Depression as a Risk Factor for Mortality in Patients With Coronary Heart Disease: A Meta-analysis

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Background: Prospective studies on physically healthy subjects have shown an association between depression and the subsequent development of coronary heart disease (CHD). The relative risk in meta-analytic aggregation is 1.64 (confidence interval [CI], 1.29–2.08) for any CHD event. However, the adverse impact of depression on CHD patients has not yet been the subject of a meta-analysis. **Objective:** To quantify the impact of depressive symptoms (eg, BDI, HADS) or depressive disorders (major depression) on cardiac or all-cause mortality. We analyzed the strength of the relationship, the time dependency, and the differences in studies using depressive symptoms or a clinical diagnosis as predictors of mortality. **Method:** English and German language databases (Medline, PsycInfo, PSYNDEX) from 1980 to 2003 were searched for prospective cohort studies. Sixty-two publications were identified. The inclusion criteria were met by 29 publications reporting on 20 studies. A random model was used to estimate the combined overall effect as crude odds ratios (OR) or adjusted hazard ratios (HR [adj]). **Results:** Depressive symptoms increase the risk of mortality in CHD patients. The risk of depressed patients dying in the 2 years after the initial assessment is two times higher than that of nondepressed patients (OR, 2.24; 1.37–3.60). This negative prognostic effect also remains in the long-term (OR, 1.78; 1.12–2.83) and after adjustment for other risk factors (HR [adj], 1.76; 1.27–2.43). The unfavorable impact of depressive disorders was reported for the most part in the form of crude odds ratios. Within the first 6 months, depressive disorders were found to have no significant effect on mortality (OR, 2.07; CI, 0.82–5.26). However, after 2 years, the risk is more than two times higher for CHD patients with clinical depression (OR, 2.61; 1.53–4.47). Only three studies reported adjusted hazard ratios for clinical depression and supported the results of the bivariate models. **Conclusions:** Depressive symptoms and clinical depression have an unfavorable impact on mortality in CHD patients. The results are limited by heterogeneity of the results in the primary studies. There is no clear evidence whether self-report or clinical interview is the more precise predictor. Nevertheless, depression has to be considered a relevant risk factor in patients with CHD. **Key words:** depression, coronary heart disease, mortality, meta-analysis, depressive symptoms, risk factor.

AMI = acute myocardial infarction; **AP** = angina pectoris; **BDI** = Beck Depression Inventory; **CABG** = coronary artery bypass graft; **CHD** = coronary heart disease; **CI** = confidence interval; **DIS** = Diagnostic Interview Schedule; **DS** = Zerssen Self-Rating Scale; **DSM** = Diagnostic and Statistical Manual of Mental Disorders; **ECG** = electrocardiogram; **f/u** = follow-up period; **GMS** = Global Mood Scale; **HADS** = Hospital Anxiety and Depression Scale; **HDL** = high-density lipoprotein; **HPA** = hypothalamic–pituitary–adrenocortical axis; **HR (adj)** = adjusted hazard ratio; **IL** = interleukin; **LVEF** = left ventricular ejection fraction; **Medline** = database of the U.S. National Library of Medicine; **MI** = myocardial infarction; **MD** = major depression; **OR** = odds ratio; **PSE** = Present State Examination; **PsycInfo** = database of the American Psychological Association; **PSYNDEX** = database of the Center for Psychological Information and Documentation at the University of Trier, Germany; **PTCA** = percutaneous transluminal coronary angioplasty; **RR** = relative risk; **SBP** = systolic blood pressure; **SCID** = Structured Clinical Interview for DSM; **SDS** = Zung Self-Rating Depression Scale; **TNF** = tumor necrosis factor.

INTRODUCTION

Coronary heart disease (CHD), in particular acute myocardial infarction (MI), is the major cause of morbidity and mortality in adults in the United States and in other industrialized countries (1,2). After an MI, the risk of mortality is still high, with more than half a million deaths in the United States (3). Even if the patient survives the hospital stay, there is a 10% to 30% chance that he or she will die in the next 2 years; the death rate shows a high correlation with age (4).

Several prospective studies on healthy people have demonstrated the predictive role of depression or depressive symptoms in the development of CHD. The results of two recent metaanalyses support the hypothesis that depression is a risk factor for the development of CHD (5,6). The risk of becoming inflicted with CHD was 60% higher in depressed patients (relative risk [RR], 1.64; confidence interval [CI], 1.29–2.08). It is noteworthy that according to these analyses, clinical depression proved to be a substantially better predictor for the development of CHD in initially healthy people (RR, 2.69; CI, 1.63–4.43) than depressive symptoms (RR, 1.49; 1.16–1.92).

