Differential associations between specific depressive symptoms and cardiovascular prognosis in patients with stable coronary heart disease

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Abstract

Objectives—The purpose of this research was to evaluate the relationship between cognitive and somatic depressive symptoms and cardiovascular prognosis.

Background—Depression in patients with stable coronary heart disease (CHD) is associated with poor cardiac prognosis. Whether certain depressive symptoms are more cardiotoxic than others is unknown.

Method—in the Heart and Soul study, 1019 patients with stable CHD were assessed with the Patient Health Questionnaire (PHQ) to determine the presence of the 9 depressive symptoms included in the DSM-IV. Mean age of patients was 67 years, and 82% were male. A comparison was made on a new cardiovascular event (myocardial infarction, stroke, transient ischemic attack, congestive heart failure) or death (mean follow-up duration = 6.1±2.0 years) based on cognitive and somatic sumscores and for patients with or without each of those specific depressive symptoms. Demographic characteristics, cardiac risk factors, and cardiac medication were controlled for.

Results—After adjustment for demographic data and cardiac risk factors, each somatic symptom was associated with 14% greater risk of events (HR:1.14;95%CI:1.05–1.24;p=0.002). Fatigue (HR:1.34;95%CI:1.07–1.67;p=0.01), appetite problems (HR:1.46;95%CI:1.12–1.91;p=0.005), and sleeping difficulties (HR:1.26;95%CI:1.00–1.58;p=0.05) were most strongly predictive of cardiovascular events. In contrast, cognitive symptoms (HR:1.08;95%CI:0.99–1.17;p=0.09) were not significantly associated with cardiovascular events.

Conclusion—in patients with stable CHD, somatic symptoms of depression were more strongly predictive of cardiovascular events than cognitive symptoms, although the confidence intervals surrounding these estimates had substantial overlap. These findings are highly consistent with
previous studies. Further research is needed to understand the pathophysiological processes by which somatic depressive symptoms contribute to prognosis in CHD patients.

Keywords

depression; stable coronary heart disease and prognosis

Introduction

The most important causes of Disability-Adjusted Life Years are predicted to be coronary heart disease (CHD) and major depression in the year 2020 (1). Patients with CHD are at increased risk for developing depression (2). On the other hand, patients with depression are at increased risk for developing cardiovascular disease, including congestive heart failure (CHF), myocardial infarction (MI), stroke and cardiovascular (CV) death (3–5). During the last decades, the effects of depression in CHD patients have been extensively studied (3,6,7). Several randomized controlled trials (RCTs) have been undertaken evaluate the efficacy of antidepressant therapy in patients with CHD. However, in most of these studies, treatment had only minor effects on reducing depressive symptoms (8).

A reason for these findings may be the heterogeneity of depression as a syndrome (9). Depression is a syndrome consisting of 9 depressive symptoms, according to the DSM-IV criteria (10). Several researchers over time have distinguished somatic symptoms from cognitive symptoms of depression (11–13). In recent years, this distinction was applied to CHD patients (14). It was found that somatic symptoms of depression had a relatively high prevalence (15), were more strongly associated with cardiovascular prognosis (14,16–18), medical comorbidity (13), and heart rate variability (19). At this time, it is still to be determined which of these symptoms has the most cardiotoxic contribution in terms of CV prognosis in patients with stable CHD.

We hypothesize the existence of differential associations of specific depressive symptoms on CV prognosis. We chose to investigate this research question in a population with stable CHD because in this sample the depressive symptoms may be less confounded by complaints that are frequently expressed in the direct aftermath of an acute coronary event, like for example fatigue. The identification of certain cardiotoxic symptoms within the diagnosis of depression would be an important step in the development of antidepressive interventions that are aimed to alleviate the depression-associated risk of CV events.

