1-1-2013

Adjusted prognostic association of post-myocardial infarction depression withmortality and cardiovascular events: an individual patient data meta-analysis

Anna Meijer
University Medical Centre Groningen

Henk Jan Conradi
University of Amsterdam

Elske H. Bos
University Medical Centre Groningen

Matteo Anselmino
University of Turin

Robert M. Carney
Washington University, St Louis

See next page for additional authors

Citation

Meijer A, Conradi HJ, Bos EH, Anselmino M, Carney RM, Denollet J, Doyle F, Freedland KE, Grace SL, Hosseini SH, Lane DA, Pilote l, Parakh K, Rafanelli C, Sato H, Steeds RP, Welin C, de Jonge P. Adjusted prognostic association of post-myocardial infarction depression withmortality and cardiovascular events: an individual patient data meta-analysis. British Journal of Psychiatry. 2013;203:90-102.

Authors
Anna Meijer, Henk Jan Conradi, Elske H. Bos, Matteo Anselmino, Robert M. Carney, Johan Denollet, Frank Doyle, Kenneth E. Freedland, Sherry L. Grace, Seyed Hamzeh Hosseini, Deirdre A. Lane, Louise Pilote, Kapil Parakh, Chiara Rafanelli, Hiroshi Sato, Richard P. Steeds, Catharina Welin, and Peter de Jonge

Adjusted prognostic association of post-myocardial infarction depression with mortality and cardiovascular events: an individual patient data meta-analysis

A. Meijer, H.J. Conradi, E.H. Bos, M. Anselmino, R. Carney, J. Denollet, F. Doyle, K.E. Freedland, S.L. Grace, S.H. Hosseini, D.A. Lane, L. Pilote, K. Parakh, C. Rafanelli, H. Sato, R.P. Steeds, C. Welin, P. de Jonge

Abstract

Background: The association between depression after myocardial infarction (post-MI) and increased risk of mortality and cardiac morbidity may be due to cardiac disease severity.

Aims: To combine original data from studies on the association between post-MI depression and prognosis into one database. To investigate to what extent post-MI depression predicts prognosis independently of disease severity.

Method: Individual patient data meta-analysis of studies, using multilevel, multivariable Cox regression analyses.

Results: Sixteen studies participated, creating a database of 10,175 post-MI patients. HRs for post-MI depression were 1.32 (95%CI 1.26-1.38, $p<0.001$) for all-cause mortality, and 1.19 (95%CI 1.14-1.24, $p<0.001$) for cardiovascular events. HRs adjusted for disease severity were attenuated by 28% and 25% respectively.

Conclusions: The association between post-MI depression and prognosis is attenuated after adjustment for cardiac disease severity. Still, depression remains independently associated with prognosis, with a 22% increased risk of all-cause mortality and a 13% increased risk of cardiovascular events per standard deviation in depression z-score.

Declaration of interest: None.

Introduction

In patients after myocardial infarction (MI), the prevalence of major depression (MDD) or elevated depressive symptoms is relatively high at approximately 20% (1), compared to around 5% in otherwise healthy people of comparable age (2). Elevated symptoms of depression, as measured with symptom questionnaires like the Beck Depression Inventory (BDI), are present in around 30% of MI patients (1). Post-MI depression has been associated with a worse prognosis, and investigations into the strength of this association have been summarized in a number of meta-analyses, which showed depressed MI patients are 1.59 to 2.71 times more likely to die early or have new cardiovascular events than are non-depressed patients (3-5). Such meta-analyses based on summary data, however, have serious limitations. By conducting an individual patient data meta-analysis (IPD), a new statistical approach in this field, the main limitations can be overcome.

A major point of discussion in this field is whether depression is an independent risk factor for worsened cardiac outcomes, or whether its association with outcome is the result of non-causal mechanisms (6). Most importantly, cardiac disease severity may confound the association between post-MI depression and prognosis. Depression and disease severity, as measured by, for example, LVEF or Killip class, are associated, and evidence suggests that patients with more severe cardiac disease have a higher risk of depression (7-9). This may be the result of a psychological response to the disease and its consequences, as well as of physiological mechanisms involved in cardiac disease leading to symptoms of depression, such as elevated inflammation (10) and changes in

functioning of the autonomic nervous system (ANS) or the hypothalamic-pituitary-adrenal (HPA) axis (11, 12). Evidently, patients with more severe disease are also at higher risk of adverse cardiac outcomes, such as new cardiac events, rehospitalization and cardiac mortality. Similarly, other medical risk factors, such as smoking, and diabetes, are likely to be associated with both disease severity and depression (13, 14). Therefore more severe disease and exposure to other risk factors could result in both a higher prevalence of depression as well as worsened cardiac prognosis, and thereby confound the association between depression and CAD outcomes.

Individual studies find conflicting results when the association between post-MI depression and prognosis is adjusted for disease severity, some finding it to be attenuated, while others conclude the association remains unchanged. Previous systematic reviews and meta-analyses were only able to provide estimates of unadjusted associations, or very limited estimates of adjusted associations. This is due to the wide variability of adjustments in individual studies, making comparisons across studies impossible. Investigating the effects of adjustment is important, however, as variables related to cardiac disease severity (15-17) and other health-related variables (13, 14, 18-20) are prognostic factors for all-cause mortality (ACM) and cardiovascular events (CVE), and are associated with depression.

The only way to adequately investigate the effects of cardiac disease severity and other medical risk factors on the association between post-MI depression and prognosis is to combine data from individual studies into a single database First, with one large dataset, all combined data will be analyzed with the same techniques, whereas in summary data meta-analyses, results are based on different statistical techniques, limiting

their comparability. Second, the combined dataset offers the possibility of performing new analyses both within and across studies to investigate research questions that have not been investigated in the original studies (21). Third, this will allow us to consistently adjust for the same variables across studies, providing us with a better estimate of their role in the association between post-MI depression and prognosis. Fourth, the combined database will contain more raw patient data, which increases statistical power, generalizability, and reliability of the results (22-25), providing a more precise estimate of the association between post-MI depression and prognosis, and of the effects of the individual variables (24). Finally, time-to-event analyses can be performed, to not only utilize information on whether or not an event occurred, but also when it occurred (25), which is one of the main advantages of IPD meta-analysis (26). The objective of this study, therefore, is to conduct an IPD meta-analysis that allows for adjustment for a number of important disease severity variables and other health factors that are routinely collected in studies of post-MI depression.

Methods

Literature search and selection of studies

Search strategy

Studies included in this individual patient data (IPD) meta-analysis were previously selected for two regular, summary data (SD) meta-analyses on post-MI depression and cardiac prognosis(5, 27). A literature search was performed on January 5th, 2011 to identify prognostic studies that investigated the association between post-MI depression

and cardiac prognosis since 1975. Depression treatment studies in which baseline depression scores and all-cause mortality or cardiovascular events outcomes were reported were also eligible. Relevant articles were selected from the electronic databases Medline (PubMed), Embase, and PsycINFO without language restrictions. Search terms related to depression and myocardial infarction were used and customized to each database. Full search strings for each database are listed in Appendix 1. In addition to the database searches, major reviews and relevant articles were cross-referenced. Search alerts for the three databases mentioned above were activated, to identify relevant studies that were published after January 5, 2011. All studies included in the summary data meta-analyses were eligible for inclusion in the current IPD meta-analysis.

Selection process

The selection process has been described in detail elsewhere (5, 27). In summary, studies were selected by two independent raters according to the following criteria: (1) patients had to be hospitalized for MI; (2) depression had to be determined within three months after MI using methods originally designed to assess depression (standard self-report questionnaires or standardized psychiatric interviews) and validated elsewhere; (3) studies had to be prospective and assess cardiovascular prognosis in a depressed patient group compared to a non-depressed control group; (4) outcome had to be all-cause mortality or cardiovascular events (the latter defined as either non-fatal cardiac events or a composite of fatal and non-fatal cardiac events); and (5) the study had to be based on original data.

Authors of all the studies included in the summary data meta-analysis were contacted and invited to participate in the project. Considerable effort was put into finding and contacting authors and in obtaining all available databases. When corresponding authors could not be contacted at the address specified in the original articles, we searched most recent articles and the internet for updated information on the authors' location, and we tried to contact other members of the research groups. Authors were asked to share original data they had on post-MI patients regarding demographics, depression, disease severity, comorbidities, medication use, and outcomes. Data were checked for potential errors, and authors were contacted regarding questions related to the design of their study or the datasets they provided.

Depression

Depression had to be measured using established self-report questionnaires or standardized structured diagnostic interviews. For the main analyses, continuous scores on the self-report questionnaires were used. Dichotomous scores were used for descriptive purposes only, and were based on structured diagnostic interviews where available, and on standard cut-off scores (literature-based) on the self-report questionnaires where no interviews were available. When multiple depression measurement instruments were used, standardized structured diagnostic interviews were preferred over self-report questionnaires in constructing dichotomous scores. When multiple self-report questionnaires were used in the same study, the one most frequently used by the other studies was selected. Across the studies, a number of different self-report depression questionnaires were used, so total depression scores on these

questionnaires were standardized to z-scores for analyses. This was done within each study. For some patients, depression questionnaire total scores and dichotomous scores were not available due to missing item scores on the questionnaire. When no more than 25% of the depression items were missing, item scores were imputed with the mean of the available items from that patient, to calculate total scores and dichotomized scores.

Disease severity: LVEF, Killip class, and history of MI

To investigate the role of cardiac factors in the association between post-MI depression and prognosis, LVEF, Killip class, and history of MI were used to quantify disease severity. These variables were selected because they are known predictors of outcome in post-MI patients (18, 19, 28-31), and they were available in a sufficient number of patients. They may result in both more symptoms of depression (7) and more adverse outcomes (12).

LVEF was dichotomized into low (<40%) and normal (≥40%), as not all studies included continuous values. Killip class was dichotomized into no heart failure (class I) and heart failure (classes II, III, and IV), as the 4-category scores were not available in all studies. History of MI was dichotomized into "yes" or "no".

Other risk factors: diabetes, smoking, and BMI

Several other health-related risk factors were expected to affect the association between post-MI depression and prognosis. Of these, diabetes (13, 18, 19, 32), smoking (14), and BMI were included in the adjusted analyses, as data on these variables were collected in a large number of the patients.

Age and sex

Age and sex were included in the analyses for the minimally adjusted comparison model. They may explain part of the association, as they are both related to the risk of depression and to physical health prognosis.

Outcome: all-cause mortality and cardiovascular events

The outcomes of all-cause mortality and new cardiovascular events were considered in the analyses. All-cause mortality includes cardiac mortality, and it was included because outcome data on all-cause mortality is generally more readily available than specific data on (cardiac) causes of mortality or morbidity. Cardiovascular events as defined most commonly by the original study authors were accepted, and could be either fatal events, non-fatal events, or a combination of both. Cardiovascular events included, for example, new MI, unstable angina (UA), and coronary artery bypass graft surgery (CABG). All-cause mortality and cardiovascular events may overlap when studies included cardiac death in both definitions.

Study characteristics

For each study the following characteristics were summarized: year that the study was initiated, percentage of males in the sample, inclusion and exclusion criteria, mean age, depression measure, percentage of depressed patients, mean depression scores, duration of follow-up, and number of outcome events.

Statistical analysis

The main analyses were performed in Stata 11 (Statacorp LP, TX, USA). All studies except one included continuous depression scores, and a number of studies in addition contained a binary measure of clinical diagnosis of depression. The one study (33) that did not contain continuous depression scores was excluded from the current analyses. First, hazard ratios (HRs) were calculated using multilevel Cox proportional hazards regression analysis for the studies with time-to-event data. Second, odds ratios (ORs) were calculated using logistic regression analysis for all studies, including those with dichotomous outcome information only (event versus no event without time-to-event data).

Multilevel model

The individual studies were included as a separate level, resulting in a multilevel model, in which the variable "study" was included as a random intercept. Patients across studies were likely to differ in systematic ways, for example because of differences in selection criteria, study methods, or cardiac care (21). Observations of subjects within studies were therefore unlikely to be fully independent. By incorporating a random effect for "study" in IPD meta-analysis, we accounted for the fact that outcome rates may vary across studies.

The possibility of a random slope was also investigated, as the strength of the association between post-MI depression and prognosis may vary significantly across studies. As this did not appear to be the case, random slopes were not included in the final models.

In the Cox regression analyses, contrast coding of -0.5/0.5 was used for dichotomous variables, to insure between-trial variances were equal between groups (e.g. male vs. female) (34, 35).

Potential bias due to standardizing depression scores within each study, with the risk of overlooking potential differences in effect due to differences in depression severity and prevalence between studies, was investigated by adding a variable to the model that describes the level of depression per study (percentage depressed based on depression questionnaire scores), as well as an interaction variable of the standardized depression scores and the percentage depressed variable. As the analysis showed that this bias was virtually non-existent, we did not include these variables in the final models.

