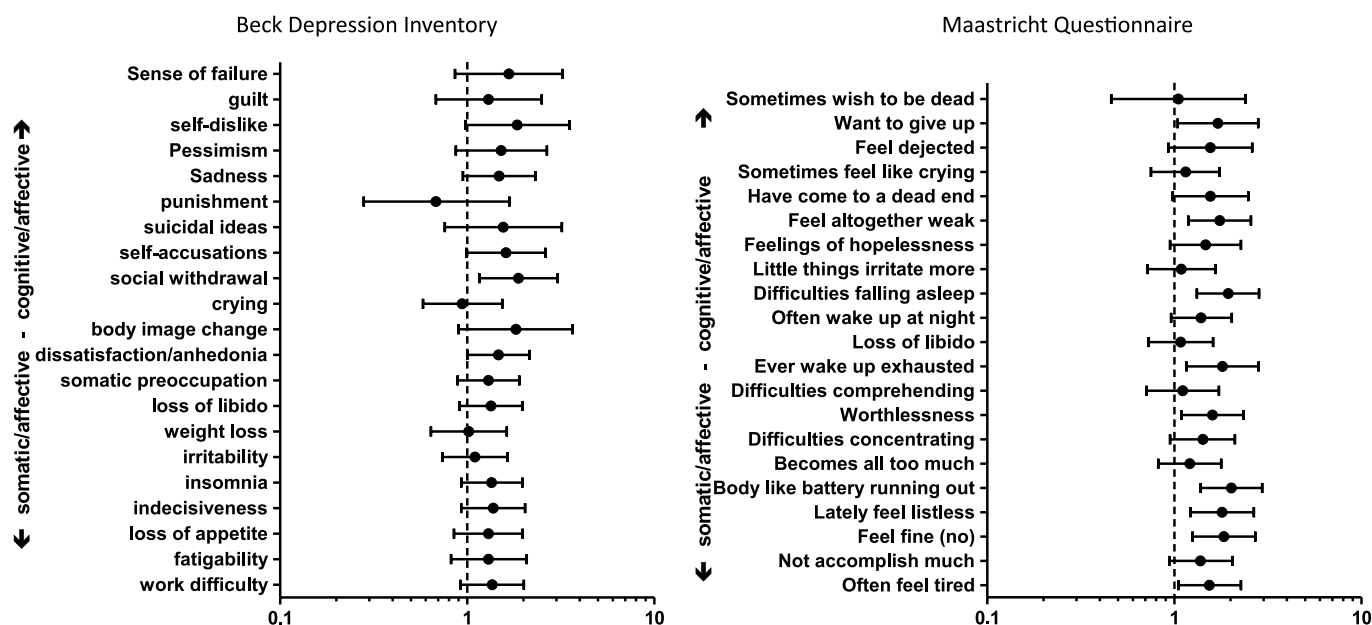

Figure 2. Risk of recurrent cardiovascular events for individual items of the BDI and MQ adjusted for age and sex.

a previous study in more than 10,000 healthy individuals, reporting an increased risk of incident MI or mortality associated with each individual item from the MQ (25). In fact, the difference between the somatic/affective and cognitive/affective dimension in cardiotoxicity was not clearly reflected in the individual items. We therefore conclude that the cardiotoxic effect of somatic/affective symptoms is due to the combination of symptoms rather than one or a few specific symptoms.

Findings from the present study suggest that vital exhaustion and somatic/affective depression cover the same concept, which is particularly associated with poor cardiac outcomes. This concept may be different from major depressive disorder (MDD) because patients experiencing vital exhaustion do not necessarily need to fulfill all criteria for MDD (11) and, similarly, somatic symptoms of depression can be present in the absence of a diagnosis of MDD. In fact, vital exhaustion or somatic/affective depressive symptoms may even be a more accurate predictor of cardiovascular prognosis than depression as a whole.

Although the increased risk associated with somatic/affective depression and vital exhaustion was independent from several parameters of cardiac disease severity, other mechanisms may explain the association. For instance, findings from some studies suggest that inflammation may underlie the vital exhaustion and somatic depression in patients with MI. Janszky and colleagues (26) found that, in women with coronary heart disease, vital exhaustion showed an association with inflammation measured, whereas depression did not. In other studies, depression was associated with inflammation, which has been proposed as one of the pathways between depression and poor cardiac outcomes (27). For instance, Dantzer and colleagues (28) reported a direct increase particularly in somatic depression after cytokine immunotherapy in patients treated for cancer or hepatitis C.

In conclusion, the present study revealed that vital exhaustion and somatic/affective depression show a strong overlap, implicating that they both represent an underlying concept, which is particularly associated with poor cardiovascular outcomes.

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