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Depressive symptoms in persons with acute coronary syndrome: specific symptom scales and prognosis

Frank Doyle

Royal College of Surgeons in Ireland, fdoyl4@rcsi.ie

Ronán Conroy

Royal College of Surgeons in Ireland

Hannah McGee

Royal College of Surgeons in Ireland

Mary Delaney

Royal College of Surgeons in Ireland

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Depressive symptoms in persons with acute coronary syndrome: specific symptom scales and prognosis

Objective

To determine which particular depressive symptom scales, derived from three scales, predicted poorer prognosis in persons with acute coronary syndrome (ACS).

Methods

Hospitalised ACS patients (n=408) completed questionnaires (depression, vital exhaustion). Mokken scaling derived unidimensional scales. Major cardiac events (cardiac mortality, ACS, unplanned revascularisation) were assessed at median 67 weeks post-event.

Results

Only depressive symptoms of fatigue-sadness predicted prognosis in univariate (hazard ratio [HR]=1.8, 95% CI 1.1–3.0, p=0.025) and multivariate analysis (HR=1.8, 95% CI 1.1–2.9, p=0.025). Symptoms of anhedonia (HR=1.6, 95% CI 0.9–2.8, p=0.102) and depressive cognitions (HR=1.3, 95% CI 0.7–2.2, p=0.402) did not.

Conclusion

Symptoms of fatigue-sadness, but not other symptoms, were associated with increased risk of major cardiac events. Depression should be considered as a multidimensional, rather than a unidimensional, entity when designing interventions.

Introduction

Depression has been consistently associated with a two-fold risk of recurrent cardiac events or mortality in those with coronary heart disease (CHD),¹⁻³ yet the treatment of depressive symptoms does not improve prognosis.^{4,5} However, depression is a very heterogeneous construct, and there may be little symptom overlap among those labelled as 'depressed'. For example, one person could experience depressed mood, anergia, substantial weight variation, sleep variation and psychomotor retardation/agitation; and another could report anhedonia, worthlessness/guilt, impaired concentration, indecisiveness or difficulty thinking, or suicidal ideation. Yet, assuming that other criteria are also met, both would be labelled with the diagnosis 'major depressive disorder', according to DSM-IV.⁶ Therefore, when researchers state that depression is associated with poorer cardiovascular prognosis, it is appropriate to ask whether specific symptoms are more associated with poorer prognosis than others.^{7,8}

Previous research has suggested that particular depressive symptoms may be more pertinent for prognosis than others.^{7,9-12} **Doyle et al.¹² compared the HADS depression subscale (HADS-D; n=316) and the fast-screen 7-item version of the Beck Depression Inventory (which does not assess somatic symptoms – BDI-FS; n=282) in independent groups of patients with acute coronary syndrome (ACS).** At one year, those who were depressed according to the HADS-D, which concentrates on anhedonia, had a significantly increased risk of all-cause mortality, while those scoring above the threshold on the BDI-FS did not. The authors concluded that anhedonia may be particularly cardiotoxic, but that the single anhedonia item on the BDI-FS may not be powerful enough to detect risk. Unfortunately, due to the assessment of independent samples, the scales could not be directly compared through latent variable analytic techniques. A factor analysis of the BDI in 2466 patients with myocardial infarction found two main factors comprising cognitive/affective symptoms, and somatic/affective symptoms.¹⁰ Only the somatic/affective factor was predictive of poorer prognosis over a mean of 2.5 years. These findings are difficult to interpret for a number of

reasons. **Somatic symptoms may be confounded by coronary disease, treatment or comorbidity factors, and these symptoms are not required for a diagnosis of major depression except in terms of number of symptoms. Therefore, using total scores on depression scales may indicate those who report symptoms akin to depression, but who do not endorse the core diagnostic symptoms – and who should therefore be regarded as false positives. Thus, it could be argued that if depression really predicts prognosis, then the core diagnostic symptoms of depression – depressed mood, anhedonia,⁶ and anergia¹³ – should be predicting outcomes. However, the symptom of depressed mood (sadness) loaded on both factors in the analysis by de Jonge et al.¹⁰ described above, rendering interpretation of the findings difficult.¹⁴ Indeed, this criticism can be made of factor analysis in general, which allows items to cross-load during latent variable analysis. Another problem with factor analysis is that binary items may lead to bias for which non-specialist statistical software does not adjust, and it may also be affected by extremely skewed distributions,^{15,16} such as typically found with BDI items. Therefore, alternative latent variable methods should be used to derive specific unidimensional symptom scales from aggregated data.**

In sum, the use of heterogeneous depression scales and symptoms,⁷ and reliance on factor analytic techniques, may limit research pinpointing cardiotoxic symptoms of depression. The present study aims to replicate and extend previous findings,¹² using different depression scales to predict prognosis. We included a measure of 'vital exhaustion' (symptoms of fatigue and demoralisation which are unrelated to cardiovascular disease severity, and which are argued to be independent of depression^{17,18}), to assess the core depressive symptom of anergia.¹³ The aims of the present paper were therefore:

- 1) to replicate previous findings¹² and to determine whether certain scales were better prognostic predictors, or more generally whether scoring above threshold on any scale predicted prognosis

2) to derive specific symptom scales in order to predict prognosis. We hypothesised that specific symptom scales would be derived, reflecting the core symptoms of depressed mood, anhedonia, and fatigue, along with another scale indicative of depressive cognitions (low self-esteem, worthlessness).