Bootstrapping

A bootstrapping procedure with 1000 replications was used for the analyses, to increase the robustness of the confidence intervals (36), and to account for the fact that some of the depression z-scores were not distributed normally.

Model construction

The models were built as follows: First, a base model to which subsequent adjusted models could be compared was created by including age, sex, and the depression z-scores as predictors of prognosis. As our primary interest was in the influence of individual variables on the association between post-MI depression and prognosis, we then added each preselected variable separately to this base model in minimally adjusted analyses. Not all studies had data on each of these variables, and to be able to compare differences

between the base and adjusted models, patients who did not have data on the relevant variable were excluded from the relevant analyses in both models. Cardiac disease severity was represented by history of MI, Killip class, and LVEF. Diabetes, smoking and BMI were added as risk factors for poor prognosis. A variable was considered to explain a substantial portion of the variance if it changed the effect size (log HR) by 5% or more (37). Variables that were also significant predictors ($p \leq 0.05$) of outcome were considered to substantially add to the variance. As not all studies had time-to-event data, additional logistic regression analyses were performed and these models were built in the same way as for Cox regression analyses.

Second, we investigated the extent to which the association between post-MI depression and prognosis was attenuated by adjusting for all of the risk factors. As not all studies had data on all variables, these multivariable analyses could only be performed with data from a limited number of studies. Nevertheless, this provides the best estimate of the extent to which post-MI depression independently predicts cardiac outcomes.

Model assumptions

The proportional hazards assumption for Cox regression was tested, as well as the assumption of linearity in the association between post-MI depression and prognosis. The model assumptions were met in most cases. In the few cases that they were not, the effects of violation of the assumption were further investigated and determined to be minimal. Analyses were therefore run for these models in the same way as the other models, for the sake of clarity and interpretability of the results.

Patient characteristics

Patient characteristics were presented separately for depressed and non-depressed patients. Differences in these characteristics between depressed and non-depressed patients were assessed with independent samples t-tests for normally distributed continuous variables, and Mann-Whitney U-tests for non-normally distributed continuous variables. Dichotomous and categorical variables were compared using Pearson's Chi-square test.

Effects of non-participation of eligible studies

To investigate whether there were any systematic differences (acquisition bias) between participating and non-participating studies that may affect the results of the meta-analysis (38), we compared results of included and excluded studies concerning strength of the association and study characteristics.

Results

Study participation

A total of 6,145 articles were identified through the literature search, cross-referencing, and personal communication. Of those, 28 studies were ultimately included in the meta-analysis. Two additional studies were identified through search alerts (39) and personal communication (40), resulting in a total number of 30 eligible studies. The authors of 16 studies provided data for the IPD meta-analysis, resulting in a combined database of 10,175 patients[1]. Figure 1 is a flow-chart of the literature search and data acquisition.

[1] The data of one study were not used for the current analyses, as there were no continuous depression scores (Rafanelli). However, these data will be available for future substudies.

Fourteen studies were not included, seven because authors could not be contacted, five because data were not available, and two because the authors were not interested in participating. An overview of participating studies is given in Table 1. Complete reports of study design and methodology of the individual studies are published elsewhere (20, 31, 39-56). Appendix 2 is an overview of non-participating studies.

Study characteristics

The 16 participating studies originated from 9 different countries. The mean sample size was 615 patients per study (SD 711), ranging from 61 to 2,889 patients. Studies originated from 1985 to 2006. Mean age per study ranged from 56-65 years (m=61), and the mean percentage of males ranged from 33%-85% (m=72%). All studies included MI patients based on standardized diagnostic criteria. Most of the exclusion criteria concerned life-threatening illnesses or psychiatric disorders other than depression, MI due to a surgical procedure (e.g. CABG, valve replacement, etc.), or cognitive or communication difficulties.

Depression was measured with a self-report depression questionnaire, a structured clinical interview, or both. The self-report depression scales that were used included the BDI-1A, BDI-II, BDI-Fast Screen (FS), the depression subscale of the Hospital Anxiety and Depression Rating Scale (HADS-D), and Zung Self-rating Depression Scale (SDS). Structured clinical interviews included the Depression Interview and Structured Hamilton (DISH), the Composite International Diagnostic Interview (CIDI), and the Structured Clinical Interview for DSM Disorders (SCID). The percentage of depressed patients was lower when based on diagnostic interviews (11%-15%) than when based on elevated

symptoms on self-report questionnaires (17%-69%). Follow-up time ranged from 350 to 2,428 days (1 – 6.7 years), with a mean of 1,151 days (3.2 years).

Patient characteristics

Individual patient data were combined for 10,175 MI patients. 4,043 patients (40%) had a major depression, or elevated symptoms of depression and 6,132 patients (60%) were not depressed [2]. Nineteen percent of patients had a history of one or more MIs prior to the index MI, 23% had low LVEF, and 18% had a Killip class higher than I. Twenty-one percent of those measured had comorbid diabetes, 45% were (ever) smokers, and the mean BMI was 27 (Table 2).

Adjusted association between post-MI depression and prognosis: Cox regression analyses

Base model (adjusted for age and sex)

Figure 2 shows survival curves for the two outcomes all-cause mortality and cardiovascular events, with separate lines for depressed and non-depressed patients, and adjusted for age and sex.

Rates of all-cause mortality were stable over time, and were consistently higher for depressed patients than for non-depressed patients. The rate of cardiovascular events was highest soon after the MI, and became relatively stable after about 1 year. The rate of cardiovascular events was higher for depressed than for non-depressed patients.

[2] Note that some studies may have oversampled depressed patients, so these numbers may overrepresent depression percentages in MI patients.

The base Cox regression model for all-cause mortality (adjusted for age and sex) produced an HR for depression (z-scores) of 1.32 per SD (95%CI 1.26-1.38, p<0.001). Adjustment for age and sex increased the strength of the association between post-MI depression and all-cause mortality by 17% (see Table 3).

In the cardiovascular events model the HR (adjusted for age and sex) for depression (z-scores) was 1.19 per SD (95% CI 1.14-1.24, p<0.001). Adjustment for age and sex did not substantially alter the strength of the association between post-MI depression and cardiovascular events (Table 4).

Univariate models

All three cardiac disease severity variables explained a substantial portion of the association between post-MI depression and all-cause mortality, with the dichotomized variables for Killip class and LVEF explaining 19% and 15%, respectively, and history of MI explaining 8%. Of the general health variables diabetes, smoking, and BMI, only diabetes explained a considerable part (7%) of the association between post-MI depression and all-cause mortality. Table 3 is a summary of the results of unadjusted and adjusted analyses.

For cardiovascular events, all three variables relating to cardiac disease severity explained a substantial portion of the association with post-MI depression, with the dichotomized variables for Killip class and LVEF explaining 12% and 10%, respectively, and history of MI explaining 9%. Of the general health variables diabetes, smoking, and BMI, again only diabetes explained a considerable part (7%) of the association (Table 4).

Multivariable models

The following results are based upon the three studies that included all variables (i.e., history of MI, Killip class, LVEF, diabetes, smoking, and BMI). When combining all general health and disease severity related variables in one model, the adjusted HR for all-cause mortality was 1.23, compared to 1.33 unadjusted, an attenuation of 28%. All variables except sex and BMI independently explained part of the association between post-MI depression and prognosis. Figure 3 (top panel) is a survival curve of the model adjusted for age, sex, history of MI, LVEF, Killip class, diabetes, BMI, and smoking. Note that this figure is based on the three studies only that contained all these variables.

Adjusting for the three cardiac disease-related variables only, the HR for all-cause mortality was 1.22 compared to 1.32 unadjusted, an attenuation of 29%. This means that the cardiac disease-related variables are responsible for nearly all of the attenuation in the full model. Model fit improved when age, sex, history of MI, LVEF, Killip class, and diabetes were subsequently added. Model fit did not improve after further adjustment for BMI and smoking.

For cardiovascular events, when combining all general health and disease severity-related variables in one model, the adjusted HR was 1.12, compared to 1.17 unadjusted, an attenuation of 25%. All variables except BMI independently explained part of the association between post-MI depression and prognosis. Figure 3 (bottom panel) is a survival curve of the model adjusted for age, sex, history of MI, LVEF, Killip class, diabetes, BMI, and smoking. Note that this figure is based on the two studies only that contained all these variables.

Adjusting for the three cardiac disease-related variables only, the HR for cardiovascular events was 1.13 compared to 1.17 unadjusted, an attenuation of 21%. This means that the cardiac disease-related variables were responsible for most of the attenuation in the full model. Congruent with the all-cause mortality analyses, model fit improved when subsequently adjusting for age, sex, history of MI, LVEF, Killip class, and diabetes. Model fit did not improve after further adjustment for BMI and smoking.

Adjusted association between post-MI depression and prognosis: logistic regression analyses

Five studies (2,468 patients) did not have time-to-event data, and therefore logistic regression analyses were performed in addition to the Cox regression analyses. Of the 8,366 patients who had depression z-scores as well as outcome data on all-cause mortality, 1,136 patients (14%) died. Of 3,206 depressed patients, 636 (12%) died, and of 3,206 non-depressed patients, 500 (16%) died. Of the 8,878 patients who had depression z-scores as well as outcome data on cardiovascular events, 3,067 experienced a fatal or non-fatal cardiac event (35%). Of 3,747 depressed patients, 1,449 (39%) experienced a fatal or non-fatal cardiac event, and of 5,135 non-depressed patients, 1,168 (32%) experienced an event. Base model (adjusted for age and sex).

The base logistic regression model for all-cause mortality (adjusted for age and sex) produced an OR for depression (z-scores) of 1.41 per SD (95%CI=1.34-1.49, $p<0.001$) (Table 5). Adjustment for age and sex increased the strength of the association between post -MI depression and all-cause mortality by 18%.

The OR for depression in the cardiovascular events model (adjusted for age and sex) for depression (z-scores) was 1.25 per SD (95%CI=1.19-1.32, p<0.001) (Table 6). Adjustment for age and sex did not substantially alter the strength of the association between post-MI depression and cardiovascular events.

Univariate logistic models

For the all-cause mortality and cardiovascular events analyses, the variables diabetes, history of MI, LVEF and Killip class each explained a substantial part (≥more than 5%) of the association between post-MI depression and all-cause mortality and improved model fit. The variables smoking and BMI did not add to the model (Tables 5 and 6).

Multivariable logistic model

When all variables were added to the model at once, 3 studies and 2,225 patients remained, and the adjusted OR for depression was 1.24 per SD (95% CI=1.07-1.44, p<0.001) in the all-cause mortality model. The added variables explained 30% of the association between post-MI depression and all-cause mortality. When including the variables relating to cardiac disease severity only (i.e., history of MI, LVEF, Killip class), the OR was 1.27 per SD (95% CI = 1.17-1.37, p<0.001). These variables explained 25% of the association (Table 5).

The complete model for cardiovascular events included 2 studies and 1964 patients, and resulted in an OR for depression of 1.18 per SD (95%CI=1.00-1.39, p=0.053). The variables explained 23% of the association between post-MI depression and cardiovascular events. The association was no longer significant after adjusting for

all variables. When including the variables relating to cardiac disease severity only (history of MI, LVEF, Killip class), the OR was 1.19 per SD (95%CI = 1.12-1.26, p<0.001). These variables explained 19% of the association (Table 6).

Participation

Of the 30 studies that were included in the summary data meta-analyses, the authors of 14 studies participated and contributed their data. In addition, 2 studies that were published after the summary data meta-analysis contributed their data. Combining all available studies resulted in inclusion of 51% (10,175 of 19,859) of eligible patients.

To estimate the impact of non-participation of studies on the association, 2-year ORs for post- MI depression were compared for included and excluded studies, as 2-year follow-up data were available for most studies. For comparison purposes, this was done on the studies that were included in the original summary data meta-analysis. For excluded studies that reported on all-cause mortality, the unadjusted OR was 1.98 (95%CI 1.62-2.42, p<0.001) and for included studies, the unadjusted OR was 2.45 (95%CI 1.46-4.14, p<0.001), with no significant difference. However, for cardiovascular events, the ORs of excluded and included studies differed significantly (p=0.04), with an unadjusted OR of 1.83 (95%CI 1.40-2.39, p<0.001) for excluded studies and 1.34 (95%CI 1.17-1.54, p<0.001) for included studies.