Methods

Design and patients

This study is based on data from the Heart and Soul Study, a prospective cohort study, focused on psychosocial factors and health outcomes in patients with stable coronary heart disease. Details regarding methods of the Heart and Soul Study have been described previously (20). Patients had to meet the following inclusion criteria: a) history of MI or coronary revascularization, b) angiographic evidence of at least 50% stenosis in at least one coronary vessel, and c) a diagnosis of CHD by an internist or cardiologist. Exclusion criteria were: a) a history of MI in the past 6 months, b) poor exercise tolerance: unable to walk one block, or c) planning to move from the local area within 3 years.

We initially mailed letters to 15,438 patients who had ICD-9 codes for CHD based on administrative databases at 2 Veterans Affairs medical centers, 1 university medical center, and 9 public health clinics in northern California. Since administrative data is not necessarily correct or current, many of these letters were mailed to bad addresses or to
persons who did not meet eligibility criteria. Of the 2495 patients who returned a form indicating that they would be interested in participating, 370 were excluded based on pre-defined exclusion criteria and 505 could not be reached by telephone. Of the 1620 patients who were confirmed to meet eligibility criteria, 596 declined to participate, and 1024 (63%) enrolled. Between September 2000 and December 2002, all participants completed a baseline assessment, including a medical history interview, fasting blood draw, a physical examination, an exercise treadmill test with a stress echocardiogram, a comprehensive health status questionnaire and 24-hours urine collection. All participating patients signed an informed consent form. The study protocol was approved by the institutional review boards of the participating hospitals.

Baseline characteristics

Baseline characteristics of the study sample included socio-demographic data, history of cardiovascular disease, and cardiac disease severity. The socio-demographic characteristics consisted of age, gender, and marital status, and were determined by questionnaire. History of cardiovascular disease was determined by self-report and included myocardial infarction, congestive heart failure and stroke. All participants underwent resting echocardiography using an Acuson Sequoia ultrasound system (Mountain View, California) with a 3.5 MHz transducer. Standard 2-dimensional views and performed planimetry with a computerized digitization system were obtained to determine left ventricular ejection fraction (LVEF). Smoking was determined by self-report, and BMI (kg/m^2) was assessed. Participants were instructed to bring their medication bottles to their appointment, and study personnel recorded all current medications, including dose and frequency use.

Assessment of depressive symptoms

The 9-item Patient Health Questionnaire (PHQ) (10) was used to determine the presence and severity of the 9 depressive symptoms of the Diagnostic and Statistic Manual-IV (DSM-IV). The PHQ is a self report checklist derived from the interview used in the Primary Care Evaluation of Mental Disorders (21). This instrument measures the presence of depressive symptoms during the previous two weeks, each scored as: not at all (0), several days (1), more than half the days (2), or nearly every day (3).

This study evaluated the effect of each depressive symptom both as a dichotomous variable using the standard cutpoint of ≥2 for the presence of the first 8 depressive symptoms and ≥1 for the presence of the symptom suicidal ideation (in concordance with the manual) (10), and as log-transformed continuous variables. The nine symptoms of depression in the PHQ, based on the DSM-IV classification of depression, include; I) depressed mood, II) loss of interest, III) appetite problems, IV) sleeping difficulties, V) psychomotor agitation/retardation, VI) fatigue, VII) feelings of worthlessness, VIII) concentration problems, IX) suicidal ideation.

Somatic and cognitive depressive symptoms

Following earlier work, depressive symptoms were categorized as follows: depressed mood, lack of interest, worthlessness, concentration problems and suicidal ideation were considered to be cognitive symptoms. Appetite problems, sleeping difficulties, psychomotor agitation/retardation and fatigue were considered to be somatic symptoms (18,19).

Endpoints and follow-up

After the baseline examination, we conducted annual telephone follow-up interviews with participants (or their proxy), asking specifically about hospitalization for “heart trouble.” For any reported event, medical records, EKGs, death certificates, and coroner’s reports were
retrieved and reviewed by two independent blinded adjudicators. In the event of disagreement, the adjudicators conferred, reconsidered their classification, and requested consultation from a third blinded adjudicator as necessary. The primary study endpoints were cardiovascular events, including heart failure, myocardial infarction, stroke, transient ischemic attack, or death.