Method

Study design and participants

A prospective cohort study design was used to determine the association of depressive symptoms with major adverse cardiovascular events (MACE) - a combination of cardiovascular mortality, recurrent ACS or unplanned revascularisation. Non-cardiac mortality was omitted. Ethical approval was obtained. As scoring above cut-off on two of the scales was previously demonstrated to be associated with poorer prognosis,¹² patients' medical teams or general practitioners were informed if patients scored above the 90th percentile of normative data. Across 12 participating hospitals, consecutive patients with confirmed ACS were invited to participate in the survey. Staff could choose not to recruit a participant if they deemed the patient to be too distressed.¹⁹ Each centre was awarded a nominal fee (€10) per patient recruited, which was paid to the relevant Coronary Care fund. Relevant medical risk factors were collated for each participant. **Medical records were accessed one year after recruitment. Patients were recruited from January 2006 to September 2007, with final chart access in September 2008.**

Measures

Hospital Anxiety and Depression Scale – Depression subscale (HADS-D)

The HADS-D is a 7-item depression scale,²⁰ with an optimal threshold score of >7 ,²¹⁻²³ which was adopted in the present study. The HADS-D has an average sensitivity and specificity of approximately 0.80 for the identification of major depression.²²

Beck Depression Inventory – Fast Screen (BDI-FS)

The BDI-FS is a 7-item scale that focuses on cognitive symptoms of DSM-IV criteria,^{24,25} with a recommended cut-off score of >3 that yields a sensitivity of >0.90 and specificity of >0.85 for detecting major depressive disorders.^{26,27} We omitted the suicidality item of the BDI-FS as it was not predictive of one-year mortality outcomes in unpublished analyses from a previous study, and did not correlate well with other scale items.¹² Also, the suicidality question may be considered intrusive by patients, thus lessening the likelihood of a response.²⁸ Thus, a 6-item BDI-FS was used with the recommended threshold (>3) maintained.

Maastricht Questionnaire – 10 item (MQ-10)

The brief 10-item version of the Maastricht Questionnaire (MQ-10) was used as a measure of anergia.²⁹ The scale items are scored as binary (yes=1, no=0). The recommended cut-off (>4) was used. Predictive validity has been reported previously.²⁹

Co-morbidities

Major co-morbidities were recorded and recoded as per the Charlson Comorbidity Index (CCI).^{30,31} To prevent subsequent multicollinearity with variables assessed separately (i.e. history of MI, heart failure diabetes), a second, modified CCI total score was generated omitting these items.

Statistics

Mokken scaling

Mokken scaling is a non-parametric, iterative scale-building technique, suitable for skewed and binary items. It is based on Guttman scaling, which forms a unidimensional, ordinal scale of binary items along a continuum. Thus, a positive response to one particular item indicates which of the other items have also been answered positively. For example, if someone indicates that they are ‘very depressed’ (the most ‘difficult’ item), they should also have endorsed the less extreme choices of ‘somewhat depressed’ and ‘moderately depressed’. Mokken scaling is a stochastic version of Guttman scaling which can also use

polytomous items, and uses Loevinger's H statistic as an indicator of scale fit.³² The H-value represents $[1 - (\text{observed Guttman errors}/\text{predicted Guttman errors})]$. Observed Guttman errors are the number of times a 'mistake' is made by respondents as items are endorsed as if *not* in an ordered sequence, and expected Guttman errors are the probability that the items are chosen by chance. Thus, a co-efficient of ≤ 0.5 represents a scale with items at a maximum 50% Guttman error rate. By convention, $0.3 \geq c < 0.4$, $0.4 \geq c < 0.5$ and $c \geq 0.5$ indicate weak, moderate and strong scales respectively. To derive specific symptom scales, a recommended procedure was followed.¹⁶ It was expected that a high co-efficient (approximately $c > 0.5$) would be required, and only such results are presented. Mokken scale analysis was conducted using a procedure written for Stata SE 9.2³³ by Jean-Benoit Hardouin.³⁴

Generating scale scores for derived symptom scales

To generate total scale scores in the present study, all items within any scales with binary items were collapsed into binary (e.g. for the fatigue-sadness scale 79% of participants endorsed a score of zero on the BDI-FS item, this item was collapsed by recoding the other options as 1). This allowed the items to be totalled. For the anhedonia scale, all items were 4-point options, so this was totalled. These adjustments had negligible impact on the overall scale Loevinger H co-efficient (data not shown), indicating that no precision was lost. **In order to directly compare the effect sizes of the derived scales in prognostic analyses**, these were then divided into top quartiles (1) and other (0).

Missing data

Missing data was imputed using regression techniques, which compares very favourably with other missing data techniques.³⁵ Missing data on scale items were calculated from other scale items, age and sex. For example, if a participant did not answer BDI-FS item 3, the score was imputed from the following variables (BDI-FS items 1, 2, 4, 5, 6, age, sex). Imputation ranged from 1-10% for all items.

Multi-site cluster sampling

Analysis was conducted using robust variance estimation commands to account for original clustering of patients within hospitals. Patients in the same hospital will be more similar – i.e. correlated – than patients randomly sampled from the entire population. This leads to underestimation of standard errors and confidence intervals and a greater than 5% rate of type I errors. Huber-White robust variance estimation adjusted standard errors (and therefore confidence intervals and significance tests) for the homogeneity introduced by cluster sampling.

Multivariate predictors of MACE

Odds-ratios (ORs) were elicited using logistic regression when comparing those with elevated scale scores to those without. Cox regression was used to elicit hazard ratios (HRs) for event occurrence. **To prevent overfitting, a restricted multivariate model was required, dependant on the number of MACE.**³⁶ In order to **manually** build a multivariate model, non-psychometric variables which predicted endpoints with a p-value <.15 were included in a multivariate model (age, sex, smoking, diabetes, history of CHD, history of revascularisation, length of hospital stay, left ventricular function <40%). Incomplete data was available for employment status, and this variable was therefore omitted. Variables which had a p-value >0.5 were immediately deleted. After this, any covariate with a p-value <.15 was retained. Age was initially analysed as a continuous variable. However, further investigation showed that there was clear evidence of a threshold effect for survival. Those over 65 years of age were at increased risk, but younger age categories did not differ (data not shown). Age was therefore used as a categorical variable (over 65 years versus younger). Psychometric variables were then added to this multivariate model.

Results

Study participation

In terms of demographic variables, there was no difference in age, sex, having private health insurance, or working status between those who responded to the questionnaire when compared to those who did not (data not shown).

