The impact of pre-morbid and post-morbid depression onset on mortality and cardiac morbidity among coronary heart disease patients: A meta-analysis

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Abstract

Background—Depression is associated with increased cardiac morbidity and mortality in the general population and in coronary heart disease (CHD) patients. Recent evidence suggests that patients with new-onset depression post-CHD diagnosis have worse outcomes than those who had previous or recurrent depression. This meta-analysis investigated timing of depression onset in established CHD and CHD-free cohorts to determine what timeframe is associated with greater mortality and cardiac morbidity.

Methodology/Principal Findings—The MEDLINE, EMBASE, and PsycINFO databases were searched systematically to identify articles examining depression timeframe which specified an endpoint of all-cause mortality, cardiac mortality, re-hospitalization, or major adverse cardiac events (MACEs). A meta-analysis was conducted to estimate effect sizes by timeframe of depression.

Twenty-two prospective cohort studies were identified. Nine studies investigated pre-morbid depression in CHD-free cohorts in relation to cardiac death. Thirteen studies in CHD-patient samples examined new-onset depression in comparison to previous or recurrent depression. The pooled effect size (risk ratio) was 0.76 (95% CI 0.48–1.19) for history of depression only, 1.79 (95% CI 1.45–2.21) for pre-morbid depression onset, 2.11 (95% CI 1.66–2.68) for post-morbid or new depression onset, and 1.59 (95% CI 1.08–2.34) for recurrent depression

Conclusions/Significance—Both pre-morbid and post-morbid depression onsets are potentially hazardous, and the question of timing may be irrelevant with respect to adverse cardiac outcomes. However, the combination of pre-morbid depression with the absence of depression at

the time of a cardiac event (i.e., historical depression only) is not associated with such outcomes, and deserves further investigation.

Keywords

coronary heart disease; depression; timing of onset; mortality; morbidity; outcome; meta-analysis

Introduction

Depression is common and persistent, with a burden of about 5% in the general population and 20% among cardiac patients [1]. Patients with a depressive history are twice as likely to have recurrent depression after a myocardial infarction (MI) both in hospital and after hospitalization [2]. Likewise, among patients who become depressed after an MI, half of them have had a previous history of depression [3]. In addition to this mental health burden, depression is related to both greater risk of developing coronary heart disease (CAD [2, 4]) and poorer prognosis among patients with established CAD [5]. Indeed, several meta-analyses [6–8] have demonstrated this relationship between depression and CHD.

Recently, there has been particular interest in the timeframe of depression in relation to patient outcomes, which would have important mechanistic and screening implications. Some studies have shown that CHD patients with a history of pre-morbid depression have greater mortality and cardiac morbidity risk compared to patients who have never been depressed [1–3]. Conversely, other research has shown that new-onset depression at the time of a cardiac hospitalization is particularly prognostic. Our group and others [9–13] have shown that new-onset depression during cardiac hospitalization or immediate post-hospitalization was related to greater risk of mortality and cardiac morbidity when compared to historical or recurrent depression. However, recent studies [14] report inconsistent findings. To shed light on this important question, this quantitative review and synthesis tested whether the timeframe of depression was related to greater mortality and cardiac morbidity.

For the purposes of this meta-analysis, ‘depression’ refers to unipolar clinical depression as diagnosed through a clinical assessment, or elevated depressive symptoms above an established cut-off point assessed by a validated self-report questionnaire [15]. Timeframe of depression can be classified as pre-morbid or post-morbid onsets. Pre-morbid onset could consist of 1 of the following: (1) Pre-CHD depression: (1a) CHD-free individuals who had depression before CHD diagnosis but their post-CHD depression status at the time of cardiac event is unknown, as their study endpoints were cardiac diagnosis and cardiac death; (1b) History of Depression Only: CHD patients who had one or more episodes of depression before their current CHD diagnosis without being currently depressed; (1c) Recurrent depression: CHD patients who had depression before and after their initial CHD diagnosis; (2) Post-morbid onset refers to New-onset or Incident depression among CHD patients whose initial depression occurred after their CHD diagnosis. Non-incident depression refers to recurrent depression, which involves direct assessment of post-morbid depression status and retrospective assessment of pre-morbid depression status among CHD patients. Finally,

new-onset depression is divided into 2a) in-hospital or within 30 days after hospitalization, and 2b) post-hospitalization onset within 1-year. See Figure 1 for a graphic illustration.

The objective of this meta-analysis was to compare the effects on cardiac morbidity and mortality of the following depression timeframes: I) Each timeframes of depression; II) Pre-morbid Onset (1a, 1b, and 1c) vs. Post-morbid Onset (2a & 2b); III) Incident/ New-onset (2a & 2b) vs. Non-incident (Recurrent; 1c); and IV) New-onset in-hospital depression vs. New-onset post-hospitalization within 1-year (2a vs. 2b).

Methods

Inclusion Criteria

The meta-analysis that the meta-analysis was reported in a manner consistent with MOOSE [16], and the flow diagram is based on PRISMA template [17].

For a study to be included in this meta-analysis, depression or depressive symptoms had to be assessed by standardized and validated measures or by a structured clinical interview. Historical depression status could also be assessed based on patients' self-report or indication in medical records. Results had to be reported for depressed versus non-depressed patients.

Subjects included either CHD-free cohorts or CHD patients of any age. CHD patients included those who had a confirmed diagnosis of acute coronary syndrome; (unstable angina to MI), underwent a revascularization procedure (coronary artery bypass grafting or percutaneous coronary intervention), or those with angiographically-defined CHD.

In CHD-free cohorts, depression had to be assessed pre-cardiac diagnosis. In each study, the cohort must be free of cardiac diseases and was followed from prior to CHD onset until cardiac mortality was ascertained. In CHD cohorts, the studies included in this meta-analysis were those which ascertained depression status at two time-points at least, with post-diagnosis. Studies were included if they had a clear indication of historical depression ascertainment and / or post-morbid depression assessed at time of hospitalization (within one month) and / or post-hospitalization (within 12 months).

Studies were included if outcomes reported included at least one of the following: In CHD-free cohorts, only studies reported cardiac mortality was included as an outcome. In CHD cohorts, we extracted outcome in the following order: cardiac mortality, all-cause mortality, a composite outcome combining cardiac morbidity and mortality, and cardiac morbidity, as defined as readmission or re-hospitalization due to a major adverse cardiac event (MACEs; i.e., MI, need for revascularization, stroke, heart failure, and arrhythmic events).

In addition to the criteria outlined above, the following were also applied: (1) prospective cohort design with clinical depression or depressive symptoms as the exposure, (2) the timeframe of the depression before, during, or after a cardiac-related hospitalization must be clearly defined and included in analyses, and (3) paper published in a peer-reviewed English-language journal. In the case of multiple publications of the same cohort, the most recent article that best addressed the research question was chosen.