Discussion

Main results

The association between post-MI depression and all-cause mortality and cardiovascular events was partly attenuated, but remained significant, after adjustment for cardiac disease severity and other health variables. In Cox regression analyses, adjusting for cardiac disease severity, i.e. history of MI, LVEF and Killip class, resulted in an attenuation of 29% in the all-cause mortality model and 21% in the cardiovascular events model. Adjustment for the health-related variables smoking and BMI did not result in an attenuation of the association between post-MI depression and all-cause mortality or cardiovascular events, but adjustment for diabetes attenuated the association for both outcomes by 7%. In logistic regression analyses, results were similar,

The fact that, after attenuation for variables indicating cardiac disease severity, the association between post-MI depression and prognosis remains can mean several things. First, adjustments for more variables indicating disease severity may result in stronger attenuation. Second, other mechanisms than disease severity are likely to be involved, which may be either mediators in the association between depression and cardiac disease occurring after depression onset, or causal factors preceding both depression and cardiac disease. For example, depression has been associated with changes in ANS functioning, and in HPA-axis activity (11, 57, 58), increased inflammation (11, 59) and platelet reactivity (11, 60, 61)These physiological processes may be particularly disturbed in depressed MI patients and they are all involved in the development and progression of cardiovascular disease. They may therefore be mediating mechanisms through which

depression in MI patients can affect prognosis. They may, however, also be involved in both the onset of depression and of cardiac disease progression, in which case they are confounders of the association between post-MI depression and prognosis.

In addition to physiological mechanisms, behavioral mechanisms may be involved as mediators. Depression in MI patients has been associated with a range of behaviors that are unhealthy and may increase the risk of mortality and new cardiac events. Depressed patients have poor medication adherence (62-64), and low adherence to rehabilitation programs (65). Moreover, they display more generally unhealthy behaviors, such as maintaining a high-fat diet, smoking, and a lack of physical exercise (66-68).

These unhealthy behaviors may be the result of psychological mechanisms associated with depression. For example, low self-efficacy in depressed cardiac patients may imply they are less likely to believe they can control and influence their prognosis, for example by changing unhealthy behavior patterns. In a sample of heart failure patients, low self-efficacy was associated with poor adherence (69), and in another study, low self-efficacy predicted poor self-management behaviors in MI patients (70). Interestingly, self-efficacy appears to be associated with poor adherence and health status independently of depression (69-71). However, evidence also suggests that the association between self-efficacy and worsened prognosis is caused by worse cardiac disease severity in patients with low self-efficacy (72), which is consistent with the confounding role of disease severity in the association between depression and prognosis.

The attenuation after adjusting for LVEF and Killip class was somewhat stronger for all-cause mortality than for cardiovascular events in both time-to-event (LVEF 15 vs. 10%, Killip class 19 vs. 12%) and logistic (LVEF 12 vs. 8%, Killip class 13 vs. 7%)

regression analyses. This is unexpected, as these variables appear to be more strongly related to cardiac disease than to all-cause mortality and would therefore be expected to explain more of the association between depression and cardiac outcomes than of the association between depression and all-cause mortality. Potentially, however, poor Killip class and low LVEF, symptoms of heart failure, are markers of poor health in general. Heart failure is often comorbid with other serious health problems, such as lung disease, obesity and diabetes, with 40% of heart failure patients having more than 5 comorbid conditions (73). Any of these health problems may escalate and cause mortality, not just cardiac disease (73). This may explain why adjusting for LVEF and Killip class attenuates the association between depression and all-cause mortality more than it does the association between depression and cardiovascular events, as patients with low LVEF or Killip class have a higher risk of dying early of any cause, not just cardiac causes, than do patients with normal LVEF or Killip class.

Results in the context of previous studies

The attenuation of the association between post-MI depression and cardiac prognosis after adjustment is a consistent finding in studies in this field (4, 15-17), but identifying the factors that cause this attenuation has proven to be difficult thus far. In the summary data meta-analysis preceding this IPD meta-analysis (5), reported analyses adjusting for a number of factors, including disease severity-related variables, attenuated the association between post-MI depression and prognosis by on average 21%. However, adjusted analyses were reported in a limited number of studies only, using different sets of variables, and adjustment was done for several variables at once, making it impossible to

see to what extent individual variables were responsible for attenuation. The fully adjusted model in this IPD meta-analysis resulted in slightly higher attenuation than the summary data meta-analysis. Similar, but greater, attenuation was found in another summary data meta-analysis by Nicholson et al.(4). They reported that a pooled OR of adverse outcomes in depressed versus non-depressed MI patients, adjusted for diverse variables, was attenuated by 41%. So overall, it appears that in this study we have identified the disease specific variables that are responsible for the largest portion of the attenuation known so far.

The summary data meta-analysis preceding this IPD meta-analysis resulted in ORs of 2.25 for all-cause mortality, 2.71 for cardiac mortality, and 1.59 for cardiovascular events. Similar effect sizes were reported in other meta-analyses (3, 4). The current IPD meta-analysis resulted in HRs of 1.32 for all-cause mortality and 1.19 for cardiovascular events. This apparent difference in the effect size is mainly due to the fact that these ORs and HRs are based on different analyses. The associations in the previous meta-analysis were based on (maximally) two-year follow-up data, dichotomized depression scores, and logistic regression analysis. The main associations in the current IPD meta-analysis are based on longer follow-up data, continuous depression scores, and Cox regression analyses. In previous meta-analyses, dichotomous depression scores were used, so the effect sizes represented the increase in risk associated with the difference between depressed and non-depressed patients, which is a large difference. Using continuous depression scores, the HR in this IPD meta-analysis represent the increase in risk associated with one SD increase in continuous depression scores, so the steps involved are smaller, and results are more precise. All these

differences, and the fact that the risk of spurious results due to low numbers of events is small in the IPD meta-analysis, explain these apparently different results in the IPD meta-analysis compared to the summary data meta-analysis. As depression is by nature a continuous variable instead of a dichotomous variable, expressing the effect on prognosis per SD is more accurate than expressing it dichotomously.

Strengths and limitations

Individual studies often lack power to adjust for several variables, and summary data meta-analyses are limited to combining reported data. Instead, combining individual patient data provides more statistical power, consistent analysis of data across studies, and the possibility for additional analyses not performed in the original studies. Most important for the current study is that IPD meta-analysis allowed us to investigate in detail some of the variables responsible for the attenuation of the association between post-MI depression and prognosis. In addition, time-to-event analyses could be performed. As time-to-event analyses combine the occurrence and timing of events (25), they are more reliable and stable than, for example, ORs, which are often used in summary data meta-analyses. This resulted in a relatively accurate estimate of the effect of cardiac disease severity on the association between post-MI depression and prognosis.

There were also a number of limitations to this study: First, the analyses were to some extent limited in power, as, in addition to not all studies participating, some of the participating studies did not contain all variables that were selected for analyses. For example, for analyses with Killip class and LVEF, a limited number of studies (6 and 5) were available. However, these analyses are still based on a large number of patients, and

there is no other way to perform such analyses. Therefore they do have an added value in summarizing the role of these variables in the association between post-MI depression and prognosis.

With regard to participation, of 30 eligible studies, 16 were included, of which the majority were from Western, first world countries. Although low, this level of participation is common for IPD meta-analyses of observational studies (21). For example, Schmid et al. achieved participation of 11 of 14 of the researchers of clinical trials (74), but Sternberg et al. achieved participation of 13 of 24 (54%) observational studies (75), and Wicherts et al. of 64 of 249 studies (26%) (76). For cardiovascular events, the ORs in eligible non-included studies were higher than those in included studies (1.83 vs. 1.34). This suggests that, for this outcome, the IPD meta-analysis potentially underestimates the strength of the association. However, the higher, more extreme ORs in the non-included studies came from the smaller studies. These, if included, would have had a relatively smaller effect on the overall combined OR than the larger included and non-included studies, of which the ORs were more moderate. In addition, there were no other appreciable differences between eligible studies that were included and those that were excluded. We therefore concluded that the data available for this IPD meta-analysis, and the results of the analyses, are fairly representative of MI patients in first world countries, and that the benefits of analyzing IPD outweighed the potential effects of excluding relevant studies.

Two of the studies included were trials of depression treatment (ENRICHD, MIND-IT). As these studies collected information on both depression and outcomes, they were considered relevant for answering our research question. These data may differ from

that of observational studies, as patients were treated for depression, which may affect depression as well as all-cause mortality and cardiovascular outcomes. However, the depression scores that were included in the analyses for this study were obtained before treatment started and were therefore not affected by the interventions. In addition, the interventions were at best moderately effective in reducing depression and did not have an effect on all-cause mortality and cardiovascular outcomes (77-79).

Second, an inherent problem of IPD meta-analyses is that individual studies use different methods to assess relevant variables. In the current IPD meta-analysis, variables were harmonized across studies, with the main issue being depression measurement. However, such harmonization always contains the risk of combining measurements based on different underlying constructs (80). For depression, however, most studies used the BDI, making their data comparable. The other questionnaires used were the BDI-FS, HADS-D, and Zung SDS, which are highly correlated with the BDI. Item Response Theory methods of harmonization could not be used here, as they require individual depression item scores, which were not available for 4 of the 16 studies. Standardizing depression scores within each study may introduce bias by leveling out any differences in depression severity and prevalence between studies, which may affect the strength of the association between post-MI depression and prognosis. If the strength of the association is different for patients with less severe vs. more severe depression, this would not be accounted for by these standardization method. We therefore investigated whether this bias was present in our study by adding a variable to the model that describes the level of depression per study (percentage depressed based on depression questionnaire scores), as well as an interaction variable of the standardized depression scores and the percentage

depressed variable. If this interaction variable would be a significant predictor in the model, this would mean that the association between depression and prognosis is moderated by level of depression. This, however, was not the case (HR 1.00, 95% CI 0.99-1.01, p = 0.915). We are therefore confident that this potential bias did not affect our results.

Third, although LVEF, history of MI, and Killip class are important predictors of post-MI mortality and morbidity, they are not the only risk factors associated with worsened prognosis. Other important variables that are related to disease severity, for example, heart rate, blood pressure, treatment with PTCA or CABG, etc. (81), could not be included in the analyses. Similarly, a number of non-cardiac comorbidities, such as chronic obstructive pulmonary disease (COPD) and kidney disease are known to be associated with worsened outcomes (82). Also, the type of treatment in the acute phase and subsequent pharmacological treatment can affect outcomes. Finally, behavioral variables that were not incorporated in the model can attenuate the association. In a sample of stable CAD patients, Whooley et al. found that physical activity is an important confounder of the association (37). Adding these variables to a prediction model is likely to result in additional attenuation of the association between post-MI depression and prognosis. However, related research suggests the association may still remain. Kronish et al., for example, found that depression after acute coronary syndrome (ACS) remained associated with all-cause mortality, even after adjusting for GRACE risk score and LVEF (83) and Meurs et al. found similar results after adjusting the association for GRACE risk score in MI patients (84).

Finally, the outcome of all-cause mortality is somewhat imprecise in investigating the association between post-MI depression and prognosis. First, in some studies, cardiac deaths may be included in the outcome "cardiovascular events" as well as in the outcome "all-cause mortality". Therefore, the results of the analyses for the two outcome measures are based in part on the same event data. Second, as all-cause mortality includes non-cardiac cases of mortality, the results of this study might encompass a part of the association between post-MI depression and prognosis that is not specific to cardiac disease. However, the reason to use all-cause mortality was that the outcome data available in studies of post-MI depression often include mortality without specified causes of death. This was preferred over excluding studies without cardiac-specific outcome measures, as it would considerably reduce the number of available studies and otherwise relevant data. In addition, all-cause mortality includes cardiac mortality, and data on cardiac mortality and morbidity were analyzed separately to obtain results that were maximally specific. As all-cause mortality includes non-cardiac mortality, the proportion of variance in the association between post-MI depression and all-cause mortality explained by cardiac disease severity may be smaller than it would be when only cardiac mortality were included. This is because part of the association between post-MI depression and all-cause mortality is non-specific for cardiac disease and may therefore not be affected by adjusting for cardiac disease related variables.

Conclusions

This study represents an important step forward in understanding the association between post-MI depression and prognosis, as it is the first time that the amount of attenuation of

this association by cardiac disease severity has been systematically quantified. Therefore, an important part of the inconsistencies in previous literature, due to conflicting results and methodological issues, has been solved. It appears more severe cardiac disease is a common underlying factor resulting in both poorer prognosis and higher risk of depression. In addition, however, post-MI depression remains independently associated with poorer cardiac prognosis, despite this attenuation. This means either that it is depression itself that adversely affects outcomes, or that unknown mechanisms can further explain the association.

Future research should focus not only on the mechanisms through which post-MI depression is associated with poorer cardiac outcomes, but also on better ways to treat post-MI depression. As depression is widely recognized to be an extremely heterogeneous concept, with many different etiologies, symptoms profiles, and clinical courses, there currently is a movement towards more individualized treatments. Within such individualized depression care for MI patients, integrating depression treatment and treatment of major indicators of cardiac disease severity could help improve prognosis, which post-MI depression treatments as of yet have not achieved.