Sample profile

Of the 505 eligible patients invited to participate, 430 completed the composite questionnaire (85% response rate), and scaling analysis was conducted on all 430 questionnaires (Fig 1). **Baseline risk factor, demographic and recurrent ACS information was available from medical charts of 408 participants who completed a questionnaire (95%).**

Fig 1 here

Descriptive statistics [prevalence scoring above threshold (mean, standard deviation)] for each of the scales was as follows: HADS-D – 11% (3.5, 3.0), BDI-FS – 24% (2.1, 2.7), MQ-10 – 43% (4.2, 2.9). Combining these scales, 49% (212/430) of the sample were found to have elevated depressive symptoms of some form.

Table 1 shows the profile of the sample, comparing those who had elevated depressive symptoms to those who had not. Those with depression were more likely to be smokers, have diabetes, have a positive history of CHD and subsequent revascularisation, but less likely to be employed. Depressed persons also had slightly lower total cholesterol, but there was substantial missing data for employment and cholesterol. Depressed persons were also less likely to have experienced a cardiac arrest. No age or gender differences were significant, but there were trends for those with depression to be younger and female.

Table 1 about here

Table 1 also shows univariate prognostic information for demographic, CHD risk factor, disease severity and co-morbidity variables. Age over 65, having a history of diabetes, CHD or revascularisation, having a longer hospital stay and having left ventricular function <40% all increased the hazard of endpoints. Smoking and being employed were protective of events. CCI total score was associated with endpoints, but the modified CCI score was not.

In multivariate analysis using the described technique, the following variables were retained: age, sex, history of CHD and length of hospital stay (data not shown).

Mokken scaling

Overall, three 'strong' scales are derived from the data (Table 2). The first scale, which is 9 items, assessed a 'fatigue-sadness' cluster of symptoms. Five of the items clearly address fatigue, and are from the MQ-10. Other items are either ambiguous or address an element of hopelessness (MQ-10 8, 9, 7), or address sadness (BDI-FS 1). The sadness item was the last to join the scale (items towards the top of the table display the most 'difficult' items, i.e. the items least likely to be endorsed, and vice versa).

The second scale clearly measures the symptom of anhedonia. That the single BDI-FS anhedonia item joins with these HADS-D anhedonia items provides this scale with good content validity.

The final derived scale from the state depression items clearly assessed perceptions of worthlessness, pessimism and overall negative cognition. This scale is labelled 'depressive cognitions'.

Psychometric predictors of MACE

Original depression scales

Univariate and multivariate analyses of the original and derived scales are displayed in Table 3.

Table 3 here

Scoring above threshold on the HADS-D was a significant predictor of MACE in univariate and multivariate analysis, but no other scale was significant. This association was not attenuated when controlling for other depressive symptom scales (data not shown).

In order to assess whether depressive symptoms in general were predicting risk, data were combined. Scoring above threshold on any of the HADS-D, BDI-FS or MQ-10 was not associated with outcome (HR=1.2, 95% 0.7–1.9 CI, p=0.572).

Derived depressive symptom scales

In univariate analyses with the derived scales, only fatigue-sadness was predictive of outcome (Table 3). Fatigue-sadness also predicted MACE in multivariate analysis. However, anhedonia also predicted MACE in adjusted analyses. Depressive cognitions remained non-significant. When both fatigue-sadness and anhedonia were included in the multivariate models, fatigue-sadness predicted MACE (HR=1.8, 95% CI 1.02–3.4, p=0.045), but anhedonia did not (HR=1.4, 95% CI 0.8–2.3, p=0.237) (other model data not shown). The Kaplan-Meier survival curves for derived scales are shown in Fig 2.

Fig 2 here

Discussion

The present study was the first to use Mokken scaling in ACS patients in an attempt to derive unidimensional, 'pure' symptom scales and predict prognosis. The study also replicated findings published previously. Results are discussed in terms of Mokken scaling, prognostic findings and implications for interventions. **Although the current sample are largely comparable to a previous Irish cohort,¹² smoking was surprisingly protective of MACE, which is probably accounted for by a younger age of presentation in smokers (data not shown).**

Scaling results

Mokken scaling has been successfully used in previous research to derive ordinal and unidimensional scales from original questionnaires, including depression.^{16,37-39} In the present study, the items broke down into several specific scales, which only partially supported the hypothesised scales of depressed mood, anhedonia, fatigue and depressive cognitions. The first scale derived was labelled "fatigue-sadness". The items in this scale clearly addressed fatigue, sadness and possibly the element of hopelessness. Thus, the first derived scale was reflective of two of the core diagnostic symptoms of depression, and the symptom of hopelessness which is not a requirement for either ICD-10 or DSM-IV criteria. The BDI-FS sadness item was the most 'difficult' item to endorse in the fatigue-sadness scale, but it clustered with MQ-10 fatigue items throughout several analyses of varying thresholds (data not shown). Similar findings have been reported previously in confirmatory factor analyses, with fatigue and sadness loading on the same factor.^{10,40,41} The rest of the scale also incorporated items which could be argued to assess a level of pessimistic views of the future, although overall this scale is indicative of fatigue. It is plausible that such symptoms would cluster together in a clinical setting.

The next derived scale was labelled 'anhedonia'. It consisted of three HADS-D items (4, 2, 12) and the one anhedonia item (4) from the BDI-FS. The fact that the BDI-FS items scaled with the HADS-D anhedonia items gives this scale excellent content validity. This can be considered a 'pure' symptom

scale that assesses one of the core diagnostic symptoms of major depression. Thombs et al.,⁴⁰ during a confirmatory factor analysis of the BDI-II, also found evidence of a two-item 'pure' anhedonia factor that scaled separately to cognitive or somatic factors.