Search Strategy and Data Sources

MEDLINE, EMBASE, and PsycINFO were searched for articles published from 1990 to May 2009. The search strategy included 4 components: CHD, depression, timeframe of depression, and mortality and cardiac morbidity (see Appendix A for search terms). All the database searches were conducted by information specialists at the University Health Network. Next, reference lists of selected papers were hand-searched. Finally, authors of key studies were contacted to identify any other relevant publications.

Study selection

Using a conservative threshold for exclusion, one investigator (YL) examined all abstracts and selected articles for full-text examination. Two investigators (YL & SGW) independently used standardized forms to assess the eligibility of all full-text articles. Inter-observer agreement was assessed using Cohen's kappa (κ), and differences were resolved by discussion with a third rater (SLG). RefWorks [18] software was used to create a database of reference material identified through electronic and manual searches.

Two investigators independently applied standardized forms to abstract data elements from included studies as shown in Tables 1 and 2. In some cases, primary authors were contacted for specific data elements or clarification.

Quality Assessment

A study quality assessment manual was prepared based on the Newcastle-Ottawa Scale for observational studies [19] (Appendix B). This instrument consists of 8 questions assessing quality in 3 broad categories: patient selection, comparability of study groups, and outcome assessment. Extra points were assigned to studies that adjusted for cardiac risk factors and anti-depressant use. Assessment results in a maximum possible score of 9 for each study, with studies rated 6 or more deemed of highest quality. Each study was rated independently by 2 investigators (YL & SG), with ratings reported in Tables 1 and 2.

Statistical Analyses

Meta-analyses were performed using the software Comprehensive Meta-Analysis, version 2 [20]. For each study, effect size (ES) was calculated as the risk ratio (RR) comparing depression timeframes to the non-depressed group on the likelihood of mortality or cardiac morbidity. Hazard ratios (HRs) were treated as RRs because HR can be referred to the RR-averaged-over-time [21]. To pool data across the studies, adjusted RRs with 95% confidence intervals (CI) or the dichotomous frequency data (depressed vs. not depressed) were retrieved from each study to compute a pooled ES in RR. A mixed-effects model [22] was adopted which incorporated a random effects model to combine studies within each timeframe (i.e., new-onset, recurrent, and history-only in CHD cohort studies and pre-morbid depression in CHD-free cohort studies) and a fixed-effects model to combine these timeframes to yield an overall ES across studies as these timeframes were from the same study. To estimate the overall ES, each RR was weighted by the inverse of its variance, the weighted RR were summed across studies, and then divided by the sum of the weights.

Publication bias was assessed by means of the Begg and Mazumdar rank correlation test [23] and Egger's regression asymmetry test [24].

Heterogeneity Analysis

A test of heterogeneity was used to compare differences in ES based on timeframe of depression. The statistical heterogeneity between the studies was evaluated using the *Cochran's Q* test and I^2 statistic to test the appropriateness to combine results [25].

Sensitivity Analysis

Potential causes of heterogeneity were explored by performing sensitivity and subgroup analyses. The influence of low-quality studies on the pooled estimates was tested in a sensitivity analysis by including and excluding them, using a test of interaction with a predetermined 2-tailed α of 0.05 to compare differences between original and corrected ESs [26]. The current meta-analysis also explored the influence of the method of depression ascertainment, length of follow-up, adjustment of mortality confounders and study outcome of cardiac and all-cause mortality on the ESs among cohort studies.

Results

Study selection and evaluation

A flow diagram of the literature search is shown in Figure 2. Inter-observer agreement was $\kappa = 0.749$, indicating "good" [27] concordance between raters for article inclusion decisions. Ultimately, 22 studies were included in the meta-analysis, yielding 39 ESs. The quality of the studies was generally good, with 13 out of 22 studies (59.1%) rated as 6 stars or higher on the Newcastle-Ottawa Scale [19].

Description of the Included Studies

Tables 1 and 2 summarize the characteristics of the included CHD cohort and CHD-free cohort studies, respectively. Studies are presented in alphabetical order based on first author, and in addition Table 1 was organized by depression ascertainment either in-hospital or post-hospitalization.

Included cohorts reported inception ranging between 1971 and 2001, and had follow-up from 6 months to 37 years (CHD cohort studies ranged from 6 months to 12 years; CHD-free cohort studies ranged from 4 to 37 years). Sample sizes ranged from 145 to 62,839, with a total of 127,590 participants (CHD cohort studies ranged from 145 to 13,708 participants; CHD-free cohort studies ranged from 660 to 62,839 participants). In CHD-free cohorts, the prevalence of pre-morbid depression ranged from 2–15%. In CHD cohorts, the prevalence of new-onset depression ranged from 5.5–27.9%, recurrent depression from 5.1–41.4%, and history of depression only from 0–20.7%.

Depression Measurement

Seven of the 22 studies assessed major depression by clinical interview using DSM-III or IV criteria, 1 study used self-report physician-diagnosed depression, and 1 study identifying patients with depression through the *International Classification of Diseases*, 9th Revision

(ICD-9) codes from a cardiac registry. Sixteen studies administered a validated questionnaire of depressive symptoms, in which 9 different measures are represented (See Tables 1 and 2).

Study Outcomes

Twelve studies reported cardiac mortality, 6 studies reported all-cause mortality, and 3 studies reported both outcomes separately. Four studies reported a composite endpoint such as fatal and non-fatal cardiac events, all-cause mortality, and cardiac-related readmission.

Fifteen studies reported adjusted HRs, and four of these adjusted for disease severity. Eight studies reported crude rates of mortality/ cardiac morbidity. The HRs, crude rates, and adjusted factors are listed in Tables 1 and 2 where applicable.

The assumption of no publication bias was reasonable, considering that the *p* values for the Begg's and Egger's tests based on the 14 studies for which complete data were available in the original publication or through contact with authors were 0.771 and 0.774, respectively.

Heterogeneity

The appropriateness of combining studies according to the timeframe of depression appeared reasonable. The I^2 statistics within depression timeframes ranged from low to high, although all *Q*-statistics were significant except that for history of depression only. The results are as follows: Overall depression ($Q=82.63$, $df=39$, $p<0.0001$, $I^2=53.8\%$); overall depression in CHD-cohort ($Q=63.9$, $df=30$, $p<0.0001$; $I^2=53.1\%$); pre-morbid depression onset in CHD-free cohort ($Q=18.24$, $df=8$, $p=0.02$; $I^2=56.1\%$); post-morbid depression/new-onset depression ($Q=30.17$, $df=12$, $p=.003$; $I^2=60.2\%$); recurrent depression ($Q=16.86$, $df=9$, $p=0.051$; $I^2=46.6\%$); and history of depression only ($Q=6.72$, $df=7$, $p=.459$; $I^2=0\%$).

Quantitative Data Synthesis: Effect of Depression on Outcomes

The overall ES (RR) of depression at any time-period on mortality and cardiac morbidity in all studies was 1.70 (95% CI 1.48–1.96), indicating that depression is associated with a risk for mortality and cardiac morbidity that is almost twice the risk for non-depressed patients. Overall results are displayed in Figure 3, where each white diamond represents the pooled ES and 95% CI for timeframe of depression and the black diamond represents the overall ES for all studies combined. The overall ES of depression at any time-period on mortality and morbidity outcomes among CHD-cohort and CHD-free cohort were 1.76 (95% CI 1.40–2.21) and 1.70 (95% CI 1.41–2.05) respectively.