Acknowledgements: We would like to acknowledge Dr. B.D. Thombs and Dr. R.C. Ziegelstein for their critical review of the paper, and R.B.K. Wanders for input in statistical matters.

Contributions: AM was involved in the study design, reviewed articles for inclusion, contacted authors, carried out the collection and management of data, extracted data, conducted and interpreted analyses, and drafted the manuscript with the input of the other authors. PdJ was responsible for the study concept and design, reviewed articles for inclusion, contacted authors, contributed to the analysis and interpretation of results, and conducted a critical revision of the manuscript. HJC was involved in the study design, and conducted a critical revision of the manuscript. EHB was involved in the study design, conducted and interpreted analyses, and conducted a critical revision of the manuscript. MA, RC, JD, FD, KEF, SLG, SHH, DAL, LP, KP, CR, HS, RPS, and CW were responsible for acquisition of data and critical revision of the manuscript. All authors had full access to all of the data (including statistical reports and tables) and take responsibility for the integrity of the data and the accuracy of the data analysis. PdJ is the guarantor.

Ethical approval: Ethical approval was obtained by the individual studies, for which patients signed informed consent forms. The medical ethics committee of the University Medical Centre Groningen stated that no additional informed consent was required for the current study.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that (1) A.M., H.J.C., and P. de J. have support from a Vidi grant from the Dutch Medical Research Council (grant no. 016.086.397); (2) none of the authors have any relationships with companies that might have an interest in the submitted work in the previous 3 years; (3) their spouses, partners or children do not have financial relationships that may be relevant to the submitted work; (4) none of the authors have non-financial interests that may be relevant to the submitted work.

Figure 1: study selection and data acquisition

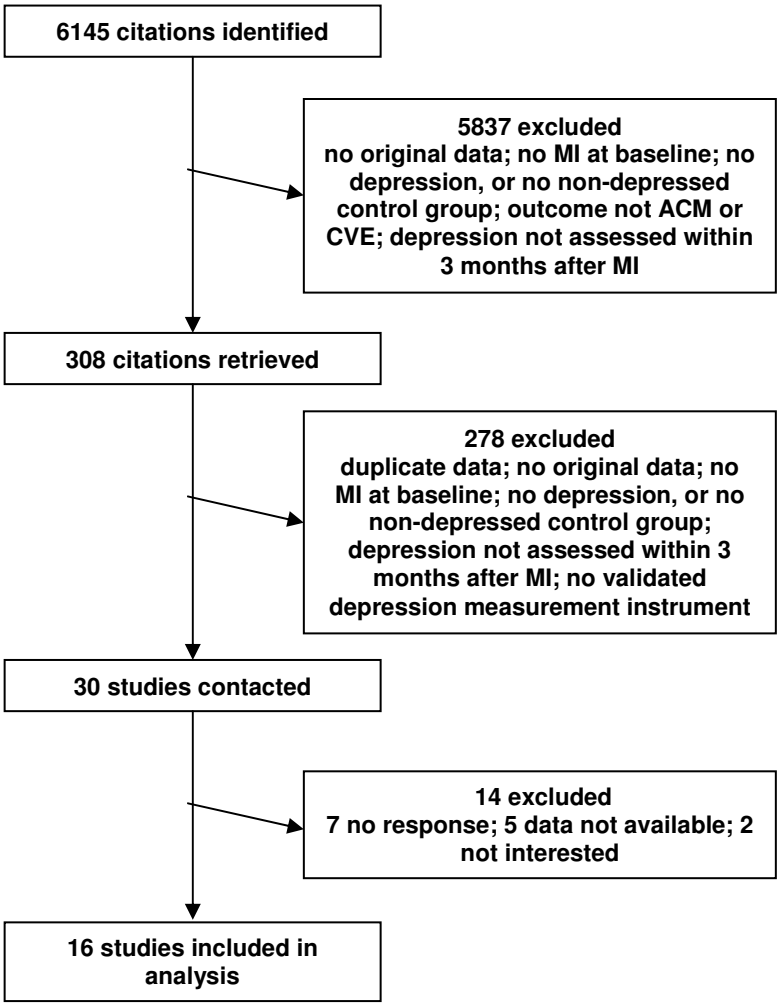


Table 1: Overview of participating studies

PI, study name, country	Start of study	N[3] / % male	Inclusion criteria	Exclusion criteria	Mean age	Depression measurement instrument[1] and cut-off score	N / % depressed	Mean depression score (SD)	Mean follow-up time (days)	No. of events ACM / CVE
R. Carney, J. A. Blumenthal ENRICHD and ancillary HRV study[2] USA(41-43)	1996 / 1997	2848 / 58%	standardized criteria for MI; low social support or depression ancillary study: no depression or social isolation, otherwise eligible for ENRICHD	other life-threat. med. illn.; cogn. impairm.; too ill; other major psych. disord.; unable/refused to participate	61	BDI-1A ≥ 10	1951 / 69%	14.13 (8.87)	ACM: 834 CVE: 609	ACM: 350 CVE: 1151
J. Ormel, P. de Jonge, MIND-IT The Netherlands(40)	1999	1814/77%	standardized criteria for MI age ≥ 18	other life-threat. med. illn.; MI during hosp. for other reason; psych. depr. treatm; part. in conflicting clin. trial	61	BDI 1-A ≥ 10	BDI: 474 / 26%	6.77 (6.18)	ACM: 2167 CVE: 1517	ACM: 278 CVE: 784
J. Ormel, P. de Jonge DepreMI The Netherlands(44)	1997	528 / 81%	standardized criteria for MI	other life-threat. med. illn.; cogn. impairm.; too ill; unable to communicate; MI during hosp. for other reason	61	modified Dutch version of CIDI 2.1 BDI 1A ≥ 10	CIDI: 73 / 15% BDI: 117 / 23%	6.80 (6.12)	ACM: 2663 CVE: 1851	ACM: 116 CVE: 237
J. Denollet The Netherlands(20)	2003	501 / 78%	Standardized criteria for MI; Age > 30	other life-threat. med. illn.; cogn. Impairm.	60	BDI-1A ≥ 10	132 / 26%	7.03 (6.18)	ACM: 1374 CVE: 1284	ACM: 38 CVE: 82
F. Doyle, H. M. McGee Ireland(55)	2003	433 / 75%	standardized criteria for ACS (only MI patients were included in the IPD meta-analysis)	nr	63	HADS-D > 7 BDI-FS > 3	HADS-D or BDI-FS: 75 / 17%	HADS-D: 4,14 (3,26) BDI-FS: 1.88 (2.69)	ACM: 356 CVE: na	ACM: 17 CVE: na

F. Doyle, H.M. McGee Ireland(56)	2006	285 / 80%	standardized criteria for ACS (only MI patients were included in the IPD meta-analysis)	patient too distressed	61	HADS-D > 7 BDI-FS (6-item) > 3	either HADS-D or BDI-FS: 78 / 27% HADS-D: 33 / 12%; BDI-FS 69 / 24%	HADS-D: 3,52 (3,07) BDI-FS: 2.15 (2.84)	ACM: 427 CVE: 427	ACM: 19 CVE: 67
S. Bergerone Italy(45)	1999	98 / 78%	standardized criteria for MI	in-hosp. mort.; other major psych. disord.; alcoholism; antidepr. therapy	62	struct. int. based on DSM-IV criteria BDI 1A ≥ 10	MDD: 14 / 14% BDI: 35 / 34%	BDI: 8.34 (8.48)	ACM: 1485 CVE: 1485	ACM: 6 CVE: 29
S.H. Hosseini Iran(39)	2004	540 / 69%	standardized criteria for MI	other life-threat. med. illn.; MI result of CABG or angiogr.; too ill	58	BDI 1A ≥ 10	355 / 66%	14.20 (9.80)	na (24 months)	ACM: naCVE: 55
D.A. Lane UK(46, 47)	1997	288 / 75%	standardized criteria for MI	other life-threat. med. illn.; cogn. impairm.; MI result of CABG or angiogr.; unable to communicate; too ill	63	BDI 1A ≥ 10	89 / 31%	7.72 (6.26)	ACM: 976 CVE:na	ACM: 38 CVE: na
L. Pilote Canada(48)	1996	553 / 81%	acute MI; surv. up to 24 hours after hosp. adm.; adm. through emergency dept.	phys. unable to respond to quest.; unable to communicate	60	BDI 1 ≥10	193 / 35%	9.07 (7.93)	ACM: 350 CVE: 205	ACM: 32 CVE: 222
K. Parakh, R.C. Ziegelstein USA(49)	1995	284 / 57%	standardized criteria for MI	other life-threat. med. illn.; cogn. impairm.; too ill	65	SCID BDI 1A ≥10	MDD: 29 / 10% BDI: 56 / 20%	BDI: 5.76 (6.15)	ACM: 2428 CVE: na	ACM: 153 CVE: na
C. Rafanelli Italy(33)	1995	61 / 85%	standardized criteria for MI; first MI	nr	59	modified SCID (minor and major depression	7 / 11%	na	na (24 months)	ACM: 4 CVE: 22
H. Sato OACIS Japan(51)	1998	1042 / 80%	standardized criteria for MI	in-hosp. mort.; other major psych. disord.; unable to communicate	63	ZSDS ≥ 40	438 / 42%	38.03 (9.07)	na (12 months)	ACM: na CVE: 283

R.P. Steeds UK(52)	1999	131 / 33%	MI; age < 75	nr	60	BDI-II ≥ 14	52 / 40%	12.42 (9.09)	ACM: 457 CVE: na	ACM: 11 CVE: na
S.L. Grace Canada(53)	1997	468 / 72%	confirmed MI; age ≥ 18	too ill; unable to communicate	61	BDI 1A ≥ 10	136 / 28%	7.93 (7.22)	na (12 months)	ACM: 29 CVE: 101
C. Welin Sweden(54)	1985	270 / 84%	standardized criteria for MI; first MI; age < 65	nr	56	ZSDS ≥ 40	96/ 36%	36.76 (8.58)	na (120 months)	ACM: 65 CVE: 73

[1] Depression measurement instrument used in the current individual patient data meta-analysis.

[2] Part of the non-depressed control group came from an ancillary study and part of the patients in the non-depressed control group had low social support. Depressed patients were oversampled for the purpose of the study.

[3] Number of patients included in IPD-meta-analysis.

Abbreviations: ACM: All-cause mortality; ACS: acute coronary syndrome; BDI: Beck Depression Inventory; BDI-FS: Beck Depression Inventory Fast Scale; CIDI: Composite International Diagnostic Interview; CVE: cardiovascular events; DepreMI: Depression after Myocardial Infarction; ENRICHD: Enhancing Recovery in Coronary Heart Disease; HADS-D: Hospital Anxiety and Depression Scale-Depression subscale; HRV: heart rate variability; MDD: major depression disorder; MI: myocardial infarction; MIND-IT: Myocardial Infarction and Depression Intervention Trial; na: not available; nr: not reported; OACIS: Osaka Acute Coronary Insufficiency Study; PI: primary investigator; SCID: Structured Clinical Interview for DSM; SD: standard deviation; ZSDS: Zung Self-rating Depression Scale

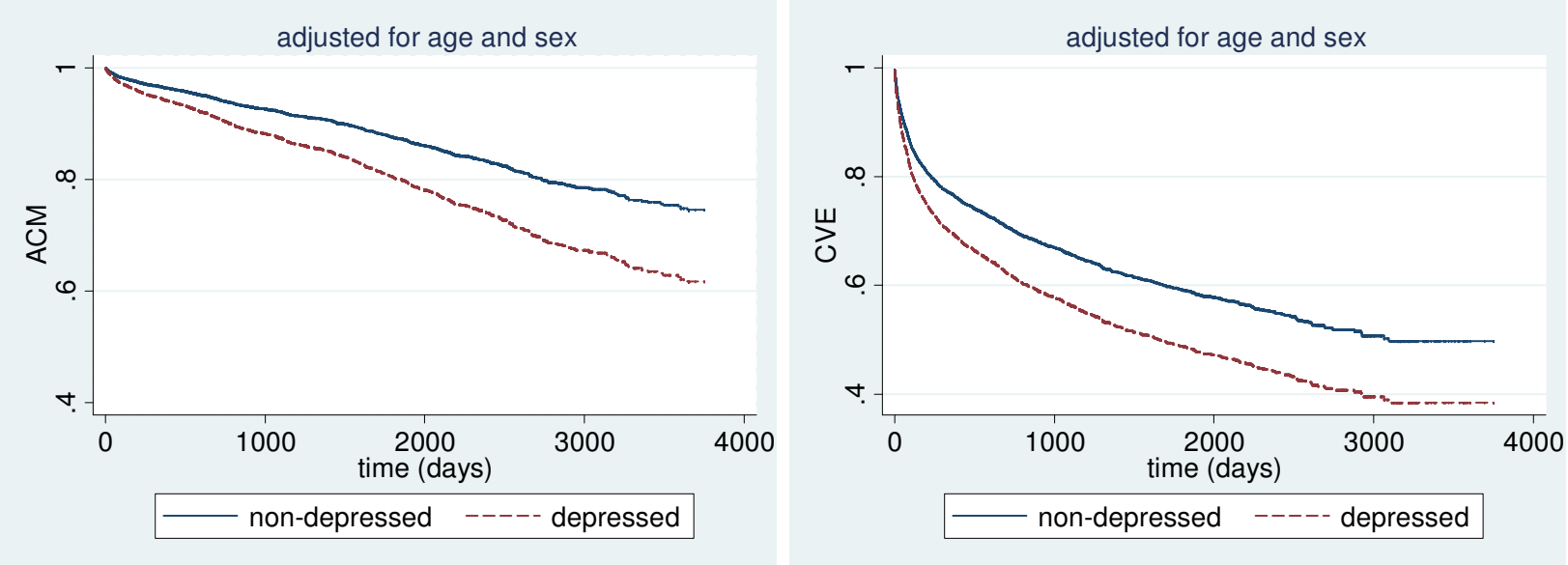
Table 2: Baseline patient characteristics by depression status