The last scale derived supports the hypothesis of a 'depressive cognitions' scale. This consists of three BDI-FS items (5, 2, 3) and the crying item (10) from the MQ-10. It appears that this measures the state of thinking negatively about oneself and feeling bad about it. This also supports previous work which has shown such cognitive symptoms cluster together in cardiac patients.¹⁰

Original depression scales and prognosis

When analysing the scales as recommended, the HADS-D was predictive of MACE, but the BDI-FS was not, replicating previous research.¹² Other prognostic research using the HADS-D has shown mixed findings.^{11,42-44} One reason for this is that the HADS-D may assess something particular in the Irish population, which is not assessed by other scales. The HADS-D, while concentrating mainly on anhedonia, also contains items which could be argued to assess other elements of depression. Item 8 could be argued to assess fatigue. This item combination may mean that, of the scales used here, the overall HADS-D score is the best measure of the hypothesised cardiotoxic symptoms.⁷

Although the BDI-FS did not predict outcomes, an inspection of individual items showed that item 1 'Sadness' was predictive of MACE (data not shown). Thus, this single item was not sensitive enough to predict outcomes when combined in a cluster of other items which mainly assessed depressive cognitions.

The MQ-10 was not a predictor of MACE. This contrasts with previous findings, which showed that this scale was predictive of both onset of cardiac events and prognosis post-event in Dutch samples.²⁹ The MQ-10 has not previously been validated in an Irish sample, which may explain the findings.

The present study also attempted to determine whether depressive symptoms in general were predictors of prognosis. Combining data using recommended thresholds showed no association with prognosis. This may partially explain heterogeneous findings regarding depression and prognosis,^{1,7} and provides support for the investigation of specific symptom patterns.

Derived symptom scales and prognosis

It was hypothesised that if the core symptoms of depressed mood, anhedonia, or fatigue predicted prognosis, then this may provide evidence of depression being a risk factor for clinical outcomes. The results showed that fatigue-sadness was a significant predictor of MACE, and that this association survived multivariate adjustment. Poor left ventricular function has been hypothesised to account for the relationship between depression and outcomes.¹ However, this variable was not significant in the present multivariate model, and was therefore excluded from most analyses. However, in analysis including left ventricular function of <40%, the association between fatigue-sadness and MACE was not attenuated (data not shown). With low left ventricular function, symptoms of fatigue would probably be expected. That the association is still independent of this measure highlights the robustness of the findings. However, these results are clouded somewhat by the mixing of the fatigue and sadness items, but also by the items from the MQ-10 which appear to measure hopelessness or pessimistic future views. However, no individual MQ-10 items were associated with MACE (data not shown). Therefore, it is unlikely that these items were driving the association between the fatigue-sadness scale and outcomes – this was more likely to be the case for the BDI-FS sadness item. Alternatively, it may be the clustering of sadness and hopelessness and fatigue which was especially cardiotoxic.⁴⁵ Previous research addressing these issues has been inconsistent, and has used only single items to assess hopelessness.^{9,46} Further research is needed to extricate these issues, and should involve validated hopelessness scales.

The somewhat 'purer' anhedonia measure had somewhat comparable effect sizes to fatigue-sadness when predicting MACE. In multivariate analysis anhedonia was predictive of the endpoint. However, when fatigue-sadness was included in the model predicting MACE, the association between anhedonia and outcome was non-significant. This finding suggests that **the study did not have the power to consistently detect the association between anhedonia and MACE, or that** anhedonia may not be as important as fatigue-sadness for cardiovascular prognosis. One could speculate that the subtype of depression characterised by anhedonia is simply less cardiotoxic than that characterised by fatigue-sadness. It is possible that depression characterised by anhedonia may have differential behavioural or physiological sequelae than depression characterised by fatigue or sadness. Although other studies have been suggestive of associations with anhedonia and clinical events,^{11,12} no other study has been identified that has derived an anhedonia scale and assessed its relative predictive value in comparison to other symptoms.

The measures used should not be confounded by assessment of other somatic, heterogeneous symptoms that may simply be a reflection of comorbidities or CHD severity. Previous studies have also addressed the issue of potential confounding from somatic symptoms. Thombs et al.,⁴¹ when predicting outcomes in 477 MI patients, used structural equation modelling to partial out the variance of somatic symptoms that were unrelated to depression, but to still maintain variance from somatic symptoms that were related to depression. Although the general depression factor predicted 12-month all-cause mortality, it is unclear whether a factor without somatic symptoms would have predicted prognosis – de Jonge et al.¹⁰ found that such a factor was not associated with outcomes.

Depressive cognitions were not predictive of outcomes. This finding supports research outlined previously.^{10,41} Indeed, Martens et al.⁴⁷ showed that depressed cardiac patients demonstrate fewer such cognitions than do psychiatric samples. It is therefore questionable what scale items reflecting these depressive cognitions contribute to research in this area. It is possible

that, although perhaps clinically useful, these items are simply adding noise to data, especially total scale scores, when the primary aim is to predict prognosis. This would therefore question the recommendations of the National Heart, Lung, and Blood Institute Working Group Report on assessment and treatment of depression in patients with cardiovascular disease, which called for the use of the BDI in such research.⁴⁸ The cumulative evidence suggests that several BDI items should be ignored when considering cardiovascular prognosis in future research.

Limitations & Strengths

The present study has a number of strengths and limitations. We assessed cardiac events only, producing results which were not inflated by non-cardiac events. Analyses accounted for within-site variability – a technique not typically used in other multi-centre studies. It is possible that patients had recurrent ACS, but were admitted to hospitals other than their index admission centre, leading to an underestimation of events. **No data was available on possible depression treatments received post-event.** Also, follow-up was a median of approximately 15 months. There may be different results over a longer period.⁴⁹ **The number of endpoints and danger of overfitting did not allow for the adjustment of all cardiovascular and demographic covariates,³⁶ and therefore necessitated use of a less-than-ideal stepwise covariate adjustment technique.**

Previous research has suggested that the timing of the depressive episode is relevant for prognosis.^{19,50,51} This data was unfortunately unavailable in the present study, and it is therefore impossible to speculate whether symptoms of fatigue-sadness better reflect the new-onset depression which has been shown to be particularly cardiotoxic in other research.