Comparisons of Specific Timeframes of Depression

When comparing across timeframes of depression onset, the magnitude of risk significantly varied ($Q=15.77$, $df=3$, $p=0.001$). For pre-morbid depression in CHD-free cohorts (1a) the ES was 1.79 (95% CI 1.45–2.21). In CHD cohorts, the ES for new-onset depression (2a & 2b) was 2.11 (95% CI 1.66–2.68), while the ESs for recurrent depression (1c) and history only (1b) were 1.59 (95% CI 1.08–2.34) and 0.76 (95% CI 0.48–1.19) respectively. *Q*-statistics for comparing each timeframe of depression are shown in Table 3.

Pre-morbid vs. Post-morbid Depression Onset Timeframe among CHD and CHD-free Cohorts (1 vs. 2)

All CHD and CHD-free cohort studies were grouped by timeframe of depression according to whether it was a pre- or post-cardiac event or procedure. The pooled ES for post-morbid onset (new-onset) was 2.11 (95% CI 1.66–2.68), whereas pre-morbid onset (all other timeframes) was 1.52 (95% CI 1.25–1.84; Fig. 4). The difference in ESs was significant ($Q=4.42$, $df=1$, $p=0.036$).

Incident (New-onset) vs. Non-Incident Depression (Recurrent) in CHD Cohorts (2a & 2b vs. 1c)

All CHD cohort studies were grouped by whether the depression occurred pre- or post-diagnosis / procedure. The pooled ES of incident depression (2.11 95% CI 1.66–2.68) was greater than that of non-incident depression (1.59 95% CI 1.08–2.34). This difference in ESs was not significant ($Q=1.47$, $df=1$, $p=0.225$; Fig. 5).

New-onset Depression In-hospital vs. New-onset Depression Post-hospitalization in CHD Cohorts (2a vs. 2b)

Fourteen studies reported new-onset depression, of which 8 studies defined new-onset depression during cardiac hospitalization (within 1 month after a CHD event) and 6 defined new-onset post-hospitalization (2–12 months after a CHD event). The ES of new-onset depression in-hospital was 2.33 (95% CI 1.63–3.32), and post-hospitalization was 1.77 (95% CI 1.37–2.89). These ESs were not significantly different ($Q=1.50$, $df=1$, $p=0.22$; Fig. 6).

Sensitivity Analysis

To explore the reliability of results, sensitivity analyses were performed with regard to study quality, method of depression assessment, length of patient follow-up and variable adjustment. First, 13 high quality studies (6 studies from CHD cohorts [9–12, 28, 29], 7 from CHD-free cohorts [30–36]) were selected to test the sensitivity of results. The corrected overall ESs for all timeframes of depression was 1.60 (95% CI 1.40–1.84). The corrected ESs for new-onset depression was 1.66 (95% CI 1.41–1.95), for recurrent was 1.20 (95% CI 0.68–2.09), for history of depression only was 0.400 (95% CI 0.180–0.880), and for pre-morbid depression was 1.88 (95% CI 1.40–1.84). These were not significantly different from the ESs estimated using all 22 studies ($p=0.632$ – 0.889), except in the case new-onset depression ($p=0.001$), which was lower.

When comparing pre-morbid onset (1.54 95% CI 1.28–1.87) to post-morbid depression onset overall (6 95% CI 1.41–1.95), the relationship remained but the differences become non-significant ($Q=0.501$, $df=1$, $p=0.479$). When comparing incident (1.66 95% CI 1.41–1.95) to non-incident depression (1.20 95% CI 0.683–2.09), the finding remained non-significant ($Q=1.205$, $df=1$, $p=0.272$). In summary, only the new-onset depression estimates were affected by study quality, but other results remained unchanged.

The 7 studies of CHD patients that used a “gold standard” depression measure (i.e., structured clinical interview or physician diagnosis) were selected [2, 9–11, 13, 29, 37]. The ESs for these 7 studies were not significantly different from those when all studies were

included ($p=0.490-0.919$). Therefore, estimates did not appear to be affected by method of depression ascertainment.

The influence of the length of follow-up among the CHD cohort studies was also explored. Seven studies with a follow-up length of 1 year or greater were selected [2, 9, 11, 12, 28, 29, 38, 39]. The ESs for these 7 studies were not significantly different than those for all included studies ($p=0.66-0.79$). Therefore, estimates did not appear to be affected by length of follow-up.

The influence of the statistical adjustment for confounding variables such as disease severity among the CHD cohort studies was explored. Four studies adjusted for CHD disease severity in their analyses [9, 11, 28, 29]. The ESs for these 4 studies were not significantly different than the ESs for all included studies ($p=0.33-0.584$). Therefore, it can be concluded that estimates were not influenced by the adjustment of prognostic indicators.

Finally, the influence of studies using only cardiac and all-cause mortality outcomes was tested. Four studies were excluded [10, 13, 29, 37]. The corrected overall ESs for all timeframes of depression was 1.75 (95% CI 1.47–1.90). The corrected ESs for new-onset depression was 2.33 (95% CI 1.66–3.27), for recurrent was 1.47 (95% CI 0.761–2.84), for history only was 0.710 (95% CI 0.374–1.35), and for pre-morbid depression was 1.76 (95% CI 1.40–2.21). These were not significantly different from the ESs estimated using all 22 studies ($p=0.120-0.583$).

Discussion

Over and above the psychosocial burden of depression in heart disease, depression is linked to worse outcomes including mortality and cardiac morbidity. The aim of the current meta-analysis was to determine the impact of the timing of depression onset relative to the timing of CHD diagnosis or cardiac event on health outcomes. This meta-analysis confirmed the adverse effect of depression on outcome, with 1.75-times greater cardiac morbidity and mortality seen in the presence of depression at any time-point. Sensitivity analyses suggest that this relationship is unaffected by method of depression assessment, length of patient follow-up, disease severity, or type of outcome. Overall, the magnitude of risk is greatest in patients with new-onset depression. However, after controlling for study quality, there was no significant difference in the effect of depression that occurs pre- or post-CHD diagnosis or cardiac event. Ultimately, the results of this meta-analysis confirm the hazardous effects of comorbid depression in the cardiovascular context.