For patients to be diagnosed with heart failure, they had to be hospitalized for a clinical syndrome meeting at least two of the following criteria: paroxysmal nocturnal dyspnea, orthopnea, elevated jugular venous pressure, pulmonary rales, third heart sound, cardiomegaly or pulmonary edema on chest radiography. A clear change in these symptoms from the patients’ usual clinical status and either peripheral hypoperfusion (in the absence of other causes) or peripheral or pulmonary edema requiring intravenous diuretic inotropic, or vasodilator therapy was a necessary condition (22). Standard criteria were used for defining non-fatal MI (23). Stroke was defined as new neurological deficit, which must not have been the result of brain trauma, tumor, infection or other cause. Transient ischemic attack was defined as a focal neurological deficit (in the absence of head trauma) lasting between 30 seconds and 24 hours, with rapid evolution of the symptoms to the maximal level of deficit in less than 5 minutes and with subsequent complete resolution. Death was determined by death certificates and coroner’s reports.

**Statistical analysis**

We used Cox proportional hazards regression (i.e. survival analysis) to estimate the differential effects of the nine depressive symptoms on cardiac events. Hazard ratios (HR) with 95% confidence intervals (CI) are reported. The Cox regression procedure is a method of estimating time-to-event models in the presence of censored cases. Cases are censored either at the occurrence of the first cardiovascular event or at the end of follow-up, whichever comes first. Cox regression analyses were conducted for evaluating the effects of each specific depressive symptom, controlling for age and gender. Second, multivariate effects were evaluated after controlling for variables previously found to predict cardiovascular events in this cohort (age, gender, diabetes mellitus, history of MI, history of stroke, history of heart failure, LVEF, BMI, smoking) (22) and for use of cardioprotective medications (aspirin, beta blocker, statin, and renin-angiotensin system inhibitor). Each depressive symptom was entered both as a log-transformed continuous variable and as a dichotomous variable. Interactions were checked between the specific depressive symptoms and gender and age. All statistical analyses were performed using SPSS version 14.0.

**Results**

Of the 1024 enrolled CHD patients, 1019 (>99%) were available for follow-up. Patient characteristics are presented in Table 1. The prevalence of each specific depressive symptom is presented in Table 2. A total of 399 events occurred (myocardial infarction, heart failure, stroke, TIA or death) during an average of 6.1 ± 2.0 years follow-up.

In age-adjusted analyses, both somatic and cognitive symptoms were associated with an increased risk of cardiovascular events. The annual rate of events ranged from 5.9% among those with no somatic symptoms to 12.6% among those with 4 somatic symptoms, and from 6.4% among those with no cognitive symptoms to 11.4% among those with 5 cognitive symptoms (Figure 1). Each somatic symptom was associated with a 21% increased rate of cardiovascular events (HR:1.21;95%CI:1.11–1.31; p<.0001), and this association remained strong after adjustment for potential confounding variables (HR:1.14;95%CI:1.05–1.24) (Table 2). Each cognitive symptom was associated with a 12% increased rate of cardiovascular events in age-adjusted analyses (HR:1.12;95%CI:1.03–1.21;p=0.006). After
further adjustment for potential confounding variables, the cognitive sumscore did not significantly predict cardiovascular events (HR: 1.08; 95% CI: 0.99–1.17; p = 0.09).

When entered as dichotomous variables, several symptoms were associated with cardiovascular events in age adjusted models. After further adjustment for age, gender, diabetes mellitus, history of MI, history of stroke, history of heart failure, left ventricular ejection fraction, body mass index, smoking, and use of cardioprotective medications, 3 of the somatic symptoms (fatigue, appetite problems and sleeping difficulties) were independently predictive of cardiovascular events (Table 2). These were also the 3 most common symptoms. None of the cognitive symptoms were independently predictive of cardiovascular events. We observed no evidence for an interaction of specific depressive symptoms with age or gender in predicting cardiovascular events (all p values for interaction = NS). In Figure 2 the HRs and 95% CI of specific depressive symptoms with cardiovascular events are visualised in a forest plot.