It could be argued that the omission of somatic items is a weakness of the present study. However, such items have shown mixed results when predicting prognosis,^{10,52} and they may be confounded by coronary disease, treatment or comorbidity factors. Comorbidities were assessed, and did not account for the present findings. **Future research could also assess**

specific somatic symptoms, and compare these to other symptom scales when predicting prognosis.

Implications for practice and interventions

Given the failure of intervention trials to reduce depression and cardiovascular mortality, and increasing evidence that specific symptoms of depression are more cardiotoxic than others, it may be time to revisit the notion that the syndrome of major depression is a risk factor for poorer cardiovascular prognosis. The results of the present study suggest that depression is multidimensional, and that only some aspects of depression are relevant for poorer outcomes post-ACS. Furthermore, global measurements of depression severity could be re-considered. If specific cardiotoxic symptoms need to be the focus of intervention, they should be measured on several unidimensional scales, rather than a total score on a single multidimensional scale being adopted as a unidimensional variable. The adoption of multidimensional measures may throw more light on the results of intervention trials. This may be especially pertinent, given the recent findings which show that although tricyclic and serotonin reuptake inhibitors are equally efficacious when compared on total depression scale scores, they actually differ significantly in terms of which symptom dimensions they affect.^{53,54}

Conclusions

In the present study, only symptoms of fatigue-sadness consistently predicted prognosis, whereas anhedonia and depressive cognitions did not. Specific symptoms of depression may need to be considered when predicting cardiovascular outcomes. This suggests that depression should not be considered as a unidimensional state, but as a multidimensional one.

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References

1. Nicholson A, Kuper H, Hemingway H. Depression as an aetiologic and prognostic factor in coronary heart disease: a meta-analysis of 6362 events among 146 538 participants in 54 observational studies. *Eur Heart J* 2006;27(23):2763-74.
2. van Melle JP, de Jonge P, Spijkerman TA, et al. Prognostic association of depression following myocardial infarction with mortality and cardiovascular events: a meta-analysis. *Psychosom Med* 2004;66(6):814-822.
3. Barth J, Schumacher M, Herrmann-Lingen C. Depression as a risk factor for mortality in patients with coronary heart disease: a meta-analysis. *Psychosom Med* 2004;66(6):802-813.
4. The ENRICHD Investigators. Effects of treating depression and low perceived social support on clinical events after myocardial infarction: the Enhancing Recovery in Coronary Heart Disease Patients (ENRICHD) Randomized Trial. *JAMA* 2003;289(23):3106-3116.
5. van Melle JP, de Jonge P, Honig A, et al. Effects of antidepressant treatment following myocardial infarction. *Br J Psychiat* 2007;190:460-6.
6. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (text-revised), DSM-IV-TR. 4th ed. Washington, DC: American Psychiatric Association, 2000.
7. Doyle F, Conroy R, McGee H. Challenges in reducing depression-related mortality in cardiac populations: cognition, emotion, fatigue or personality? *Health Psychol Rev* 2007;1(2):137-72.
8. Carney RM, Freedland KE. Does treating depression improve survival after acute coronary syndrome?: Invited commentary on... Effects of antidepressant treatment following myocardial infarction. *Br J Psychiat* 2007;190:467-8.
9. Pedersen SS, Denollet J, Daemen J, et al. Fatigue, depressive symptoms, and hopelessness as predictors of adverse clinical events following percutaneous coronary intervention with paclitaxel-eluting stents. *J Psychosom Res* 2007;62(4):455-461.
10. de Jonge P, Ormel J, van den Brink RH, et al. Symptom dimensions of depression following myocardial infarction and their relationship with somatic health status and cardiovascular prognosis. *Am J Psychiat* 2006;163(1):138-44.
11. Herrmann C, Brand-Driehorst S, Buss U, Ruger U. Effects of anxiety and depression on 5-year mortality in 5,057 patients referred for exercise testing. *J Psychosom Res* 2000;48(4-5):455-462.
12. Doyle F, McGee HM, De La Harpe D, Shelley E, Conroy R. The Hospital Anxiety and Depression Scale depression subscale, but not the Beck Depression Inventory-Fast Scale, identifies patients with acute coronary syndrome at elevated risk of 1-year mortality. *J Psychosom Res* 2006;60(5):461-7.
13. World Health Organisation. The ICD-10 Classification of Mental and Behavioural Disorders: Diagnostic Criteria for Research. Geneva: WHO, 1993.
14. Thombs BD, Grace SL, Ziegelstein RC. Do symptom dimensions of depression following myocardial infarction relate differently to physical

- health indicators and cardiac prognosis? *Am J Psychiat* 2006;163(7):1295-6; author reply 1296.
15. Tabachnik BG, Fidell LS. Using multivariate statistics. 4th ed: Boston, Allyn & Bacon, 2000.
 16. Meijer RR, Baneke JJ. Analyzing psychopathology items: a case for nonparametric item response theory modeling. *Psychol Methods* 2004;9(3):354-68.
 17. Meesters C, Appels A. An interview to measure vital exhaustion. I. Development and comparison with the Maastricht Questionnaire. *Psychol Health* 1996;11(4):557-571.
 18. Meesters C, Appels A. An interview to measure vital exhaustion. II. Reliability and validity of the interview and correlations of vital exhaustion with personality characteristics. *Psychol Health* 1996;11(4):573-581.
 19. Dickens C, McGowan L, Percival C, et al. New onset depression following myocardial infarction predicts cardiac mortality. *Psychosom Med* 2008;70(4):450-5.
 20. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiat Scand* 1983;67(6):361-370.
 21. Herrmann C. International experiences with the Hospital Anxiety and Depression Scale--a review of validation data and clinical results. *J Psychosom Res* 1997;42(1):17-41.
 22. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. *J Psychosom Res* 2002;52(2):69-77.
 23. Roberts SB, Bonnici DM, Mackinnon AJ, Worcester MC. Psychometric evaluation of the Hospital Anxiety and Depression Scale (HADS) among female cardiac patients. *Br J Health Psychol* 2001;6:373-383.
 24. Beck AT, Guth D, Steer RA, Ball R. Screening for major depression disorders in medical inpatients with the Beck Depression Inventory for Primary Care. *Beh Res Ther* 1997;35(8):785-791.
 25. Beck AT, Steer RA, Brown GK. Manual for the Beck Depression Inventory-Fast Screen for Medical Patients. San Antonio, TX: Psychol Corporation, 2000.
 26. Beck AT, Steer RA, Ball R, Ciervo CA, Kabat M. Use of the Beck Anxiety and Depression Inventories for primary care with medical outpatients. *Assessment* 1997;4(3):211-219.
 27. Scheinthal SM, Steer RA, Giffin L, Beck AT. Evaluating geriatric medical outpatients with the Beck Depression Inventory-FastScreen for medical patients. *Aging Ment Health* 2001;5(2):143-148.
 28. McGee H, Doyle F, Delaharpe D, Shelley E, Conroy R. Impact of briefly-assessed depression on secondary prevention outcomes after acute coronary syndrome: a one-year longitudinal survey. *BMC Health Serv Res* 2006;6:9.
 29. Appels A. Een korte stresstest voor de poliklinische situatie. *Hart Bulletin* 2001;32(1):8-10.
 30. Han-Yi Wang, Ghee Chew, Kung C-T, Kun-Jung Chung, Lee W-H. The use of Charlson Comorbidity Index for patients revisiting the Emergency Department within 72 hours. *Chang Gung Med J* 2007;30(5):437-444.