These results are consistent with a previous meta-analysis demonstrating the negative effect of depression in CHD-free cohorts [7]. However, the effect of pre-morbid depression on outcomes among CHD-free and established CHD cohorts appears somewhat contradictory. In the CHD cohorts, reporting only history without a present episode of depression was unrelated to cardiac morbidity and mortality. This inconsistency can likely be explained by bias in the self-report of depression history and/or retention bias. With regard to the latter, it is possible that pre-morbidly depressed patients who survived to participate in a CHD cohort study had some sort of survival advantage, while most other depressed individuals died

around the time of their CHD events and thus were not included in the CHD cohorts [9]. Indeed in our previous study [12] and a study by Lesperance and colleagues [2], historical depression tended to have a protective effect, and a trend toward a protective effect is seen in this meta-analysis as well ($ES=0.76$). CHD patients who experienced one or more depressive episodes prior to their cardiac event and survived might have been treated with anti-depressant therapy for example, and may have successfully responded [40]. Moreover, these survivors may have more adaptive coping strategies and lead a healthier lifestyle, or a stronger social support system, or they may have been more likely to participate in effective psychotherapy. Alternatively, these patients may have a qualitatively different type of depression, perhaps unrelated to the acute inflammatory mechanism[41]. Future research is needed to better understand whether a retention bias is at play, and if it is, to determine the explanation for the survival advantage of historical depression for some individuals.

Regarding the issue of depression post-CAD, there has been much debate in the literature regarding whether incident depression has some sort of acute mechanistic impact on outcome, or whether the presence of chronic processes are particularly hazardous (see [4, 42–44]). When the outcomes from CHD-cohort studies were examined, both new-onset and recurrent depression were significantly related to approximately twice the risk of adverse outcomes. However, the magnitude of effect for new-onset depression was lessened when only high-quality studies were tested, and there was no significant difference in the magnitude of effect for new-onset versus recurrent depression. Overall these results suggest that both new-onset and recurrent depression in CHD patients are predictive of adverse outcomes. Some of the inconsistencies in the previous literature regarding timing [13] may be due to smaller sample sizes which we have been able to overcome in this synthesis, or be explained by different definitions adopted for pre- and post-CHD depression. Moreover, the effect of retention bias should again be considered, because only patients who survived to follow-up assessment with recurrent depression would be included in the analyses. The problem of early mortality cannot be overcome, and therefore comparisons of new- to late-onset or recurrent depression should be interpreted with particular caution. Clearly, more sophisticated methodological approaches incorporating simultaneous assessment of explanatory mechanisms and theories [4, 45] will be needed to better understand the impact of post-CHD depression timing. On the whole, depression onset around the time of hospitalization is a risk factor for cardiac events, and this hazard continues when depression is chronic, and these cases should be given continued clinical attention.

Limitations

Caution is warranted when interpreting these results. First, the current study synthesized only studies published in English, which may limit the generalizability of these findings. Second, the severity of depression was not taken into consideration. This may have increased the heterogeneity of our findings. Third, the definition of depression applied herein may have biased results. Only 6/22 (27.3%) studies applied DSM-III or -IV criteria for major depression and 1/22(4.5%) applied ICD-9 codes. While the sensitivity analysis showed that results were not affected by the method of depression assessment, depressive symptoms as assessed in the remaining studies could be related (or not) to a major depressive episode. Moreover, dysthymia and minor depression were not considered, which

may have a confounding effect on results. Fourth, receipt and type of depression treatment and was not taken into consideration, and only a few of the included studies controlled for these factors in their multivariate analyses [9, 11, 33, 36, 46]. Fifth, history of depression ascertainment was based mainly on self-report as present or absent which is subject to bias. Sixth, caution is warranted in drawing conclusions regarding statistical significance between effect sizes after sensitivity analysis due to low power. Finally, due to the limited amount of research in this area, we adopted a broad definition of CHD and a composite endpoint, and this may have increased the heterogeneity of findings.

Conclusions

This meta-analysis showed that those with both pre-morbid and post-CHD depression have 1.5–2 times higher risk of mortality and cardiac morbidity. There may be a subgroup of individuals whose depression is successfully remitted before CHD onset who have a survival advantage. They should be investigated to better understand what interventions can improve prognosis. Ultimately, new onset depression post-diagnosis may be particularly hazardous, however this cannot be conclusively determined due to retention or survival biases which cannot be overcome.

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Glossary

CHD	coronary heart disease
MI	myocardial infarction
MACEs	major adverse cardiac events
ES	effect size
RR	risk ratio
HR	Hazard ratio
CI	confidence intervals
DSM	Diagnostic and Statistical Manual
ICD	International Classification of Diseases

References

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. [PubMed: 16423120]
2. Lesperance F, Frasere-Smith N, Talajic M. Major depression before and after myocardial infarction: its nature and consequences. *Psychosom Med.* 1996; 58:99. [PubMed: 8849624]

3. Spijkerman T, de Jonge P, van den Brink RH, Jansen JH, May JF, Crijns HJ, Ormel J. Depression following myocardial infarction: first-ever versus ongoing and recurrent episodes. *Gen Hosp Psychiatry*. 2005; 27:411. [PubMed: 16271655]
4. Lett HS, Blumenthal JA, Babyak MA, Sherwood A, Strauman T, Robins C, Newman NF. Depression as a risk factor for coronary artery disease: evidence, mechanisms, and treatment. *Psychosom Med*. 2004; 66:305. [PubMed: 15184688]
5. Frasure-Smith N, Lesperance F, Talajic M. Depression following myocardial infarction. Impact on 6-month survival. *JAMA*. 1993; 270:1819. [PubMed: 8411525]
6. 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. [PubMed: 15564343]
7. Rugulies R. Depression as a predictor for coronary heart disease: a review and meta-analysis. *Am J Prev Med*. 2002; 23:51–61. [PubMed: 12093424]
8. 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. [PubMed: 15564344]
9. 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
10. de Jonge P, Rob HS, van den Brink RHS, Spijkerman TA, Ormel J. Only Incident Depressive Episodes After Myocardial Infarction Are Associated With New Cardiovascular Events. *J Am Coll Cardiol*. 2006; 48:2204. [PubMed: 17161246]
11. Dickens C, McGowan L, Percival C, Tomenson B, Cotter L, Heagerty A, Creed F. New onset depression following myocardial infarction predicts cardiac mortality. *Psychosom Med*. 2008; 70:450. [PubMed: 18434496]
12. Grace SL, Abbey SE, Kapral MK, Fang J, Nolan RP, Stewart DE. Effect of depression on five-year mortality after an acute coronary syndrome. *Am J Cardiol*. 2005; 96:1179. [PubMed: 16253578]
13. Parker GB, Hilton TM, Walsh WF, Owen CA, Heruc GA, Olley A, Brotchie H, Hadzi-Pavlovic D. Timing is everything: the onset of depression and acute coronary syndrome outcome. *Biol Psychiatry*. 2008; 64:660. [PubMed: 18602090]
14. Glassman AH, Bigger JT Jr, Gaffney M. Psychiatric characteristics associated with long-term mortality among 361 patients having an acute coronary syndrome and major depression: seven-year follow-up of SADHART participants. *Arch Gen Psychiatry*. 2009; 66:1022. [PubMed: 19736359]
15. Goldston K, Baillie AJ. Depression and coronary heart disease: a review of the epidemiological evidence, explanatory mechanisms and management approaches. *Clin Psychol Rev*. 2008; 28:288. [PubMed: 17601644]
16. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA*. 2000; 283:2008. [PubMed: 10789670]
17. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ*. 2009; 339:b2700. [PubMed: 19622552]
18. RefWorks - COS [computer program]. 2001.
19. Wells, GA., Shea, B., O'Connell, D., Peterson, J., Welch, V., Losos, M., Tugwell, P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomised studies in meta-analyses. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm
20. Comprehensive Meta-Analysis [computer program]. New Jersey, USA: 2006. Version 2
21. Newman, SC. Biostatistical methods in epidemiology. 2001. p. 382
22. Hedges L. A random effects model for effect sizes. *Psychol Bull*. 1983; 93:388.
23. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics*. 1994; 50:1088. [PubMed: 7786990]

24. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997; 315:629. [PubMed: 9310563]
25. Huedo-Medina TB, Sanchez-Meca J, Marin-Martinez F, Botella J. Assessing heterogeneity in meta-analysis: Q statistic or I² index? *Psychol Methods*. 2006; 11:193. [PubMed: 16784338]
26. Altman DG, Bland JM. Interaction revisited: the difference between two estimates. *BMJ*. 2003; 326:219. [PubMed: 12543843]
27. Altman, DG. *Practical statistics for medical research*. London, UK: Chapman and Hall; 1991.
28. Blumenthal JA, Lett HS, Babyak MA, White W, Smith PK, Mark DB, Jones R, Mathew JP, Newman MF. NORG Investigators. Depression as a risk factor for mortality after coronary artery bypass surgery. *Lancet*. 2003; 362:604. [PubMed: 12944059]
29. May HT, Horne BD, Carlquist JF, Sheng X, Joy E, Catinella AP. Depression after coronary artery disease is associated with heart failure. *J Am Coll Cardiol*. 2009; 53:1440. [PubMed: 19371828]
30. Nolen-Hoeksema S, Morrow J, Fredrickson BL. Response styles and the duration of episodes of depressed mood. *J Abnorm Psychol*. 1993; 102:20. [PubMed: 8436695]
31. Ahto M, Isoaho R, Puolijoki H, Vahlberg T, Kivela SL. Stronger symptoms of depression predict high coronary heart disease mortality in older men and women. *Int J Geriatr Psychiatry*. 2007; 22:757. [PubMed: 17133654]
32. Ferketich AK, Schwartzbaum JA, Frid DJ, Moeschberger ML. Depression as an antecedent to heart disease among women and men in the NHANES I study. National Health and Nutrition Examination Survey. *Arch Intern Med*. 2000; 160:1261. [PubMed: 10809028]
33. Ford DE, Mead LA, Chang PP, Cooper-Patrick L, Wang NY, Klag MJ. Depression is a risk factor for coronary artery disease in men: the precursors study. *Arch Intern Med*. 1998; 158:1422. [PubMed: 9665350]
34. Penninx BW, Guralnik JM, Mendes de Leon CF, Pahor M, Visser M, Corti MC, Wallace RB. Cardiovascular events and mortality in newly and chronically depressed persons > 70 years of age. *Am J Cardiol*. 1998; 81:988. [PubMed: 9576158]
35. Penninx BW, Beekman AT, Honig A, Deeg DJ, Schoevers RA, van Eijk JT, van Tilburg W. Depression and cardiac mortality: results from a community-based longitudinal study. *Arch Gen Psychiatry*. 2001; 58:221. [PubMed: 11231827]
36. Surtees PG, Wainwright NW, Luben RN, Wareham NJ, Bingham SA, Khaw KT. Depression and ischemic heart disease mortality: evidence from the EPIC-Norfolk United Kingdom prospective cohort study. *Am J Psychiatry*. 2008; 165:515. [PubMed: 18245176]
37. Connerney I, Shapiro PA, McLaughlin JS, Bagiella E, Sloan RP. Relation between depression after coronary artery bypass surgery and 12-month outcome: a prospective study. *Lancet*. 2001; 358:1766. [PubMed: 11734233]
38. Borowicz L Jr, Royall R, Grega M, Selnes O, Lyketsos C, McKhann G. Depression and cardiac morbidity 5 years after coronary artery bypass surgery. *Psychosomatics*. 2002; 43:464. [PubMed: 12444229]
39. Hata M, Yagi Y, Sezai A, Niino T, Yoda M, Wakui S, Soeda M, Nohata I, Shiono M, Minami K. Risk analysis for depression and patient prognosis after open heart surgery. *Circ J*. 2006; 70:389. [PubMed: 16565553]
40. Flint AJ, Rifat SL. The effect of treatment on the two-year course of late-life depression. *Br J Psychiatry*. 1997; 170:268. [PubMed: 9229035]
41. Pina IL, Apstein CS, Balady GJ, Belardinelli R, Chaitman BR, Duscha BD, Fletcher BJ, Fleg JL, Myers JN, Sullivan MJ. American Heart Association Committee on exercise, rehabilitation, and prevention. Exercise and heart failure: A statement from the American Heart Association Committee on exercise, rehabilitation, and prevention. *Circulation*. 2003 Mar 4; 107(8):1210–1225. [PubMed: 12615804]
42. 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. [PubMed: 12377300]
43. Grippo AJ, Johnson AK. Biological mechanisms in the relationship between depression and heart disease. *Neuroscience and biobehavioral reviews*. 2002; 26:941. [PubMed: 12667498]

44. Narita K, Murata T, Hamada T, Takahashi T, Omori M, Suganuma N, Yoshida H, Wada Y. Interactions among higher trait anxiety, sympathetic activity, and endothelial function in the elderly. *J Psychiatr Res.* 2007; 41:418. [PubMed: 16494899]
45. Davidson KW, Rieckmann N, Lesperance F. Psychological theories of depression: potential application for the prevention of acute coronary syndrome recurrence. *Psychosom Med.* 2004; 66:165. [PubMed: 15039500]
46. Whang W, Kubzansky LD, Kawachi I, Rexrode KM, Kroenke CH, Glynn RJ, Garan H, Albert CM. Depression and risk of sudden cardiac death and coronary heart disease in women: results from the Nurses' Health Study. *J Am Coll Cardiol.* 2009; 53:950. [PubMed: 19281925]
47. Hui PN, Wan M, Chan WK, Yung PM. An evaluation of two behavioral rehabilitation programs, qigong versus progressive relaxation, in improving the quality of life in cardiac patients. *J Altern Complement Med.* 2006; 12:373. [PubMed: 16722787]
48. Branger PJ, van der Wouden JC, Schudel BR, et al. Electronic communication between providers of primary and secondary care. *BMJ.* 1992; 305:1068. [PubMed: 1467688]
49. Lesperance F, Frasere-Smith N, Laliberte MA, et al. An open-label study of nefazodone treatment of major depression in patients with congestive heart failure. *Can J Psychiatry.* 2003; 48:695. [PubMed: 14674053]
50. Fonarow GC, Albert NM, Curtis AB, et al. Improving Evidence-Based Care for Heart Failure in Outpatient Cardiology Practices: Primary Results of the Registry to Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting (IMPROVE HF). *Circulation.* 2010; 122:585. [PubMed: 20660805]