	Depressed patients (n=4,043)	Non-depressed patients (n=6,132)	p-value difference	N measured
Demographic characteristics				
Age	60.5 (12.2)	61.4 (11.6)	<0.001	10,171
Sex (% male)	63.3	75.7	<0.001	10,175
Employment status (% employed)	43.1	46.6	0.004	6,528
Partner status (% with partner)	63.7	73.7	<0.001	6,412
Cardiac disease severity				
History of MI (% yes)	21.8	17.0	<0.001	9,646
LVEF (% of patients <40%)	27.0	21.3	0.001	3,505
Killip class (% poor)	21.6	15.7	<0.001	7,532
PTCA (%)	48.7	43.6	<0.001	7,679
History of PTCA (%)	13.4	9.3	<0.001	4,830
CABG (%)	11.5	8.5	<0.001	8,139
History of CABG (%)	11.4	8.2	<0.001	4,849
Thrombolysis (%)	32.5	34.8	0.037	8,065
Congestive HF (%)	29.0	12.3	<0.001	6,104
Other risk factors				
Diabetes (%)	27.8	17.3	<0.001	10,060
Smoking (%)	43.1	45.6	0.017	9,942
BMI (mean, (SD))	27.6 (5.6)	26.7 (4.5)	<0.001	7,188
Hyperlipidemia / hypercholesterolemia (%)	48.7	45.5	0.004	8,405
Hypertension (%)	31.0	35.8	<0.001	8,301
History of hypertension (%)	55.2	44.4	<0.001	5,348
Medication use				
Hypolipidemics (%)	42.7	44.7	0.230	4,004
Beta-blockers (%)	68.7	74.0	<0.001	8,833

Aspirin (%)	86.3	87.8	0.051	7,561
Calcium-channel blockers / antagonists (%)	19.3	14.9	<0.001	7,056
ACE-inhibitors (%)	48.1	49.6	0.160	8,550
Antidepressant use (%)	10.1	3.2	<0.001	5,507

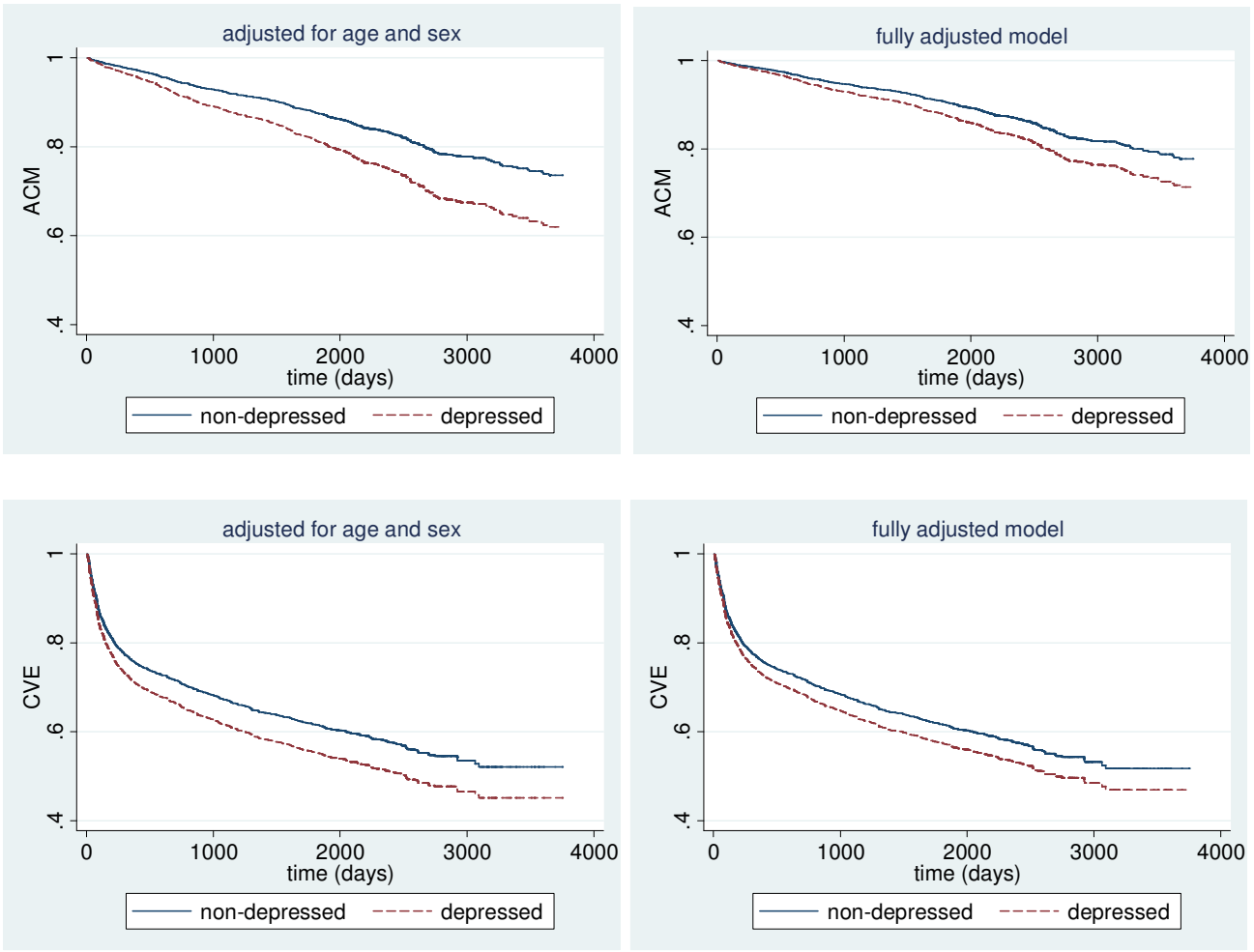
ACE: angiotensin converting-enzyme; BMI: body mass index; CABG: coronary artery bypass graft; HF: heart failure; LVEF: left ventricular ejection fraction; MI: myocardial infarction; PTCA: percutaneous transluminal coronary angioplasty; SD: standard deviation

Figure 2: survival curves all-cause mortality and cardiovascular events adjusted for age and sex



Left panel: all-cause mortality survival curves based on 10 studies and 7691 patients. Right panel: cardiovascular events survival curves based on 7 studies and 6616 patients.

Figure 3: Survival curves all-cause mortality and cardiovascular events for the base and fully adjusted models



Top panel: All-cause mortality survival curves based on 3 studies and 2239 patients. Bottom panel: Cardiovascular events survival curves based on 2 studies and 1973 patients.

Table 3: Hazard ratios for all-cause mortality, unadjusted and adjusted for cardiac disease severity and other health-related variables

	HR unadjusted[1] (95% CI)	HR adjusted[1] (95% CI)	% change	N / n studies[2]
Sociodemographic variables				
Age, sex[3]	1.26 (1.18-1.35)***	1.32 (1.26-1.38)***	+17%	7,628 / 10
Cardiac disease severity variables				
History of MI	1.32 (1.26-1.39)***	1.29 (1.24-1.36)***	-8%	7,543 / 10
LVEF (low vs normal)	1.30 (1.23-1.39)***	1.25 (1.18-1.33)***	-15%	3,115 / 5
Killip class (I vs II, III or IV)	1.31 (1.25-1.38)***	1.25 (1.18-1.32)***	-19%	5,924 / 6
General health variables				
Diabetes	1.31 (1.25-1.38)***	1.29 (1.22-1.36)***	-7%	7,587 / 10
Smoking	1.33 (1.27-1.39)***	1.33 (1.27-1.39)***	-1%	7,485 / 10
BMI	1.34 (1.27-1.41)***	1.34 (1.28-1.41)***	0%	6,133 / 7
Model including all variables				
(Age, sex) history of MI, LVEF, Killip class, diabetes, smoking, BMI	1.33 (1.23-1.44)***	1.23 (1.15-1.31)***	-28%	2,226 / 3
(Age, sex) history of MI, LVEF, Killip class	1.32 (1.24-1.40)***	1.22 (1.13-1.31)***	-29%	2,400 / 3

ACM: all-cause mortality; BMI: body mass index; CI: confidence interval; HR: hazard ratio; LVEF: left ventricular ejection fraction; MI: myocardial infarction

Note that column 2 represents unadjusted HRs, based on analyses including only those patients that had scores available for the variables concerned

[1] depression is included in all the models as a continuous variable (z-score)

[2] depending on availability of these variables in each study

[3] the model including depression, age, and sex is the comparison model

*** p<0.001

** p<0.01

Table 4: Hazard ratios for cardiovascular events, unadjusted and adjusted for cardiac disease severity and other health-related variables

	HR unadjusted[1] (95% CI)	HR adjusted[1] (95% CI)	% change	N / n studies[2]
Sociodemographic variables				
Age, sex[3]	1.18 (1.13-1.23)***	1.19 (1.14-1.24)***	+2%	6,556 / 7
Cardiac disease severity variables				
History of MI	1.19 (1.13-1.24)***	1.17 (1.12-1.22)***	-9%	6,475 / 7
LVEF (low vs normal)	1.18 (1.12-1.25)***	1.16 (1.10-1.23)***	-10%	2,904 / 5
Killip class (I vs II, III or IV)	1.17 (1.12-1.22)***	1.15 (1.11-1.20)***	-12%	5,410 / 5
General health variables				
Diabetes	1.19 (1.14-1.24)***	1.17 (1.13-1.22)***	-7%	6,522 / 7
Smoking	1.19 (1.13-1.24)***	1.19 (1.13-1.24)***	0%	6,416 / 7
BMI	1.18 (1.12-1.25)***	1.18 (1.12-1.25)***	0%	5,757 / 5
Model including all variables				
(Age, sex) history of MI, LVEF, Killip class, diabetes, smoking, BMI	1.17 (1.05-1.30)**	1.12 (1.01-1.25)*	-25%	1,962 / 2
(Age, sex) history of MI, LVEF, Killip class	1.17 (1.09-1.26)***	1.13 (1.07-1.19)***	-21%	2,178 / 3

BMI: body mass index; CI: confidence interval; CVE: cardiovascular events; HR: hazard ratio; LVEF: left ventricular ejection fraction; MI: myocardial infarction

Note that column 2 represents unadjusted HRs, based on analyses including only those patients that had scores available for the variables concerned

[1] depression is included in all the models as a continuous variable (z-score)

[2] depending on availability of these variables in each study

[3] the model including depression, age, and sex is the comparison model

*** p<0.001

** p<0.01

* p<0.05

Table 5: Odds ratios for all-cause mortality, unadjusted and adjusted for cardiac disease severity and health related variables

All-cause mortality	OR unadjusted[1] (95% CI)	OR adjusted[1] (95% CI)	% change	N / n studies[2]
Sociodemographic variables				
Age, sex***	1.33 (1.25-1.41)***	1.41 (1.34-1.49)***	+18%	8.362 / 12
General health variables				
Diabetes	1.41 (1.33-1.48)***	1.37 (1.30-1.45)***	-7%	8273 / 12
Smoking	1.42 (1.35-1.49)***	1.42 (1.34-1.49)***	-1%	8192 / 12
BMI	1.43 (1.35-1.52)***	1.40 (1.35-1.52)***	0%	6132 / 7
Cardiac disease severity variables				
History of MI	1.41 (1.33-1.487)***	1.37 (1.30-1.44)***	-8%	8007 / 11
LVEF	1.36 (1.25-1.49)***	1.31 (1.21-1.43)***	-12%	3330 / 6
Killip class	1.40 (1.33-1.48)***	1.35 (1.26-1.44)***	-13%	6367 / 7
Model Including all variables				
(Age, sex) history of MI, LVEF, Killip class, diabetes, smoking, BMI	1.37 (1.18-1.59)***	1.24 (1.07-1.44)***	-30%	2225 / 3
(Age, sex) history of MI, LVEF, Killip class	1.36 (1.24-1.50)***	1.27 (1.17-1.37)***	-25%	2399 / 3