Despite the empiric evidence that depression increases the risk of cardiovascular morbidity and mortality, there is no common accepted model that describes the underlying mechanisms (7,8). Under discussion are both "direct" and "indirect" pathways. "Direct" influences of depression on physiological factors may lead to atherosclerosis or coronary events. More indirectly, depression leads to an increase in classic coronary risk factors, which in turn may cause coronary heart disease. Finally, there may be some underlying background factors influencing the risk for both depression and coronary heart disease. The psychobiologic pathways involve at least three mechanisms. First, depression is associated with autonomic imbalance and activation of the HPA axis (9). Second, depression may lead to dysregulation of immunologic mechanisms (eg, proinflammatory cytokines such as interleukins [IL-1, IL-6] or tumor necrosis factor [TNF]), which are associated with an increased risk of CHD (10–12). Third, coagulation abnormalities and vascular endothelial dysfunction are thought to play an etiologic role in the development or the progression of atherosclerosis in depressed people. High white

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blood cell counts, fibrinogen, and raised platelet activation contribute to a prothrombotic state, thrombus formation, and myocardial ischemia (13–15).

Indirect pathways refer to psychosocial and behavioral mediators, which correlate with depression and CHD. Depression is associated with poor health behavior, maladaptive coping style, social isolation, and chronic life stress (16). Behavioral risk factors such as smoking, low physical activity, a poor diet, and the failure to adhere to medical recommendations mediate the relationship of depressive disorders with CHD (17,18). Low levels of perceived emotional support and social isolation are related to both CHD and depression (19–21). Psychosocial stressors are known to be predictors of depression in patients with CHD and are also known to be predictors of CHD and the prognosis in CHD patients (22,23).

Some narrative reviews have been published that indicate the impact of depression after a cardiac event (22,24–30). The reviews report depression as having a negative influence on outcome criteria such as cardiac morbidity, cardiac mortality, or total mortality. None of the reviews analyzes the impact of depression on mortality in CHD patients systematically. The objective of our meta-analysis was thus to fill this gap by indicating the extent of this impact. We hypothesized that depressive symptoms and clinical depression have a negative impact on survival in patients with CHD. The following questions were examined: To what extent do depressive symptoms or clinical depression increase mortality in CHD patients? Do effect sizes differ when they are computed for short-term, medium-term, or long-term follow-up periods? Is the impact of depression still present in studies that adjusted for known risk factors?

METHODS

Inclusion Criteria

Inclusion criteria consisted of: 1) the study design had to be a prospective cohort study; 2) studies had to focus exclusively on patients diagnosed with CHD or report data of a subgroup with CHD patients at baseline; 3) depression had to be assessed by standardized measures or a clinical interview in a stable clinical situation or after a cardiac event or procedure, and results had to be reported for depressed versus nondepressed patients; 4) results of at least one follow up with a minimum of 3 months had to be reported; 5) outcomes had to be a) death from cardiac cause or b) death from any cause; and 6) odds ratios of the influence of depressive symptoms or depressive disorders on survival had to be either provided or computable from the results section. For primary studies that used the Cox regression model, we used the adjusted hazard ratios reported in the study. Studies assessing depressive symptoms before a cardiac procedure were excluded because of the overlap between preoperative anxiety and depression (31,32).

Definition of Coronary Heart Disease

The patients included in this meta-analysis sustained an initial CHD event (MI, coronary artery bypass graft [CABG], percutaneous transluminal angiography [PTCA]) or angiographically validated CHD. PTCA and CABG may be diagnosed clearly, whereas the diagnosis of acute MI needs further definite criteria. According to the World Health Organization definition, two of the following indicators are necessary: 1) ischemic chest pain lasting ≥20 minutes; 2) modified enzyme patterns (elevated peak creatine phosphokinase); or 3) changes in electrocardiogram (ECG). Trials studying patients with angina pectoris but without a CHD diagnosis were excluded. Studies on populations suffering from cardiovascular diseases in general, which also include cerebrovascular diseases, were excluded (33).

Definition of Depression

Either clinical depression or depressive symptoms had to be assessed at baseline. Clinical depression could be assessed by a standardized clinical interview. Depressive symptoms were to be measured with standardized psychometric scales.

Literature Search and Data Sources

Databases in English and German were searched for relevant studies published between 1980 and 2003. The databases we used were MEDLINE (U.S. National Library of Medicine), PsycInfo (American Psychological Association), and PSYNDEX (a German database of the Center for Psychological Information and Documentation at the University of Trier, Germany). The search strategy used both free-term searches and MeSH term searches. We used the combination of 1) "depression" or "affective disorder;" 2) "coronary disease" or "myocardial ischemia;" and 3) "mortality" or "death" as subject headings or search terms (see the Appendix for detailed information). The search was not restricted by publication language or by publication type. All findings were downloaded and stored in the reference database program EndNote 6.2. The search was complemented by cross-checking references listed in narrative reviews (see "Introduction") and in a recently published systematic review by the senior author (34).