Appendix A-Search Term

CHD	DEPRESSION	TIMING	OUTCOMES
EXP MYOCARDIAL-ISCHEMIA/ EXP CORONARY-ARTERY-BYPASS/ ANGINA	EXP DEPRESSIVE DISORDER/ ADJUSTMENT DISORDER DEPRESSIVE MOOD\$ DEPRESSIVE SYMPTOM\$	TIMING TIME COURSE ONSET PRE- PREVIOUS RECUR\$ CHRONIC\$ PRESIST\$ ON-GOING FOLLOW\$ SUBSEQUENT\$ AFTER POST-	MO.FS. (mortality) PROGNOS\$ EXP HOSPITALIZATIONS/ MACE COMPLICAT\$ READMIT\$ RE-ADMIT\$ RE-HOSPITAL\$ REHOSPITAL\$ EXP DEATH/ EXP DEATH, SUDDENT/ EXP VITAL STATISTICS/
CAD	DEPRESSION	TIMING	OUTCOMES
		FIRST FIRST-EVER NEW\$ INCIDENT EPISOD\$ TRANSIENT IN-HOSPITAL CURRENT\$	

Appendix B Quality Assessment

Study ID:	Author(s)	Year:
Reviewer: ☐ Y Leung ☐ S Gravely ☐ S Grace ☐ Other:		

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE COHORT STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection

1. Representativeness of the exposed cohort
 - a. truly representative of the average depressed patients in the community*
 - b. somewhat representative of the average depressed patients in the community*
 - c. selected group of users eg nurses, volunteers
 - d. no description of the derivation of the cohort
2. Selection of the non exposed cohort
 - a. drawn from the same community as the exposed cohort*
 - b. drawn from a different source
 - c. no description of the derivation of the non exposed cohort
3. Ascertainment of exposure
 - a. secure record (eg surgical records) *
 - b. structured interview*
 - c. written self report
 - d. no description
4. Demonstration that outcome of interest was not present at start of study
 - a. yes*
 - b. no

Comparability

1. Comparability of cohorts on the basis of the design or analysis
 - a. study controls for disease severity/ modifiable CHD risk factors (the most important factor) *
 - b. study controls for history of cardiac events/ non-modifiable CHD (family history) risk factors*

Outcome

1. Assessment of outcome

- a. independent blind assessment*
 - b. record linkage*
 - c. self report
 - d. no description
- 2. Was follow-up long enough for outcomes to occur
 - a. yes (select an adequate follow up period for outcome of interest) *
 - b. no
- 3. Adequacy of follow up of cohorts
 - a. complete follow up - all subjects accounted for*
 - b. subjects lost to follow up unlikely to introduce bias - small number lost - > 80 % follow up, or description provided of those lost)*
 - c. follow up rate < 80 % and no description of those lost
 - d. no statement

Figure 1.
Depression Timeframes

Figure 2.
PRISMA Flowchart of Article Inclusion

Figure 3.
 Forrest Plot of the Effect of Timeframe of Depression on Mortality or Cardiac Morbidity
 among CHD and CHD-free Cohorts

- An effect size with 95% of confident interval of study
- ◇ An overall effect of all studies combined in a subgroup
- ◆ An overall effect of all studies combined

Figure 4.

Forrest Plot of the Effect of Pre-morbid vs. Post-morbid Depression Onset on Mortality or Cardiac Morbidity among both CHD and CHD-free cohorts

- An effect size with 95% of confident interval of study
- ◇ An overall effect of all studies combined in a subgroup
- ◆ An overall effect of all studies combined

Figure 5.

Forrest Plot of the Effect of Incident vs. Non-incident Depression on Mortality or Cardiac Morbidity among CHD Cohorts Only

- An effect size with 95% of confident interval of study
- ◇ An overall effect of all studies combined in a subgroup
- ◆ An overall effect of all studies combined

Figure 6.

Forrest Plot of the Effect of New-onset Depression In-hospital vs. New-onset Depression Post-hospitalization on Mortality or Cardiac Morbidity in CHD Cohorts

- An effect size with 95% of confident interval of study
- ◇ An overall effect of all studies combined in a subgroup
- ◆ An overall effect of all studies combined

Characteristics of Selected CHD Cohort Studies by Depression Ascertainment Timeframe

Table 1

Study	Design	Sample (size, sex, age, CHD)	Depression Assessment tool	Depression Ascertainment Timeframe	Depression Ascertainment	Categories	N	%	Endpoint	Results	Adjustment	Quality Score
Post-Morbid Depression Assessed among CHD cohorts												
In-Hospital Depression Ascertainment (with-in 1 month post-CHD event)												
Blumenthal, 2003, U.K. [28]	Prospective Cohort, single site	CAG patients w/o history of dep	CES-D	CES-D before CABG & 6 mos after CABG	No	New-onset (Pre-CABG) Persistent	78	14.1	0–12 yr all-cause mortality	New-onset at 6 mos HR=2.17 (.81–5.81); New-onset Persistent HR=2.2 (1.17–4.15); New-onset Transient HR = .99 (.48–1.99)	A, B, D, E, H & N	6
					No	New-onset (6 mo Post-CABG)	36	6.5				
					No	New-onset (Pre-CABG) Transient	108	19.5				
					No	No Dep	333	60.0				
Caney, 2009, U.S. [9]	Prospective cohort (ENRICHD), multisite	MI patients, N=1328, mean (SD) age, 59.9 (11.8), 49.1% females	DISH; BDI	within 28 days post-hospital admission, pre-MI dep was assessed by DISH; 6 mo post-enrollment	No	New-onset	370	27.9	29-mo all-cause mortality; CHD death	All Cause: New-onset HR=3.1(1.6–6.1); Recurrent HR= 2.2 (1.1–4.4), Cardiac Death: New-onset HR=2.7 (.9–4.9); Recurrent HR=1.3 (.8–2)	A, B, D, E, H, J, K, L, M & N	8
					Yes	Recurrent	550	41.4				
					Yes	History Only	0	0				
					No	No Dep	408	30.7				
Connemey, 2001, U.S. [37]	Prospective Cohort, single site	CABG patients, N=309, mean age=65, 33% female	Clinical Interview (USNIMH); BDI	Clinical Interview few days after CABG	No	New-onset (In-hospital)	39	12.6	12-mo CHD mortality/ re-admission	*New-onset= 11/39 (28.2%); Recurrent=6/24 (25%); History Only=6/48 (12.5%); No Dep=19/198 (9.6%)	N/A	5
					Yes	Recurrent	24	7.8				
					Yes	History Only	48	15.5				
					No	No Dep	198	64.1				
Grace, 2005, Canada [12]	Prospective Cohort, multisite	ACS patients, N=750, mean age, 61.6 (11.9), 35% females	BDI	In-hosp, hist of dep was assessed by self-report questionnaire	No	New-onset (In-hospital)	130	17.3	5-yr all-cause mortality	New-onset HR=1.75 (1.14–2.69), Recurrent dep HR=.98 (.56–1.72), History of dep only HR=.38 (.14–1.05)	A, E, G & O	7
					Yes	Recurrent	105	14.0				
					Yes	History only	69	9.2				
					No	No Dep	446	59.5				