When each depressive symptom was entered as a log-transformed continuous variable, the following symptoms were associated with poor cardiac prognosis: fatigue (p = 0.0001), appetite problems (p < 0.0001), sleeping difficulties (p = 0.03), depressed mood (p = 0.005), and suicidal ideation (p = 0.02) (Table 3). After multivariable adjustment, only fatigue and appetite problems remained significantly associated with cardiovascular events. Thus, when entered as continuous variables, 2 out of 4 somatic symptoms and none of the cognitive symptoms were independently predictive of cardiovascular events (Table 3).

Discussion

In a sample of 1,019 patients with stable coronary heart disease, we evaluated the association between specific symptoms of depression and cardiovascular events. Both somatic and cognitive symptoms were associated with an increased risk of cardiovascular events. However, after adjustment for cardiovascular risk factors and disease severity, somatic symptoms appeared to be more strongly predictive of cardiovascular events than cognitive symptoms of depression. Fatigue, appetite problems, and sleeping difficulties were the symptoms most strongly predictive of cardiovascular events. These results may be of importance for identifying depressed patients who are at highest risk of developing cardiovascular events and for identifying potential therapies to improve cardiovascular outcomes in CHD patients.

Earlier studies have found that somatic symptoms of depression are more strongly predictive of cardiovascular events than cognitive symptoms of depression (14, 16–18). However, given the high prevalence of somatic symptoms such as fatigue, loss of appetite and sleeping difficulties in patients following myocardial infarction, it was unclear whether these findings were restricted to this patient population. Our study extends these findings to outpatients with stable coronary heart disease by demonstrating that somatic symptoms are more strongly predictive of cardiovascular events in this patient population.

It is difficult to ascertain whether somatic depressive symptoms are due to depression or to worse underlying heart disease. Indeed, based on our findings, one might conclude that general somatic malaise or fatigue (and not depression) is the predictor of poor outcomes. However, we tried to overcome this difficulty by carefully measuring and adjusting for history of myocardial infarction, diabetes, left ventricular ejection fraction, smoking, body mass index, and use of cardio-protective medications. The extent to which differences in these variables explained the effect of somatic symptoms on cardiovascular events appeared to be limited, as bivariate and adjusted effects on cardiovascular prognosis were highly comparable. In addition, we purposefully enrolled a uniform sample of patients with stable...
CHD so that the association between depressive symptoms and cardiac prognosis would not be confounded by the severity of a recent acute coronary event. Finally, although fatigue, appetite problems and sleeping difficulties were the strongest predictors of cardiovascular events, these were also the most common depressive symptoms in this population. For example, depressed mood was associated with a 32% increased rate of cardiovascular events (HR 1.32, 0.97–1.80; p=0.08), but only 114 participants had depressed mood. In contrast, fatigue was associated with a 34% increased rate of cardiovascular events, but the 267 participants with fatigue yielded a tighter confidence interval (HR 1.34, 95% CI, 1.07–1.67; p=0.01). Thus, the lack of association between cognitive symptoms and cardiovascular events may be due in part to smaller numbers of patients with cognitive symptoms.

In this study specific depressive symptoms based on the PHQ were used. Major depressive disorder as measured by the computerized Diagnostic Interview Schedule did not predict cardiovascular events in the Heart and Soul Study (22), whereas self-reported depressive symptoms as measured by the PHQ strongly predicted cardiovascular events. It is unclear why this discrepancy occurred. It is possible that participants felt more comfortable reporting depressive symptoms on an anonymous questionnaire than in a face-to-face interview, making the interview a less accurate measure of depression.

Only one randomized trial has been adequately powered to evaluate the effect of depression treatment on cardiovascular prognosis in CAD patients. The Enhancing Recovery in Coronary Heart Disease Patients (ENRICHD) trial showed that cognitive behavioural therapy decreased depression and improved social support, but did not affect cardiovascular prognosis. One possible explanation for the lack of benefit is that patients with CHD may have depressive symptoms below the threshold levels required for antidepressant treatment to be of benefit. Two recent studies (24,25) have suggested that patients with lower grade depression may not benefit from antidepressant treatment as much as those with more severe symptoms. If most patients with CHD have low levels of depressive symptoms, then antidepressant treatment might not be effective. Although some non-randomised studies of post-MI patients have shown that use of antidepressants or a reduction in depressive symptoms was associated with a decreased risk of cardiovascular events (26–28), the observational design of these studies prevents a firm conclusion regarding causality, however.