ACM: all-cause mortality; BMI: body mass index; CI: confidence interval; HR: hazard ratio; LVEF: left ventricular ejection fraction; MI: myocardial infarction

[1] depression is included in all the models as a continuous variable (z-score)

[2] depending on availability of these variables in each study

[3] the model including depression, age, and sex is the comparison model

*** p<0.001

** p<0.01

* p<0.05

Table 6: Odds ratios for cardiovascular events, unadjusted and adjusted for cardiac disease severity and health related variables

	OR unadjusted[1] (95% CI)	OR adjusted[1] (95% CI)	% change	N / n studies[2]
Sociodemographic variables				
Age, sex	1.25 (1.19-1.31)***	1.25 (1.19-1.32)***	+1%	8,878 / 11
General health variables				
Diabetes	1.25 (1.19-1.32)***	1.24 (1.18-1.29)***	-6%	8,770 / 11
Smoking	1.25 (1.20-1.31)***	1.26 (1.20-1.32)***	0%	8,654 / 11
BMI	1.25 (1.16-1.35)***	1.25 (1.16-1.35)***	0%	6,759 / 6
Cardiac disease severity variables				
History of MI	1.24 (1.17-1.32)***	1.23 (1.16-1.29)***	-7%	8,415 / 10
LVEF	1.26 (1.18-1.35)***	1.24 (1.15-1.34)***	-8%	3,123 / 6
Killip class	1.24 (1.16-1.32)***	1.22 (1.16-1.28)***	-7%	6,874 / 7
Model Including all variables				
(Age, sex) history of MI, LVEF, Killip class, diabetes, smoking, BMI	1.24 (1.07-1.44)**	1.18 (1.00-1.40,)p=0.053	-23%	1,964 / 2
(Age, sex) history of MI, LVEF, Killip class	1.23 (1.17-1.30)***	1.19 (1.12-1.26)***	-19%	2,181 / 3

BMI: body mass index; CI: confidence interval; CVE: cardiovascular events; HR: hazard ratio; LVEF: left ventricular ejection fraction; MI: myocardial infarction

[1] depression is included in all the models as a continuous variable (z-score)

[2] depending on availability of these variables in each study

[3] the model including depression, age, and sex is the comparison model

*** p<0.001

** p<0.01

* p<0.05

Appendix 1: Search strings PubMed, Embase, and PsycINFO

PubMed

("mood disorders" [MeSH] OR depression [MeSH] OR depression [tiab] OR depressive [tiab]) AND ("myocardial infarction" [MeSH] OR "myocardial infarction" [tiab])

humans only

Embase

("mood disorder" OR "depressive symptoms" OR "depressive symptomatology" OR depressed) AND ("heart infarction" OR "myocardial infarction")

map to preferred terminology, explosion search, search terms must me major focus, search humans only, Embase only.

PsycInfo

((major depression) OR depression OR depressive) AND ((myocardial infarctions) OR (myocardial infarction))

Appendix 2: Overview of non-participating studies

First author; study name; country	Start of study	N / % male	Inclusion criteria	Exclusion criteria	Mean age	Depression measurement instrument / cut-off score	N / % depressed	Follow-up time (days)	Reason for exclusion
D.K. Ahern(85) CAPS USA	1983	351 / na	MI 6-60 days pre-enrollm., basel. Holter mon. ≥ 10 ventr. prem. compl./hour or ≥ 5 ep. of unsust. ventr. tach.; age < 75; LVEF > 20%	illiterate in English; inadequate eyesight; poor dominant hand mobility	nr	BDI, version nr; cutoff nr	140 / 40%	365	unable to contact
N. Frasure-Smith(16) EPPI / M-HART Canada	1991	896 / 68%	standardized criteria for MI	other life-threat. med. illn.; cogn. impairm.; periproc. MI; unable to commun.; too ill; lived too far away; adm. reas.	59	BDI, version nr / ≥ 10	290 / 32%	365	not interested
N. Frasure-Smith(86) Canada	1991	222 / 78%	standardized criteria for MI	other life-threat. med. illn.; cogn. impairm.; periproc. MI; unable to commun.; too ill	60	BDI, version nr / ≥ 10 DIS	66 / 31% 34 / 15%	549	not interested
J. Irvine(87) CAMIAT Canada	1990	301 / 82%	standardized criteria for MI; freq. or repet. ventr. depol. within 6 to 45 days of MI	illiterate in English and French; death before 2-week postrandomiz. clinic visit	64	BDI, version nr / ≥ 10	98 / 33%	732	unable to contact
M.W. Kaufmann(88) USA	1995	331 / 66%	standardized criteria for MI	other life-threat. med. illn.; cogn. impairm.; illiterate in English; too ill; in hosp. mortality	65	DIS / ≥ 5	87 / 26%	365	unable to contact

K.H. Ladwig(89) PILP Germany	1983	553 / 100%	standardized criteria for MI; male sex; age < 66	nr	54	KSb-S / 90%	80 / 14%	183	data not available
R.A. Mayou(90) OMIS UK	1994	344 / 73%	standardized criteria for MI	age > 80; index MI within 28 days of preceding event	63	HADS / ≥ 11	26 / 8%	549	data not available
D. Nakatani(91) OACIS Japan	1999	1803 / na	standardized criteria for MI	unable to commun.; in-hosp. mortality; major psych. disorder	na	ZSDS / ≥ 40	860 / 48%	732	data not available
J.S. Rumsfeld(92) EPHESUS USA	1999	634 / 72%	standardized criteria for MI; MI complic. by LV dysfunction and heart failure	valvular or congen. heart failure; diuretics other than eplerenone	65	MOS-D / ≥ 0.06	143 / 23%	488	unable to contact
P. Silverstone(93) UK	1984	108 / 75%	MI	nr	63	MADRS / ≥ 14	48 / 44%	8	unable to contact
K.G. Smolderen(94) PREMIER USA	2003	2347 / 68%	standardized criteria for MI; age ≥ 18	transfer from other fac. > 24 hours after MI; incarcerated; unable to commun.	61	PHQ / ≥ 10	516 / 22%	1460	data not available
C. Sørensen(95) Denmark	1999	761 / 76%	standardized criteria for MI	other life-threat. med. illn.; age > 76; major psych. disorder; unable to speak Danish; not living in Denmark	59	MDI / cutoff nr	73 / 10%	365	unable to contact
J.J. Strik(96) The Netherlands	1997	206 / 76%	standardized criteria for MI; first MI	other life-threat. med. illn.; major psych. disorder; unable to commun.; living too far away	59	SCID	63 / 31%	1095	unable to contact

S.J. Sydeman(97) USA	1996	111 / 60%	standardized criteria for MI	other life-threat. med. illn.; periproc. MI; age < 35; illiterate in English; cogn. impairm.; too ill; in-hosp. mortality	62	BDI / ≥ 10 SCID	BDI: nr SCID: 5 / 5%	183	data not available

BDI: Beck Depression Inventory; CAMIAT: Canadian Amiodarone Myocardial Infarction Arrhythmia Trial; CAPS: Cardiac Arrhythmia Pilot Study; DIS: Diagnostic Interview Schedule; EPHESUS: Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study; EPPI: Emotions and Prognosis Post-Infarct; KSb-S: Klinische Selbstbeurteilungsskalen aus dem Münchner psychiatrische Informations-System; MADRS: Montgomery-Åsberg Depression Rating Scale; MDI: Major Depression Inventory; M-HART: Montréal Heart Attack Readjustment Trial; MOS-D: Medical Outcomes Study-Depression Score; nr: not reported; OACIS: Osaka Acute Coronary Insufficiency Study; OMIS: Oxford Myocardial Incidence Study; PHQ: Patient Health Questionnaire; PILP: Post Infarction Late Potential Study; PREMIER: Prospective Registry Evaluating outcomes after Myocardial Infarction: Events and Recovery; SCID: Structured Clinical Interview for DSM; ZSDS: Zung Self-rating Depression Scale

Appendix 3: MOOSE checklist

Item	Page
Reporting of background should include	
Problem definition	4
Hypothesis statement	not applicable
Description of study outcome(s)	9
Type of exposure or intervention used	7
Type of study designs used	6
Study population	6
Reporting of search strategy should include	
Qualifications of searchers (eg, librarians and investigators)	51
Search strategy, including time period included in the synthesis and keywords	5,6, appendix 1
Effort to include all available studies, including contact with authors	6, 7
Databases and registries searched	5
Search software used, name and version, including special features used (eg, explosion)	Appendix 1
Use of hand searching (eg, reference lists of obtained articles)	5, 6
List of citations located and those excluded, including justification	Figure 1
Method of addressing articles published in languages other than English	5
Method of handling abstracts and unpublished studies	not applicable
Description of any contact with authors	6, 7
Reporting of methods should include	
Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	6
Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	7-9
Documentation of how data were classified and coded (eg, multiple raters, blinding, and interrater reliability)	not available
Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	not available
Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	reported elsewhere[5]
Assessment of heterogeneity	10
Description of statistical methods (eg, complete description of fixed or random effects models,	9-13
justification of whether the chosen models account for predictors of study results,	9-13
dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	not applicable

Provision of appropriate tables and graphics	32-34
Reporting of results should include	
Graphic summarizing individual study estimates and overall estimate	Not applicable
Table giving descriptive information for each study included	33-35
Results of sensitivity testing (eg, subgroup analysis)	Not applicable
Indication of statistical uncertainty of findings	25-28
Reporting of discussion should include	
Quantitative assessment of bias (eg, publication bias)	20
Justification for exclusion (eg, exclusion of non–English-language citations)	Appendix 2
Assessment of quality of included studies	Reported elsewhere[5]
Reporting of conclusions should include	
Consideration of alternative explanations for observed results	21, 22, 27, 28
Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	25
Guidelines for future research	28, 29
Disclosure of funding source	30-31

Authors:
Anna Meijer, MSc, Interdisciplinary Centre for Psychiatric Epidemiology, University Medical Centre Groningen, Groningen, The Netherlands; **Henk Jan Conradi**, PhD, Department of Clinical Psychology, University of Amsterdam, Amsterdam, The Netherlands; **Elske H. Bos**, PhD, Interdisciplinary Centre for Psychiatric Epidemiology, University Medical Centre Groningen, Groningen, The Netherlands; **Matteo Anselmino**, MD, PhD, Division of Cardiology, Department of Internal Medicine, San Giovanni Battista Hospital, University of Turin, Turin, Italy; **Robert M. Carney**, PhD, Department of Psychiatry, Washington University, St. Louis, USA; **Johan Denollet**, PhD, Centre of Research on Psychology in Somatic diseases, Tilburg University, Tilburg, The Netherlands; **Frank Doyle**, PhD, Division of Population Health Sciences (Psychology), Royal College of Surgeons in Ireland, Dublin, Ireland; **Kenneth E. Freedland**, PhD, Department of Psychiatry, Washington University, St. Louis, USA; **Sherry L. Grace**, PhD, School of Kinesiology and Health Science, York University, and University Health Network, Toronto, Canada; **Seyed Hamzeh Hosseini**, MD, Psychiatry and Science Behavior Research Centre, Department of Psychiatry, Mazandaran University of Medical Sciences, Sari, Iran; **Deirdre A. Lane**, PhD, University of Birmingham Centre for Cardiovascular Sciences, City Hospital, Birmingham, UK; **Louise Pilote**, MD, MPH, PhD, Divisions of General Internal Medicine and Clinical Epidemiology, McGill University Health Centre, Montréal, Canada; **Kapil Parakh**, MD, MPH, PhD, Department of Medicine, Johns Hopkins University School of Medicine, Johns Hopkins Bayview Medical Centre, Baltimore, USA; **Chiara Rafanelli**, MD, PhD, Department of Psychology, University of Bologna, Bologna, Italy; **Hiroshi Sato**, MD, PhD, School of Human Welfare Studies, Kwansei Gakuin University, Nishinomiya, Japan; **Richard Steeds**, MA, MRCP, MD, Department of Cardiology, Queen Elizabeth Hospital, Birmingham, UK; **Catharina Welin**, RN, PhD, Institute of Health and Care Sciences, The Sahlengrenska Academy, University of Gothenburg, Gothenburg, Sweden; **Peter de Jonge**, PhD, Interdisciplinary Centre for Psychiatric Epidemiology, University Medical Centre Groningen, Groningen, The Netherlands

Additional researchers involved in individual studies:
Johan Ormel, PhD, Interdisciplinary Centre for Psychiatric Epidemiology, University Medical Centre Groningen, Groningen, The Netherlands; **Serena Bergerone**, MD, Division of Cardiology, Department of Internal Medicine, San Giovanni Battista Hospital, University of Turin, Turin, Italy; **Lisa Berkman**, PhD, Centre for Population and Development Studies, Harvard University, Boston, USA; **Hannah McGee**, BA, PhD, Division of Population Health Sciences (Psychology), Royal College of Surgeons in Ireland, Dublin, Ireland; **Ronán Conroy**, BA, Division of Population Health Sciences (Epidemiology & Public Health Medicine), Royal College of Surgeons in Ireland, Dublin, Ireland; **Roy Ziegelstein**, MD, Department of Medicine, Johns Hopkins University School of Medicine, Johns Hopkins Bayview Medical Centre, Baltimore, USA

Correspondence:
Anna Meijer, Interdisciplinary Centre for Psychiatric Epidemiology, University Medical Centre Groningen, 9713 GZ Groningen, The Netherlands. Email: anna.meijer@umcg.nl

Reference list

1 Thombs BD, Bass EB, Ford DE, Stewart KJ, Tsilidis KK, Patel U, Fauerbach JA, Bush DE, Ziegelstein RC. Prevalence of depression in survivors of acute myocardial infarction. *J.Gen.Intern.Med.* 2006; **21**: 30-8.