31. Watkins LL, Schneiderman N, Blumenthal JA, et al. Cognitive and somatic symptoms of depression are associated with medical comorbidity in patients after acute myocardial infarction. *Am Heart J* 2003;146(1):48-54.
32. Watson R, Deary I, Austin E. Are personality trait items reliably more or less 'difficult'? Mokken scaling of the NEO-FFI. *Personality Individ Diff* 2007;43:1460-9.
33. Stata Statistical Software: Release 9 [program]. 9.2 version. College Station, TX: StataCorp LP, 2005.
34. MSP: Stata module to perform the Mokken Scale Procedure [program]: Boston College Department of Economics, 2004.
35. Shrive FM, Stuart H, Quan H, Ghali WA. Dealing with missing data in a multi-question depression scale: a comparison of imputation methods. *BMC Med Res Method* 2006;6:57.
36. Babyak MA. What you see may not be what you get: a brief, nontechnical introduction to overfitting in regression-type models. *Psychosom Med* 2004;66(3):411-21.
37. De Vries J, Michielsen HJ, Van Heck GL. Assessment of fatigue among working people: a comparison of six questionnaires. *Occup Environ Med* 2003;60 Suppl 1:i10-5.
38. Hemker BT, Sijtsma K, Molenaar IW. Selection of unidimensional scales from a multidimensional item bank in the polytomous Mokken IRT model. *Applied Psychol Meas* 1995;19(4):337-52.
39. Watson R, Deary IJ, Shipley B. A hierarchy of distress: Mokken scaling of the GHQ-30. *Psychol Med* 2008;38(4):575-9.
40. Thombs BD, Ziegelstein RC, Beck CA, Pilote L. A general factor model for the Beck Depression Inventory-II: Validation in a sample of patients hospitalized with acute myocardial infarction. *J Psychosom Res* 2008;65(2):115-21.
41. Thombs BD, Ziegelstein RC, Parakh K, Stewart DE, Abbey SE, Grace SL. Probit structural equation regression model: general depressive symptoms predicted post-myocardial infarction mortality after controlling for somatic symptoms of depression. *J Clinical Epidemiology* 2008;61(8):832-9.
42. Dickens C, McGowan L, Percival C, et al. Lack of a close confidant, but not depression, predicts further cardiac events after myocardial infarction. *Heart* 2004;90(5):518-22.
43. Mayou RA, Gill D, Thompson DR, et al. Depression and anxiety as predictors of outcome after myocardial infarction. *Psychosom Med* 2000;62(2):212-219.
44. Rothenbacher D, Hahmann H, Wusten B, Koenig W, Brenner H. Symptoms of anxiety and depression in patients with stable coronary heart disease: prognostic value and consideration of pathogenetic links. *Eur J Cardiovas Prev Rehabil* 2007;14(4):547-54.
45. Martens EJ, Smith OR, Denollet J. Psychol symptom clusters, psychiatric comorbidity and poor self-reported health status following myocardial infarction. *Ann Beh Med* 2007;34(1):87-94.
46. Barefoot JC, Brummett BH, Helms MJ, Mark DB, Siegler IC, Williams RB. Depressive symptoms and survival of patients with coronary artery disease. *Psychosom Med* 2000;62(6):790-5.

47. Martens EJ, Denollet J, Pedersen SS, et al. Relative lack of depressive cognitions in post-myocardial infarction depression. *J Affect Dis* 2006;94(1-3):231-7.
48. Davidson KW, Kupfer DJ, Bigger JT, et al. Assessment and treatment of depression in patients with cardiovascular disease: National Heart, Lung, and Blood Institute Working Group Report. *Psychosom Med* 2006;68(5):645-50.
49. Parakh K, Thombs BD, Fauerbach JA, Bush DE, Ziegelstein RC. Effect of depression on late (8 years) mortality after myocardial infarction. *Am J Card* 2008;101(5):602-6.
50. de Jonge P, van den Brink RH, Spijkerman TA, Ormel J. Only incident depressive episodes after myocardial infarction are associated with new cardiovascular events. *J Am Coll Card* 2006;48(11):2204-8.
51. Parker GB, Hilton TM, Walsh WF, et al. Timing is everything: The onset of depression and acute coronary syndrome outcome. *Biol Psychiat* 2008.
52. Lesperance F, Frasere-Smith N, Talajic M. Major depression before and after myocardial infarction: its nature and consequences. *Psychosom Med* 1996;58(2):99-110.
53. Uher R, Farmer A, Maier W, et al. Measuring depression: comparison and integration of three scales in the GENDEP study. *Psychol Med* 2008;38(2):289-300.
54. Uher R, Maier W, Hauser J, et al. Differential efficacy of escitalopram and nortriptyline on dimensional measures of depression. *Br J Psychiat* 2009;194(3):252-9.