Our current findings provide further support for the conceptualisation of depression as a heterogeneous syndrome in which some aspects may be more strongly related to cardiovascular prognosis than others. This raises the possibility that, in order to improve cardiovascular outcome, interventions for depression should be specifically directed at somatic symptoms. Cognitive depressive symptoms, such as feelings of worthlessness and suicidal ideation, have been specific targets for intervention in psychotherapy (29), while exercise interventions, for example, may specifically improve somatic symptoms, perhaps even irrespective of depression (22,30). However, interventions for depression such as cognitive behavioral therapy or antidepressant medication therapy probably affect both cognitive and somatic symptoms, so the specificity with which somatic symptoms can be targeted with standard interventions for depression is unclear. Perhaps efforts should be made to improve rates of exercise uptake in CHD patients, regardless of depression status, particularly given the known CHD benefits of exercise and the very low rate of adherence to this basic recommendation in both depressed and non-depressed patients.

In order to achieve a better understanding of the syndrome of depression and to develop effective treatments, it is important to identify potential mechanisms that may underlie the association between depression and coronary disease (31). Earlier studies examined how depression may lead to adverse clinical outcome (32–35). In a previous report from the...
Heart and Soul Study it was concluded that somatic depressive symptoms were associated with lower heart rate variability, whereas cognitive depressive symptoms were not (19). There are also studies that point to inflammation as an important mechanism underlying the relation between depression and cardiovascular prognosis (36). Inflammation also may be more strongly associated with somatic than with cognitive depressive symptoms (33). Taken together, these results suggest that individual symptoms of depression may have differential associations with several mechanisms, leading to a worse cardiac prognosis. Understanding the mechanisms which may lead to the worse cardiac prognosis observed in depressed CHD patients will be crucial for the design of future trials (31). Future studies are therefore needed to evaluate the mechanisms that may be involved in the deleterious effects of sleeping difficulties, fatigue, appetite problems and psychomotor changes on cardiovascular prognosis.

The strengths of this study include the cohort size, prospective ascertainment of cardiovascular morbidity and mortality with a large number of events, and the detailed baseline assessment that allowed adjustment for important confounding variables. However, some limitations of this study should be noted. First, this study only included outpatients with stable CHD, thus it cannot comment on the differential effects of depressive symptoms in healthy people or in patients following acute coronary syndrome. Second, the participants in this study were mainly older men. Therefore, the results may not be generalizable to women or to other patient populations. However, we adjusted for age and gender and found no indication for any interaction with age or sex. Third, although depressive symptoms are independently associated with poor cardiovascular prognosis in patients with CHD, we cannot completely rule out the possibility that this association is confounded by worse underlying cardiovascular disease (37) or other comorbidities (38). Finally, although the hazard ratios and p values suggest that somatic symptoms were more strongly associated with depression than cognitive symptoms, the confidence intervals surrounding these estimates had substantial overlap, so further research is necessary before any definitive conclusions can be drawn.

In conclusion, we found that somatic symptoms of depression were responsible for the increased risk of cardiovascular events in patients with stable coronary heart disease. Hopefully, this finding may lead to the development of new treatments for depression in CHD patients. The result from this study indicate the need for future research directed to the identification of the underlying pathophysiological processes by which somatic depressive symptoms contribute to prognosis in CHD patients, and to the testing of interventions to alleviate the associated risk.