2 Beekman AT, Copeland JR, Prince MJ. Review of community prevalence of depression in later life. *Br.J.Psychiatry* 1999; **174**: 307-11.

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**: 802-13.

4 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**: 2763-74.

5 Meijer A, Conradi HJ, Bos EH, Thombs BD, van Melle JP, de Jonge P. Prognostic association of depression following myocardial infarction with mortality and cardiovascular events: a meta-analysis of 25 years of research. *Gen.Hosp.Psychiatry* 2011; **33**: 203-16.

6 Frasure-Smith N, Lesperance F. Depression and cardiac risk: present status and future directions. *Heart* 2010; **96**: 173-6.

7 van Melle JP, de Jonge P, Ormel J, Crijns HJ, van Veldhuisen DJ, Honig A, Schene AH, van den Berg MP, MIND-IT investigators. Relationship between left ventricular dysfunction and depression following myocardial infarction: data from the MIND-IT. *Eur.Heart J.* 2005; **26**: 2650-6.

8 Delisle VC, Beck AT, Ziegelstein RC, Thombs BD. Symptoms of heart disease or its treatment may increase Beck Depression Inventory Scores in hospitalized post-myocardial infarction patients. *J.Psychosom.Res.* 2012; **73**: 157-62.

9 Freedland KE, Rich MW, Skala JA, Carney RM, Davila-Roman VG, Jaffe AS. Prevalence of depression in hospitalized patients with congestive heart failure. *Psychosom.Med.* 2003; **65**: 119-28.

10 Raison CL, Capuron L, Miller AH. Cytokines sing the blues: inflammation and the pathogenesis of depression. *Trends Immunol.* 2006; **27**: 24-31.

11 Evans DL, Charney DS, Lewis L, Golden RN, Gorman JM, Krishnan KR, Nemeroff CB, Bremner JD, Carney RM, Coyne JC, Delong MR, Frasure-Smith N, Glassman AH, Gold PW, Grant I, Gwyther L, Ironson G, Johnson RL, Kanner AM, Katon WJ,

Kaufmann PG, Keefe FJ, Ketter T, Laughren TP, Leserman J, Lyketsos CG, McDonald WM, McEwen BS, Miller AH, Musselman D, O'Connor C, Petitto JM, Pollock BG, Robinson RG, Roose SP, Rowland J, Sheline Y, Sheps DS, Simon G, Spiegel D, Stunkard A, Sunderland T, Tibbits P,Jr, Valvo WJ. Mood disorders in the medically ill: scientific review and recommendations. *Biol.Psychiatry* 2005; **58**: 175-89.

12 Carney RM, Freedland KE, Miller GE, Jaffe AS. Depression as a risk factor for cardiac mortality and morbidity: a review of potential mechanisms. *J.Psychosom.Res.* 2002; **53**: 897-902.

13 Golden SH, Lazo M, Carnethon M, Bertoni AG, Schreiner PJ, Diez Roux AV, Lee HB, Lyketsos C. Examining a bidirectional association between depressive symptoms and diabetes. *J.Am.Med.Assoc.* 2008; **299**: 2751-9.

14 Anda RF, Williamson DF, Escobedo LG, Mast EE, Giovino GA, Remington PL. Depression and the dynamics of smoking. A national perspective. *JAMA* 1990; **264**: 1541-5.

15 Carney RM, Blumenthal JA, Catellier D, Freedland KE, Berkman LF, Watkins LL, Czajkowski SM, Hayano J, Jaffe AS. Depression as a risk factor for mortality after acute myocardial infarction. *Am.J.Cardiol.* 2003; **92**: 1277-81.

16 Frasure-Smith N, Lesperance F, Juneau M, Talajic M, Bourassa MG. Gender, depression, and one-year prognosis after myocardial infarction. *Psychosom.Med.* 1999; **61**: 26-37.

17 Parashar S, Rumsfeld JS, Spertus JA, Reid KJ, Wenger NK, Krumholz HM, Amin A, Weintraub WS, Lichtman J, Dawood N, Vaccarino V. Time course of depression and outcome of myocardial infarction. *Arch.Intern.Med.* 2006; **166**: 2035-43.

18 Lee KL, Woodlief LH, Topol EJ, Weaver WD, Betriu A, Col J, Simoons M, Aylward P, Van de Werf F, Califf RM. Predictors of 30-day mortality in the era of reperfusion for acute myocardial infarction. Results from an international trial of 41,021 patients. GUSTO-I Investigators. *Circulation* 1995; **91**: 1659-68.

19 Mueller HS, Cohen LS, Braunwald E, Forman S, Feit F, Ross A, Schweiger M, Cabin H, Davison R, Miller D. Predictors of early morbidity and mortality after thrombolytic therapy of acute myocardial infarction. Analyses of patient subgroups in the Thrombolysis in Myocardial Infarction (TIMI) trial, phase II. *Circulation* 1992; **85**: 1254-64.

20 Denollet J, Martens EJ, Smith OR, Burg MM. Efficient assessment of depressive symptoms and their prognostic value in myocardial infarction patients. *J.Affect.Disord.* 2010; **120**: 105-11.

21 Cooper H, Patall EA. The relative benefits of meta-analysis conducted with individual participant data versus aggregated data. *Psychol.Methods* 2009; **14**: 165-76.

22 Simmonds MC, Higgins JP, Stewart LA, Tierney JF, Clarke MJ, Thompson SG. Meta-analysis of individual patient data from randomized trials: a review of methods used in practice. *Clin.Trials* 2005; **2**: 209-17.

23 Curran PJ, Hussong AM. Integrative data analysis: the simultaneous analysis of multiple data sets. *Psychol.Methods* 2009; **14**: 81-100.

24 Poppe KK, Doughty RN, Yu CM, Quintana M, Moller JE, Klein AL, Gamble GD, Dini FL, Whalley GA, MeRGE collaborators. Understanding differences in results from literature-based and individual patient meta-analyses: an example from meta-analyses of observational data. *Int.J.Cardiol.* 2011; **148**: 209-13.

25 van Walraven C. Individual patient meta-analysis--rewards and challenges. *J.Clin.Epidemiol.* 2010; **63**: 235-7.

26 Stewart LA, Tierney JF. To IPD or not to IPD? Advantages and disadvantages of systematic reviews using individual patient data. *Eval.Health Prof.* 2002; **25**: 76-97.

27 Van Melle JP, De Jonge P, Spijkerman TA, Tijssen JG, Ormel J, Van Veldhuisen DJ, Van den Brink RH, Van den Berg MP. Prognostic association of depression following myocardial infarction with mortality and cardiovascular events: a meta-analysis. *Psychosom.Med.* 2004; **66**: 814-22.

28 Khot UN, Jia G, Moliterno DJ, Lincoff AM, Khot MB, Harrington RA, Topol EJ. Prognostic importance of physical examination for heart failure in non-ST-elevation acute coronary syndromes: the enduring value of Killip classification. *JAMA* 2003; **290**: 2174-81.

29 Burns RJ, Gibbons RJ, Yi Q, Roberts RS, Miller TD, Schaer GL, Anderson JL, Yusuf S, CORE Study Investigators. The relationships of left ventricular ejection fraction, end-systolic volume index and infarct size to six-month mortality after hospital discharge following myocardial infarction treated by thrombolysis. *J.Am.Coll.Cardiol.* 2002; **39**: 30-6.

30 Volpi A, De Vita C, Franzosi MG, Geraci E, Maggioni AP, Mauri F, Negri E, Santoro E, Tavazzi L, Tognoni G. Determinants of 6-month mortality in survivors of myocardial infarction after thrombolysis. Results of the GISSI-2 data base. The Ad hoc Working Group of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-2 Data Base. *Circulation* 1993; **88**: 416-29.

31 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.Clin.Epidemiol.* 2008; **61**: 832-9.

32 Golden SH, Lazo M, Carnethon M, Bertoni AG, Schreiner PJ, Diez Roux AV, Lee HB, Lyketsos C. Examining a bidirectional association between depressive symptoms and diabetes. *JAMA* 2008; **299**: 2751-9.

33 Rafanelli C, Milaneschi Y, Roncuzzi R, Pancaldi LG. Dysthymia before myocardial infarction as a cardiac risk factor at 2.5-year follow-up. *Psychosomatics* 2010; **51**: 8-13.

34 Smith CT, Williamson PR, Marson AG. Investigating heterogeneity in an individual patient data meta-analysis of time to event outcomes. *Stat.Med.* 2005; **24**: 1307-19.

35 Smith CT, Williamson PR, Marson AG. An overview of methods and empirical comparison of aggregate data and individual patient data results for investigating heterogeneity in meta-analysis of time-to-event outcomes. *J.Eval.Clin.Pract.* 2005; **11**: 468-78.

36 Sauerbrei W, Schumacher M. A bootstrap resampling procedure for model building: application to the Cox regression model. *Stat.Med.* 1992; **11**: 2093-109.

37 Whooley MA, de Jonge P, Vittinghoff E, Otte C, Moos R, Carney RM, Ali S, Dowray S, Na B, Feldman MD, Schiller NB, Browner WS. Depressive symptoms, health behaviors, and risk of cardiovascular events in patients with coronary heart disease. *JAMA* 2008; **300**: 2379-88.

38 Clarke MJ, Stewart LA. Meta-analyses using individual patient data. *J.Eval.Clin.Pract.* 1997; **3**: 207-12.

39 Hosseini SH, Yousefnejad K, Tabiban S, Nesarhoseyni V, Bagheri B, Kiasari AM, Ghaemian A, Ghadirnejad SN, Lolati HA, Amiri FN, Ashraf H, Mokhberi V. Effects of depression and anxiety symptoms on cardiac mortality following myocardial infarction: a 2-year follow-up. *Int.J.Psych.Clin.Pract.* 2011; **15**: 91-6.

40 van den Brink RH, van Melle JP, Honig A, Schene AH, Crijns HJ, Lambert FP, Ormel J. Treatment of depression after myocardial infarction and the effects on cardiac prognosis and quality of life: rationale and outline of the Myocardial INfarction and Depression-Intervention Trial (MIND-IT). *Am.Heart J.* 2002; **144**: 219-25.

41 Carney RM, Freedland KE, Steinmeyer B, Blumenthal JA, de Jonge P, Davidson KW, Czajkowski SM, Jaffe AS. History of depression and survival after acute myocardial infarction. *Psychosom.Med.* 2009; **71**: 253-9.

42 Carney RM, Blumenthal JA, Stein PK, Watkins L, Catellier D, Berkman LF, Czajkowski SM, O'Connor C, Stone PH, Freedland KE. Depression, heart rate variability, and acute myocardial infarction. *Circulation* 2001; **104**: 2024-8.

43 Anonymous Enhancing recovery in coronary heart disease patients (ENRICHD): study design and methods. The ENRICHD investigators. *Am.Heart J.* 2000; **139**: 1-9.

44 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.Cardiol.* 2006; **48**: 2204-8.

45 Drago S, Bergerone S, Anselmino M, Varalda PG, Cascio B, Palumbo L, Angelini G, Trevi PG. Depression in patients with acute myocardial infarction: influence on autonomic nervous system and prognostic role. Results of a five-year follow-up study. *Int.J.Cardiol.* 2007; **115**: 46-51.

46 Lane D, Carroll D, Ring C, Beevers DG, Lip GY. Mortality and quality of life 12 months after myocardial infarction: effects of depression and anxiety. *Psychosom.Med.* 2001; **63**: 221-30.

47 Lane D, Carroll D, Ring C, Beevers DG, Lip GY. Do depression and anxiety predict recurrent coronary events 12 months after myocardial infarction?. *QJM* 2000; **93**: 739-44.