Table 1: Demographic and risk factor profile of the current sample (n=408 unless otherwise stated), categorised by having elevated depressive symptoms or not, and univariate associations with MACE

Variable	No depressive symptoms (n=209)	Elevated depressive symptoms (n=199)	OR	95% confidence interval (CI)		HR	95% CI	
Demographic factors								
Age (over 65=1)	62.2 (10.9)	60.4 (10.4)	0.98	0.96	1.01	2.1***	1.6	2.8
Men	83%	77%	0.7	0.5	1.1	1.4	0.9	2.0
Has a partner (1=yes)	73%	76%	1.2	0.7	2.0	0.7	0.4	1.5
Employed (1=yes) (n=321)	28%	19%	0.6***	0.5	0.8	0.4**	0.2	0.7
Private health insurance	35%	28%	0.7	0.5	1.1	0.8	0.5	1.5
Previous risk factor history								
Current smoker	27%	44%	2.2***	1.6	2.9	0.6*	0.4	0.9
Prior hypertension	50%	50%	1.0	0.8	1.4	1.2	0.7	2.0
Prior diabetes	6%	15%	2.8**	1.4	5.4	1.6	1.0	2.5
Cholesterol (mmol/l) (mean, std dev) (n=326)	4.7 (1.2)	4.4 (1.2)	0.8*	0.7	1.0	0.98	0.8	1.2
Prior CHD	27%	38%	1.7**	1.2	2.4	1.9*	1.2	3.0
Prior CAD	24%	35%	1.6**	1.1	2.4	2.0**	1.3	3.2
Prior ACS	15%	24%	1.8*	1.1	2.7	2.0**	1.3	3.2
Prior MI	12%	24%	2.2**	1.2	4.0	2.1***	1.4	3.1
Prior Angina	11%	15%	1.4	0.7	2.8	1.1	0.5	2.4
Prior revascularisation	21%	31%	1.7*	1.1	2.6	1.3	0.9	2.0
Prior CABG	8%	11%	1.3	0.7	2.4	1.6	0.6	3.8
Prior PTCA	15%	23%	1.6*	1.1	2.5	1.0	0.6	1.6
Prior Stent	11%	14%	1.2	0.8	1.9	1.5	0.9	2.5
Current hospitalisation								
Acute antiplatelet	82%	79%	0.9	0.5	1.4	0.7	0.4	1.2
Acute anticoagulant	66%	62%	0.8	0.6	1.2	0.9	0.6	1.4
Thrombolysis	27%	22%	0.8	0.4	1.4	1.1	0.4	2.8
Revascularisation received	77%	69%	0.7	0.4	1.05	0.8	0.5	1.2
PTCA/Stent	69%	62%	0.7	0.5	1.2	0.9	0.6	1.3
CABG	9%	9%	1.1	0.5	2.2	1.0	0.4	2.5
Cardiac arrest confirmed	19%	12%	0.6	0.3	1.0	1.0	0.7	1.3
Length of hospital stay (days)^	7 (5-11)	7 (5-10)	0.99	0.97	1.02	1.03**	1.01	1.05
Left ventricular function (confirmed as <40%)	16%	14%	0.8	0.6	1.2	1.4	0.8	2.4
Diagnosis of MI	70%	72%	1.1	0.7	1.7	1.0	0.7	1.4
Co-morbidities								
CCI total score	1 (1-2)	1 (1-2)	1.1	0.96	1.3	1.2*	1.0	1.4
CCI modified score	0 (0-1)	0 (0-1)	1.0	0.8	1.2	1.1	0.9	1.4

*<0.05, **<0.01, ***<0.001

^ - 32 missings imputed with median length of stay of 7 days (no discernible difference to data)

Table 2: Mokken scale analysis at c(0.5) for scales hypothesised to break down into core depressive symptoms

Derived symptom scales	Observed Guttman errors	Expected Guttman errors	Loevinger H coefficient
Scale 1: Fatigue-sadness (9-items)			
BDI-FS1 Sadness	185	388.4	0.52
MQ10-6 Do you ever wake up with a feeling of exhaustion and fatigue?	196	459.8	0.57
MQ10-8 Do you have the feeling these days that you just do not have what it takes anymore?	172	397.9	0.57
MQ10-2 Do you feel listless?	171	470.7	0.64
MQ10-1 Do you often feel tired?	80	296.1	0.73
MQ10-9 Do you believe that you have come to a "dead end"?	57	198.5	0.71
MQ10-3 Do you feel weak all over or without energy?	156	460.6	0.66
MQ-10-4 Do you sometimes have the feeling that your body is like a battery that is losing its power?	109	376.9	0.71
MQ10-7 Do you feel you want to give up trying?	62	216.8	0.71
Scale	594	1632.8	0.64
Scale 2: Anhedonia (4-items)			
HADS-D 4 I can laugh and see the funny side of things	167	356.1	0.53
HADS-D 2 I still enjoy the things I used to enjoy	217	478.3	0.55
BDI-FS 4 Loss of pleasure	185	421.3	0.56
HADS-D 12 I look forward with enjoyment to things	207	478.4	0.57
Scale	388	867.0	0.55
Scale 3: Depressive cognitions (4-items)			
BDI-FS 5 Self-dislike	190	393.6	0.52
MQ10-10 Do you sometimes cry or feel like crying?	121	260.8	0.54
BDI-FS 2 Pessimism	169	373.1	0.55
BDI-FS 3 Past failure	182	400.7	0.55
Scale	331	714.1	0.54

Table 3: Original and derived scales (upper quartiles) and univariate and multivariate associations with endpoints