Acknowledgments

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Abbreviation list

- **BMI**: body mass index
- **CV**: cardiovascular

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CHF  congestive heart failure
CHD  coronary heart disease
DSM-IV  Diagnostic and Statistical Manual-IV
LVEF  left ventricular ejection fraction
MDD  major depressive disorder
RCT  major randomized controlled trials
MI  myocardial infarction
PHQ  Patients Health Questionnaire

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Figure 1. Age-adjusted annual rate of cardiovascular events (myocardial infarction, heart failure, stroke, transient ischemic attack or death) during an average of 6.1 years follow-up by number of somatic or cognitive depressive symptoms*
*Somatic sumscore = number of somatic symptoms with score of $\geq 2$; Cognitive sumscore = number of cognitive symptoms with score of $\geq 2$ (or $\geq 1$ for suicidal ideation)
Figure 2. Association between specific depressive symptoms (entered as a dichotomous variable) and cardiovascular events*
* Hazard ratio with 95% CI, adjusted for age, gender, diabetes mellitus, history of MI, history of stroke, history of heart failure, left ventricular ejection fraction, body mass index, smoking, aspirin, beta blocker, statin, and renin-angiotensin system inhibitor.
Table 1

Baseline characteristics of the study sample.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total sample (1019)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%) or mean ± SD</td>
</tr>
<tr>
<td>Age</td>
<td>67 ±11</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>836 (82)</td>
</tr>
<tr>
<td>Married</td>
<td>436 (43)</td>
</tr>
<tr>
<td>History of MI</td>
<td>545 (54)</td>
</tr>
<tr>
<td>History of CHF</td>
<td>179 (18)</td>
</tr>
<tr>
<td>History of stroke</td>
<td>148 (15)</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>265 (26)</td>
</tr>
<tr>
<td>Left ventricular ejection fraction</td>
<td>0.62 ± 0.10</td>
</tr>
<tr>
<td>Current smoking</td>
<td>199 (20)</td>
</tr>
<tr>
<td>Body Mass Index (kg/m²)</td>
<td>28 ±5</td>
</tr>
<tr>
<td>Aspirin</td>
<td>790 (78)</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>591 (58)</td>
</tr>
<tr>
<td>Statin</td>
<td>655 (64)</td>
</tr>
<tr>
<td>Renin-angiotensin system inhibitor</td>
<td>524 (51)</td>
</tr>
<tr>
<td>Antidepressant use</td>
<td>187 (18)</td>
</tr>
</tbody>
</table>
Table 2
Age-adjusted annual rate of cardiovascular events (MI, CHF, stroke, TIA or death) among participants with and without specific depressive symptoms

<table>
<thead>
<tr>
<th>Somatic symptoms</th>
<th>With symptom</th>
<th>Without symptom</th>
<th>Age-adjusted HR (95% CI)</th>
<th>P value</th>
<th>Fully adjusted HR (95% CI)*</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>267</td>
<td>746</td>
<td>1.49 (1.20–1.84)</td>
<td>0.0003</td>
<td>1.34 (1.07–1.67)</td>
<td>0.01</td>
</tr>
<tr>
<td>Appetite problems</td>
<td>160</td>
<td>858</td>
<td>1.76 (1.37–2.28)</td>
<td>&lt;.0001</td>
<td>1.46 (1.12–1.91)</td>
<td>0.005</td>
</tr>
<tr>
<td>Psychomotor</td>
<td>85</td>
<td>934</td>
<td>1.39 (0.99–1.95)</td>
<td>0.06</td>
<td>1.31 (0.93–1.85)</td>
<td>0.13</td>
</tr>
<tr>
<td>Agitation/retardation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleeping difficulties</td>
<td>249</td>
<td>766</td>
<td>1.38 (1.11–1.72)</td>
<td>0.004</td>
<td>1.26 (1.00–1.58)</td>
<td>0.05</td>
</tr>
<tr>
<td>Somatic sumscore†</td>
<td></td>
<td></td>
<td>1.21 (1.11–1.31)</td>
<td>&lt;.0001</td>
<td>1.14 (1.05–1.24)</td>
<td>0.002</td>
</tr>
<tr>
<td>Cognitive symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depressed mood</td>
<td>114</td>
<td>900</td>
<td>1.48 (1.10–1.99)</td>
<td>0.01</td>
<td>1.32 (0.97–1.80)</td>
<td>0.08</td>
</tr>
<tr>
<td>Lack of interest</td>
<td>129</td>
<td>889</td>
<td>1.50 (1.14–1.97)</td>
<td>0.004</td>
<td>1.21 (0.91–1.61)</td>
<td>0.19</td>
</tr>
<tr>
<td>Worthlessness</td>
<td>114</td>
<td>904</td>
<td>1.36 (0.99–1.86)</td>
<td>0.06</td>
<td>1.22 (0.88–1.69)</td>
<td>0.23</td>
</tr>
<tr>
<td>Concentration problems</td>
<td>129</td>
<td>890</td>
<td>1.22 (0.90–1.64)</td>
<td>0.19</td>
<td>1.10 (0.81–1.49)</td>
<td>0.55</td>
</tr>
<tr>
<td>Suicidal ideation</td>
<td>111</td>
<td>908</td>
<td>1.26 (0.92–1.71)</td>
<td>0.15</td>
<td>1.25 (0.91–1.72)</td>
<td>0.18</td>
</tr>
<tr>
<td>Cognitive sumscore†</td>
<td></td>
<td></td>
<td>1.12 (1.03–1.21)</td>
<td>0.006</td>
<td>1.08 (0.99–1.17)</td>
<td>0.09</td>
</tr>
</tbody>
</table>