Study	Design	Sample (size, sex, age, CHD)	Depression Assessment tool	Depression Ascertainment Timeframe	Depression Ascertained		Categories	N	%	Endpoint	Results	Adjustment	Quality Score	
					Pre- Event	In- Hospital	Post- Discharge							
Hata, 2006, Japan [47]	Prospective Cohort, single site	CABG patients free of dep N=452, mean (SD) age, 65 (11), 35.2% females	CES-D	In-hosp after CABG	No	Yes	N/A	New-onset (In-hospital)	97	21.5	2-yr all-cause mortality	Hospital Death: New-onset= 11/97 (11.3%); No Dep= 0 (0%) Late Death: New-onset=10/97 (10.3%); No Dep= 10 (2.8%) All Death: New-onset= 21/97 (21.6%); No Dep= 10/355 (2.8%)	N/A	4
					No	No	N/A	No Dep	355	78.5				
Lesperance, 2006, Canada [2]	Prospective Cohort, single site	MI patients, N=222, mean (SD) age, 59.6 (24–88), 22% females	DIS; BDI	In-hosp, 6 mos & 12 mos	No	Yes	N/A	New-onset (In-hospital)	20	9.0	18-mo all-cause mortality	*New-onset in-hosp= 2/20 (10%); Recurrent = 5/15 (40%); History Only=1/46 (2.2%); No Dep=9/141 (6.4%)	N/A	4
					Yes	Yes	N/A	Recurrent	15	6.8				
					Yes	No	N/A	History Only	46	20.7				
					No	No	N/A	No Dep	141	63.5				
Parker, 2008, U.S. [13]	Prospective Cohort, single site	ACS patients, N=451, mean (SD) age, 65.7 (12.2), 29.7% females	CIDI; a checklist for DSM-IV dep symptoms	CIDI (in-hosp; retrospective to pre-ACS) & 1 mo post-discharge (DSM-IV checklist)	No	Yes	N/A	New-onset (Post-ACS; Incident)	25	5.5	2–12 mo composite outcome: readmission/CHD mortality	Death & Readmission Rates: Pre-ACS= 7 (12.7%); Post-ACS= 15 (32.6%); Non-incident (Recurrent)=12/50 (24%); Incident (New-onset)= 8/25 (32%); *History Only= 2/26 (7.7%); *No Dep= 55/346 (15.9%)	N/A	5
					Yes	Yes	N/A	Chronic (Pre-ACS; Non-incident)	30	6.7				
					Yes	No	Yes	Recurrent (Post-ACS; Non-incident)	23	5.1				
					Yes	No	N/A	History Only	27	6.0				
					No	No	N/A	No Dep	346	76.7				
Sorensen, 2005, Denmark [48]	Prospective Cohort, multisite	MI patients, N=694, mean (SD) age, 59.2 (9.6); 24.2% females	MDI	at discharge; history of depression was assessed at discharge	No	Yes	N/A	New-onset	46	6.6	1-yr all cause mortality	*New-onset= 2/46 (4.3%); Recurrent=0 (0%); History Only=1/37 (2.7%); No Dep= 9/599 (1.5%)	N/A	4
					Yes	Yes	N/A	Recurrent	12	1.7				
					Yes	No	N/A	History Only	37	5.3				
					No	No	N/A	No Dep	599	86.3				

Study	Design	Sample (size, sex, age, CHD)	Depression Assessment tool	Depression Ascertainment Timeframe	Depression Ascertained Pre-Event In-Hospital Post-Discharge	Categories	N	%	Endpoint	Results	Adjustment	Quality Score
Dickens, 2008, U.S. [11]	Prospective Cohort, single site	MI patients, N= 440, mean (SD) age, 60 (11.1), 29.6% females	HADS; 313 MI patients were interviewed by SCAN	HADS pre-MI dep (retrospective); 12 mo post-MI	No	New-onset	71	16.1	12-mo CHD mortality	New-onset, HR=2.33 (1.05–5.16), Recurrent, HR=.31 (.07–1.36); History Only=no data.	D, K, N & P	6
					Yes	Recurrent	96	21.8				
					Yes	History Only	N/A	N/A				
					No	No Dep	273	62.0				
de Jonge, 2006, Netherlands [80]	Prospective Cohort, multisite	MI patients, N= 468, mean (SD) age, 61 (11.4), 19.7% females	CIDI (assessed incident/non-incident dep)	3 & 12 mos post-MI	Yes	Recurrent	53	11.3	12-mo CHD mortality & CHD-related re-admissions	New-onset HR=1.76 (1.06–2.93), Recurrent HR=1.39 (0.74–2.61); *History Only= 5/22 (22.7%)	A, B, C & N	6
					No	New-onset	66	14.1				
					Yes	History Only	22	4.7				
					No	No Dep	327	69.9				
May, 2009, U.S. [29]	Prospective Cohort, multisite (Inter-mountain Heart Collaborative Study)	CHD pts, N=13,708, mean age=52, 55% females	IDC-9	Post CHD diagnosis	No	New-onset Post-morbid	1377	10.0	5.6-yr CHD morbidity (Heart Failure)	New-onset HR=1.5 (1.38–1.63)	A, B, D, E, F, G, I, L & N	9
					No	No Dep	12331	90.0				
Parashar, 2006, U.S. [49]	Prospective Cohort (PREMIER), multisite	MI patients, N=1875, mean (SD) age= 60.5 (12.5), 31.6% females	PHQ	In-hosp & 1 mo	No	New-onset Persistent (at 1 month)	371	19.8	6-mo all-cause mortality	*New-onset= 15/371 (4%); Recurrent dep= 4/125 (3.2%); History Only= 3/109 (2.8%), No Dep= 28/1270 (2.2%)	N/A	4
					Yes	Recurrent	125	6.7				
					Yes	History Only	109	5.8				
					No	No Dep	1270	67.7				

ACS, acute coronary syndrome; BDI, Beck Depression Inventory, CABG, coronary artery bypass surgery; CES-D, Center for Epidemiological Studies Depression scale; CHD, coronary artery disease; CIDI, Composite International Diagnostic Interview; DASS, Depression Anxiety Stress Scale; DIS, Diagnostic interview schedule; DISH, depression interview and structured Hamilton; Dep, depression; DSM, Diagnostic Statistics Manual; HADS, Hospital Anxiety & Depression Scale; HR, hazard ratio; ICD, International Classification of Disease; IHD, Ischemic Heart Disease; In-Hosp, in-hospital; MDD, major depression disorder; MDI, major depression inventory; MI, Myocardial Infarction; Mos, months; SCAN, Schedule for Clinical Assessment in Neuropsychiatry; USNIMH, US National Institute of Mental Health.