Original scales	Univariate				^Multivariate			
	HR	95% CI		p	HR	95% CI		p
HADS-D	2.5	1.3	4.8	0.006**	2.9	1.4	5.9	0.004**
BDI-FS	1.2	0.6	2.2	0.644	1.3	0.7	2.5	0.467
MQ-10	1.2	0.8	1.8	0.343	1.2	0.8	2.0	0.338
Derived scales								
Fatigue-sadness	1.8	1.1	3.0	0.025*	2.0	1.1	3.6	0.017*
Anhedonia	1.6	0.9	2.8	0.102	1.7	1.0	2.8	0.043*
Depressive cognitions	1.3	0.7	2.2	0.402	1.4	0.7	2.7	0.280

^Adjusted for age, sex, history of CHD, length of hospital stay (days)

*<0.05, **<0.01, ***<0.001

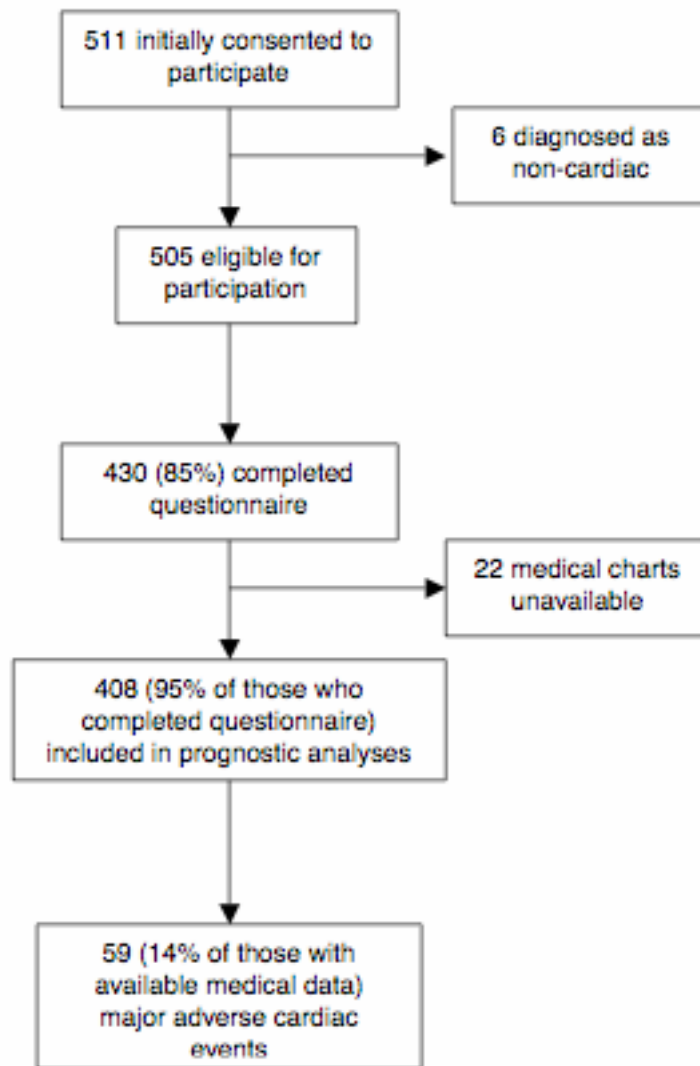


Figure 1: Flowchart of participant recruitment, medical record review and major adverse cardiac events

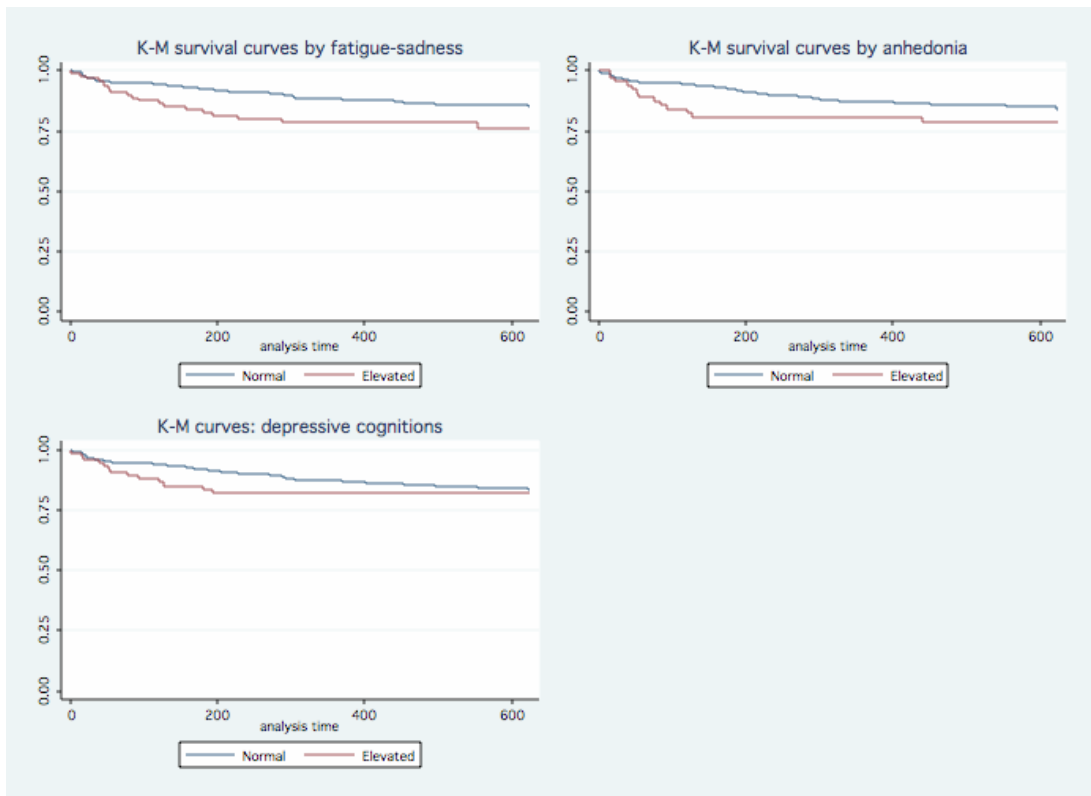


Fig 2: Kaplan-Meier survival curves for each derived scale