48 Lauzon C, Beck CA, Huynh T, Dion D, Racine N, Carignan S, Diodati JG, Charbonneau F, Dupuis R, Pilote L. Depression and prognosis following hospital admission because of acute myocardial infarction. *CMAJ* 2003; **168**: 547-52.

49 Parakh K, Thombs BD, Fauerbach JA, Bush DE, Ziegelstein RC. Effect of depression on late (8 years) mortality after myocardial infarction. *Am.J.Cardiol.* 2008; **101**: 602-6.

50 Rafanelli C, Milaneschi Y, Roncuzzi R, Pancaldi LG. Dysthymia before myocardial infarction as a cardiac risk factor at 2.5-year follow-up. *Psychosomatics: Journal of Consultation Liaison Psychiatry* 2010; **51**: 8-13.

51 Shiotani I, Sato H, Kinjo K, Nakatani D, Mizuno H, Ohnishi Y, Hishida E, Kijima Y, Hori M, Sato H, Osaka Acute Coronary Insufficiency Study (OACIS) Group. Depressive symptoms predict 12-month prognosis in elderly patients with acute myocardial infarction. *J.Cardiovasc.Risk* 2002; **9**: 153-60.

52 Steeds RP, Bickerton D, Smith MJ, Muthusamy R. Assessment of depression following acute myocardial infarction using the Beck depression inventory. *Heart* 2004; **90**: 217-8.

53 Grace SL, Abbey SE, Pinto R, Shnek ZM, Irvine J, Stewart DE. Longitudinal course of depressive symptomatology after a cardiac event: effects of gender and cardiac rehabilitation. *Psychosom.Med.* 2005; **67**: 52-8.

54 Welin C, Lappas G, Wilhelmsen L. Independent importance of psychosocial factors for prognosis after myocardial infarction. *J.Intern.Med.* 2000; **247**: 629-39.

55 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**: 461-7.

56 Doyle F, Conroy R, McGee H, Delaney M. Depressive symptoms in persons with acute coronary syndrome: specific symptom scales and prognosis. *J.Psychosom.Res.* 2010; **68**: 121-30.

57 Carney RM, Freedland KE, Rich MW, Jaffe AS. Depression as a risk factor for cardiac events in established coronary heart disease: a review of possible mechanisms. *Ann.Behav.Med.* 1995; **17**: 142-9.

58 Musselman DL, Evans DL, Nemeroff CB. The relationship of depression to cardiovascular disease: epidemiology, biology, and treatment. *Arch.Gen.Psychiatry* 1998; **55**: 580-92.

59 Howren MB, Lamkin DM, Suls J. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. *Psychosom.Med.* 2009; **71**: 171-86.

60 Musselman DL, Tomer A, Manatunga AK, Knight BT, Porter MR, Kasey S, Marzec U, Harker LA, Nemeroff CB. Exaggerated platelet reactivity in major depression. *Am.J.Psychiatry* 1996; **153**: 1313-7.

61 Laghrissi-Thode F, Wagner WR, Pollock BG, Johnson PC, Finkel MS. Elevated platelet factor 4 and beta-thromboglobulin plasma levels in depressed patients with ischemic heart disease. *Biol.Psychiatry* 1997; **42**: 290-5.

62 Rieckmann N, Kronish IM, Haas D, Gerin W, Chaplin WF, Burg MM, Vorchheimer D, Davidson KW. Persistent depressive symptoms lower aspirin adherence after acute coronary syndromes. *Am.Heart J.* 2006; **152**: 922-7.

63 Carney RM, Freedland KE, Eisen SA, Rich MW, Jaffe AS. Major depression and medication adherence in elderly patients with coronary artery disease. *Health Psychol.* 1995; **14**: 88-90.

64 May HT, Sheng X, Catinella AP, Horne BD, Carlquist JF, Joy E. Antilipidemic adherence post-coronary artery disease diagnosis among those with and without an ICD-9 diagnosis of depression. *J.Psychosom.Res.* 2010; **69**: 169-74.

65 Blumenthal JA, Williams RS, Wallace AG, Williams RB,Jr, Needles TL. Physiological and psychological variables predict compliance to prescribed exercise therapy in patients recovering from myocardial infarction. *Psychosom.Med.* 1982; **44**: 519-27.

66 Myers V, Gerber Y, Benyamini Y, Goldbourt U, Drory Y. Post-myocardial infarction depression: increased hospital admissions and reduced adoption of secondary prevention measures--a longitudinal study. *J.Psychosom.Res.* 2012; **72**: 5-10.

67 Kronish IM, Rieckmann N, Halm EA, Shimbo D, Vorchheimer D, Haas DC, Davidson KW. Persistent depression affects adherence to secondary prevention behaviors after acute coronary syndromes. *J.Gen.Intern.Med.* 2006; **21**: 1178-83.

68 Ziegelstein RC, Fauerbach JA, Stevens SS, Romanelli J, Richter DP, Bush DE. Patients with depression are less likely to follow recommendations to reduce cardiac risk during recovery from a myocardial infarction. *Arch.Intern.Med.* 2000; **160**: 1818-23.

69 Schweitzer RD, Head K, Dwyer JW. Psychological factors and treatment adherence behavior in patients with chronic heart failure. *J.Cardiovasc.Nurs.* 2007; **22**: 76-83.

70 Joekes K, Van Elderen T, Schreurs K. Self-efficacy and overprotection are related to quality of life, psychological well-being and self-management in cardiac patients. *J.Health.Psychol.* 2007; **12**: 4-16.

71 Sarkar U, Ali S, Whooley MA. Self-efficacy and health status in patients with coronary heart disease: findings from the heart and soul study. *Psychosom.Med.* 2007; **69**: 306-12.

72 Sarkar U, Ali S, Whooley MA. Self-efficacy as a marker of cardiac function and predictor of heart failure hospitalization and mortality in patients with stable coronary heart disease: findings from the Heart and Soul Study. *Health Psychol.* 2009; **28**: 166-73.

73 Page RL,2nd, Lindenfeld J. The comorbidity conundrum: a focus on the role of noncardiovascular chronic conditions in the heart failure patient. *Curr.Cardiol.Rep.* 2012; **14**: 276-84.

74 Schmid CH, Landa M, Jafar TH, Giatras I, Karim T, Reddy M, Stark PC, Levey AS, Angiotensin-Converting Enzyme Inhibition in Progressive Renal Disease (AIPRD) Study Group. Constructing a database of individual clinical trials for longitudinal analysis. *Control.Clin.Trials* 2003; **24**: 324-40.

75 Sternberg KJ, Baradaran LP, Abbott CB, Lamb ME, Guterman E. Type of violence, age, and gender differences in the effects of family violence on children's behavior problems: A mega-analysis. *Developmental Review* 2006; **26**: 89-112.

76 Wicherts JM, Borsboom D, Kats J, Molenaar D. The poor availability of psychological research data for reanalysis. *Am.Psychol.* 2006; **61**: 726-8.

77 Berkman LF, Blumenthal J, Burg M, Carney RM, Catellier D, Cowan MJ, Czajkowski SM, DeBusk R, Hosking J, Jaffe A, Kaufmann PG, Mitchell P, Norman J, Powell LH, Raczynski JM, Schneiderman N, Enhancing Recovery in Coronary Heart Disease

Patients Investigators (ENRICHD). 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**: 3106-16.

78 Zuidersma M, Conradi HJ, Van Melle J, Ormel J, De Jonge P. Depression treatment after myocardial infarction and long-term risk of subsequent cardiovascular events and mortality: a randomized controlled trial. *Journal of psychosomatic research* 2012; **in press**.

79 van Melle JP, de Jonge P, Honig A, Schene AH, Kuyper AM, Crijns HJ, Schins A, Tulner D, van den Berg MP, Ormel J, MIND-IT investigators. Effects of antidepressant treatment following myocardial infarction. *Br.J.Psychiatry* 2007; **190**: 460-6.

80 Bauer DJ, Hussong AM. Psychometric approaches for developing commensurate measures across independent studies: traditional and new models. *Psychol.Methods* 2009; **14**: 101-25.

81 Eagle KA, Lim MJ, Dabbous OH, Pieper KS, Goldberg RJ, Van de Werf F, Goodman SG, Granger CB, Steg PG, Gore JM, Budaj A, Avezum A, Flather MD, Fox KA, GRACE Investigators. A validated prediction model for all forms of acute coronary syndrome: estimating the risk of 6-month postdischarge death in an international registry. *JAMA* 2004; **291**: 2727-33.

82 Wakabayashi K, Gonzalez MA, Delhaye C, Ben-Dor I, Maluenda G, Collins SD, Syed AI, Gaglia MA,Jr, Torguson R, Xue Z, Suddath WO, Satler LF, Kent KM, Lindsay J, Pichard AD, Waksman R. Impact of chronic obstructive pulmonary disease on acute-phase outcome of myocardial infarction. *Am.J.Cardiol.* 2010; **106**: 305-9.

83 Kronish IM, Rieckmann N, Schwartz JE, Schwartz DR, Davidson KW. Is depression after an acute coronary syndrome simply a marker of known prognostic factors for mortality?. *Psychosom.Med.* 2009; **71**: 697-703.

84 Meurs M, Zuidersma M, Dickens C, de Jonge P. Examining the relation between post myocardial infarction depression and cardiovascular prognosis using a validated prediction model for post myocardial mortality. *Int.J.Cardiol.* 2012;.

85 Ahern DK, Gorkin L, Anderson JL, Tierney C, Hallstrom A, Ewart C, Capone RJ, Schron E, Kornfeld D, Herd JA. Biobehavioral variables and mortality or cardiac arrest in the Cardiac Arrhythmia Pilot Study (CAPS). *Am.J.Cardiol.* 1990; **66**: 59-62.

86 Frasure-Smith N, Lesperance F, Talajic M. The impact of negative emotions on prognosis following myocardial infarction: is it more than depression?. *Health Psychol.* 1995; **14**: 388-98.

87 Irvine J, Basinski A, Baker B, Jandciu S, Paquette M, Cairns J, Connolly S, Roberts R, Gent M, Dorian P. Depression and risk of sudden cardiac death after acute myocardial infarction: testing for the confounding effects of fatigue. *Psychosom.Med.* 1999; **61**: 729-37.

88 Kaufmann MW, Fitzgibbons JP, Sussman EJ, Reed JF,3rd, Einfalt JM, Rodgers JK, Fricchione GL. Relation between myocardial infarction, depression, hostility, and death. *Am.Heart J.* 1999; **138**: 549-54.

89 Ladwig KH, Kieser M, Konig J, Breithardt G, Borggrefe M. Affective disorders and survival after acute myocardial infarction. Results from the post-infarction late potential study. *Eur.Heart J.* 1991; **12**: 959-64.

90 Mayou RA, Gill D, Thompson DR, Day A, Hicks N, Volmink J, Neil A. Depression and anxiety as predictors of outcome after myocardial infarction. *Psychosom.Med.* 2000; **62**: 212-9.

91 Nakatani D, Sato H, Sakata Y, Shiotani I, Kinjo K, Mizuno H, Shimizu M, Ito H, Koretsune Y, Hirayama A, Hori M, Osaka Acute Coronary Insufficiency Study Group. Influence of serotonin transporter gene polymorphism on depressive symptoms and new cardiac events after acute myocardial infarction. *Am.Heart J.* 2005; **150**: 652-8.

92 Rumsfeld JS, Jones PG, Whooley MA, Sullivan MD, Pitt B, Weintraub WS, Spertus JA. Depression predicts mortality and hospitalization in patients with myocardial infarction complicated by heart failure. *Am.Heart J.* 2005; **150**: 961-7.

93 Silverstone PH. Depression and outcome in acute myocardial infarction. *Br.Med.J.(Clin.Res.Ed)* 1987; **294**: 219-20.

94 Smolderen KG, Spertus JA, Reid KJ, Buchanan DM, Krumholz HM, Denollet J, Vaccarino V, Chan PS. The association of cognitive and somatic depressive symptoms with depression recognition and outcomes after myocardial infarction. *Circ.Cardiovasc.Qual.Outcomes* 2009; **2**: 328-37.

95 Sorensen C, Brandes A, Hendricks O, Thrane J, Friis-Hasche E, Haghfelt T, Bech P. Depression assessed over 1-year survival in patients with myocardial infarction. *Acta Psychiatr.Scand.* 2006; **113**: 290-7.

96 Strik JJ, Lousberg R, Cheriex EC, Honig A. One year cumulative incidence of depression following myocardial infarction and impact on cardiac outcome. *J.Psychosom.Res.* 2004; **56**: 59-66.

97 Sydeman SJ. Impact of negative emotions on recurrent cardiovascular events following hospitalization for myocardial infarction or unstable angina 1998;.