A, age, B sex, C, education, D, disease severity, E, comorbidities, F, smoking status, G, hypertension, H, diabetes, I, family history of CHD, J, history of CHD, K, antidepressant use, L, medication use, M, initial depression score, N, cardiac function, O, cardiac diagnosis, P, recurrent cardiac events

* data obtained from authors.

Characteristics of Selected CHD-free Cohort Studies

Table 2

Study	Sample (size, sex, age, CHD)	Depression Assessment	Depression Assessment Timing	Depression Ascertained		Categories	N	%	Endpoint	Results	Adjustment	Quality Score
				Pre-Event	Post-Event							
Pre-morbid Depression Assessed among CHD Free Cohort												
Aho, 2007, Finland [31]	CHD free cohort, N=660, mean (SD) age, 71.5 (6.0), 57.5% females	ZSDS	baseline	Yes		Pre-morbid	100	15	12-yrs CHD mortality	No dep CHD mortality= 39 (15%) vs. Pre-morbid dep CHD mortality 21 (47%)	A, E, F & S	6
				No		No Dep	560	85				
Anda, 1993, U.S. (NHEFS) [30]	CHD free cohort, N=2801, mean age=57.5, 52.4% females	GWBS	baseline	Yes		Pre-morbid (at baseline)	148	5	12.4 yrs CHD mortality	Pre-morbid dep RR=1.5 (1.0–2.3)	A, B, C, D, F, H, I, J, K, M & R	7
				No		No Dep	2653	95				
Cole, 1998 [50]	CHD free cohort, N=5053, mean age=61.8 (8.3), 100% males	Self-reported physician diagnosed depression	baseline	Yes		Pre-morbid (at baseline)	154	3	12 yrs CHD mortality	Pre-morbid dep CHD mortality rate RR= 1.20 95% CI 0.53 to 2.71.	N/A	5
				No		No Dep	4899	97				
Ferketich, 2000, U.S. (NHANES I) [32]	CHD free cohort N=7903, mean age=55.1 (14.2), 63.2% female	CES-D	baseline	Yes		Pre-morbid (at baseline)	1154	15	8.3 yrs CHD mortality	pre-morbid dep RR= 2.34 (1.54–3.56) for men; 0.74 (0.40–1.48) for women	E, D, H, I, L, M & O	7
				No		No Dep	6749	85				
Ford, 1998, U.S. [33]	CHD free cohort (medical students) N=1190, mean age=26, 0% females	self-report symptoms & treatment; response validated by physicians	baseline	Yes		Pre-morbid (at baseline)	132	11	37 yrs CHD mortality	pre-morbid dep RR= 1.8 (.56–5.75)	A, H, I, J, K, L, N & Q.	6
				No		No Dep	1058	89				
Penninx, 1998, U.S. (EPESE) [34]	CHD free cohort, N=3701, mean age, 78.3 (range 70–103), 66.2% females	CES-D	baseline, 3 and 6 yrs follow-ups; 1, 2, 4, 5 yrs telephone follow-up	Yes		Pre-morbid (at baseline)	256	7	4-yrs CHD mortality	Pre-morbid newly dep mortality HR=1.45 (1.02–2.08); pre-morbid chronic dep mortality HR=91 (.59–1.41)	A, B, G, H, I, M & R	7
				Yes		Pre-morbid Chronic (3 & 6 yrs before baseline)	221	6				
				No		No Dep	3224	87				
Penninx 2001, Netherlands (LASA) [35]	CHD free cohort N=2397, mean age=69.8 (8.7), 54.5% female	CES-D; DIS	baseline	Yes		Pre-morbid major dep	43	2	4.2 yrs Cardiac mortality	Minor Depression: pre-morbid RR= 1.6 (1.0–2.8) Major Depression: pre-morbid RR= 3.8 (1.4–10.6)	A, B, C, G, H, I, L, M & R	7
				Yes		Pre-morbid minor dep	282	12				
				No		No Dep	2072	86				
Surtees, 2008, U.K. (EPIC-NORFOLK) [36]	CHD free cohort, N=19,649, age (range 41–80), 58% females	HLEQ	baseline, 12 mos	Yes		Pre-morbid (at baseline)	586	3	8.5-yrs CHD mortality	Pre-morbid major dep CHD mortality HR=2.67 (1.54–4.64)	A, B, E, H, I, J, K, L, M, R & R	7
				No		Pre-morbid (within past 12 mos)	1030	5				
				Yes		Pre-morbid history (not within past 12 mos)	1441	7				

Study	Sample (size, sex, age, CHD)	Depression Assessment	Depression Assessment Timing	Depression Ascertained		Categories	N	%	Endpoint	Results	Adjustment	Quality Score
				Pre-Event	Post-Event							
Whang, 2009, U.S. (Nurse Health Study) [46]	CHD free cohort, N=62839, age (range 30–55), 100% females	MHI-5; anti-depressant use	baseline (1992), 1996 & 2000	No	No	No Dep	16592	84				
				Yes	Yes	Pre-morbid (at baseline)	4994	8	4 yrs CHD mortality	Pre-morbid dep CHD mortality rate = 64 (1.28%);	A, B, H, I, J, K, L, M, N, P & S	4
				No	No	No Dep	57845	92		No Dep CHD mortality rate=477 (.82%)		
							106193					

CES-D, Center for for Epidemiological Studies Depression scale; CIDI, Composite International Diagnostic Interview; CHD, coronary heart disease; DIS, Diagnostic interview schedule; Dep, depression; GWBS, General Well-Being Schedule; HLEQ, Health & Life Experience Questionnaire; HR, hazard ratio; IHD, Ischemic Heart Disease; In-Hosp, in-hospital; MDD, major depression disorder; MHI, Mental Health Index; MI, Myocardial Infarction; MMPI, Minnesota Multiphasic Personality Inventory; Mos, months; ZSDS, Zung Self-report Depressive Symptoms.

A, age, B sex, C, education, D, race, E, socioeconomic status, F, marital status, G, comorbidities, H, smoking status, I, hypertension/blood pressure, J, hyperlipidemia, K, physical activity, L, diabetes, M, body mass index, N, family history of CHD, O, history of CVD, P, supplement use, Q, graduation year, R, alcohol use, S, medication use.

* data obtained from authors.

Table 3

Summary of Primary Results

	History Only	Pre-morbid	Recurrent	New Onset (In-hospital)	New Onset (Post-hospitalization)
History Only RR=0.76 (95% CI 0.48–1.19)	-	Q=10.72, p=0.001	Q=6.04, p=0.014	Q=14.26, p<0.0001	Q=5.67, p=0.017
Pre-morbid in CHD-free Cohort RR=1.79 (95% CI 1.45–2.21)		-	Q=0.19, p=0.663	Q=1.69, p=0.194	Q=0.001, p=0.980
Recurrent RR=1.59 (95% CI 1.08–2.34)			-	Q=2.00, p=0.157	Q=0.192, p=0.662
New Onset (In-hospital) RR=2.11 (95% CI 1.66–2.68)				-	Q=1.50, p=0.220
New Onset (Post-hospitalization) RR=1.77 (95% CI 1.37–2.89)					-