* Adjusted for age, sex, diabetes mellitus, history of MI, history of stroke, history of heart failure, left ventricular ejection fraction, body mass index, smoking aspirin, beta blocker, statin, and renin-angiotensin system inhibitor
† entered as a continuous variable
Table 3

Bivariate and multivariate associations of specific depressive symptoms (entered as continuous variables) with cardiovascular events.

<table>
<thead>
<tr>
<th></th>
<th>Hazard ratio* (95% CI)</th>
<th>P-value*</th>
<th>Hazard ratio† (95% CI)</th>
<th>P-value†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Somatic symptoms</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>1.21 (1.10–1.33)</td>
<td>0.0001</td>
<td>1.15 (1.04–1.27)</td>
<td>0.007</td>
</tr>
<tr>
<td>Appetite problems</td>
<td>1.27 (1.15–1.41)</td>
<td>&lt;0.0001</td>
<td>1.17 (1.06–1.30)</td>
<td>0.003</td>
</tr>
<tr>
<td>Psychomotor agitation/retardation</td>
<td>1.14 (1.00–1.29)</td>
<td>0.05</td>
<td>1.12 (0.98–1.28)</td>
<td>0.10</td>
</tr>
<tr>
<td>Sleeping difficulties</td>
<td>1.11 (1.01–1.21)</td>
<td>0.03</td>
<td>1.07 (0.98–1.18)</td>
<td>0.14</td>
</tr>
<tr>
<td><strong>Cognitive symptoms</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lack of interest</td>
<td>1.11 (0.99–1.25)</td>
<td>0.07</td>
<td>1.04 (0.93–1.17)</td>
<td>0.48</td>
</tr>
<tr>
<td>Depressed mood</td>
<td>1.19 (1.05–1.33)</td>
<td>0.005</td>
<td>1.13 (1.00–1.28)</td>
<td>0.05</td>
</tr>
<tr>
<td>Worthlessness</td>
<td>1.11 (0.98–1.26)</td>
<td>0.09</td>
<td>1.10 (0.97–1.25)</td>
<td>0.15</td>
</tr>
<tr>
<td>Concentration problems</td>
<td>1.02 (0.90–1.15)</td>
<td>0.75</td>
<td>1.00 (0.88–1.13)</td>
<td>0.94</td>
</tr>
<tr>
<td>Suicidal ideation</td>
<td>1.25 (1.03–1.53)</td>
<td>0.02</td>
<td>1.14 (0.94–1.39)</td>
<td>0.19</td>
</tr>
</tbody>
</table>

* Adjusted for age and gender
† Adjusted for age, gender, diabetes mellitus, history of MI, history of stroke, history of heart failure, left ventricular ejection fraction, body mass index, smoking aspirin, beta blocker, statin, and renin-angiotensin system inhibitor