Study Selection and Data Extraction

The search results were assessed by the second author for eligibility. This consisted of scanning the titles and abstracts. Sixty-two eligible papers remained and went into the coding process. Each eligible study was coded according to standardized criteria (35): 1) citation of reference; 2) inclusion and exclusion criteria; 3) description of the patient sample (size of sample, age, sex, subgroups); 4) time frame of measurement of mortality (short-term as >3 months and ≤6 months, medium term as >6 months and ≤2 years; long-term as >2 years); 5) variables measured at baseline (clinical depression/depressive symptoms, cardiac event, cardiac status); 6) type of outcome (cardiac mortality or total mortality); 7) statistics (adjusted hazard ratio [HR], odds ratio [OR]) or raw values; and 8) adjustment for known confounding risk factors (eg, age, sex, physical illness, smoking, hyperlipidemia, hypertension).

In the end, 20 studies published in 29 papers met the inclusion criteria. Thirty-three papers had to be excluded (see the section "Excluded Studies" in the Appendix for reasons of exclusion).

Data Management and Data Analysis

Data were extracted independently by two reviewers (J.B., M.S.). Differences were solved by discussion and ended in one final coding. Two figures are necessary to compute ORs or adjusted HRs in the meta-analysis. One is an estimate of the effect sizes and the other is the standard error of the effect size. The effect size was computed by using the OR or adjusted HR as shown in formula 1. As standard error, we used raw values as in formula 2 or estimated the standard error with the CI reported in the study.

Formula 1: $Estimate = \ln(OR)$; or $Estimate = \ln(adjHR)$

Formula 2: $Standard\ Error = \sqrt{\frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d}}$

OR = odds ratio

HR = hazard ratio

a, b, c, d: reported raw data in a cross table

Data management and data analysis were performed with Review Manager 4.2, provided by the Cochrane Collaboration (www.cochrane.org). A random effects model was used to pool the studies. The studies were weighted by the inverse variance method as described in the manual of the review manager (see www.cochrane.org/resources/handbook/section8.pdf). Summary statistics were reported as adjusted HR or OR with a CI of 95%. Values greater than 1 indicate

TABLE 1. Studies on Depression and CHD (N = 20) in Alphabetical Order

Study No., authors, publications, country	Sample characteristics (size, sex, age, CHD)	Definition and assessment of depression, symptoms vs. clinical depression	Statistics, length of follow-up	Results (total mortality, cardiovascular mortality)
Study No. 1 Barefoot et al. 1996 (37), 2000 (38) USA	1250 US adults, 1031/219 (m/f), 52 y, PTCA	Zung Self-Rating Depression Scale (SDS), cut-off = 50 (depressive symptoms)	Non-adjusted and adjusted: severity of disease, treatment >2 y (2–15 y) f/u	Cardiovascular mortality: OR nadj 1.26 (CI 1.07–1.48) cardiovascular mortality: HR adj 1.42 (1.14–1.76)
Study No. 2 Borowicz et al. 2002 (39), USA	172 US adults, 134/38 (m/f), 63.4 y, CABG	Center for Epidemiologic Studies Depression Scale (CES-D), cut-off = 16 (depressive symptoms)	Non-adjusted 5y-f/u	Cardiovascular mortality: OR nadj. 2.29 (CI 0.74–7.11)
Study No. 3 Bush et al., 2001 (40), USA	285 US adults, 158/113 (m/f), 64.8 y, post-AMI	Beck Depression Inventory (BDI) (depressive symptoms), cut-off = 10 SKID-NP (DSM-IIIR) (clinical depression)	Non-adjusted 4 months-f/u	All cause mortality: OR nadj 2.80 (CI 1.03–7.61) (depressive symptoms) OR nadj 2.20 (CI 0.73–6.59) (clinical depression)
Study No. 4 Carney et al., 1988 (41), USA	52 US adults, 38/14 (m/f), 56.2 y (<70 y), any cardiac event (PTCA, CABG, MI)	DSM-III-R (clinical depression)	Non-adjusted 1y-f/u	All cause mortality: OR nadj 2.65 (CI 0.21–31.46)
Study No. 5 Carney et al., 2003 (42) USA	766 US adults, 463/303 (m/f), 58.9 y, MI	DSM IV; Depression Interview. Major or minor depression (clinical depression)	Adjusted: age, diabetes, smoking status, left ventricular ejection fraction, bypass surgery after MI 30 month-f/u	All cause mortality: HR adj. 2.4 (CI 1.2–4.7)
Study No. 6 Connerney et al., 2001 (43), USA	309 US adults, 207/102 (m/f), 63.1 y, CABG	Beck Depression Inventory (BDI), cut-off = 10 and clinical interview n.s. (clinical depression)	Non-adjusted 12 month f/u	Cardiac mortality: OR nadj. 1.82 (CI 0.22–15.02) HR adj. 2.31 (CI 1.17–4.56)
Study No. 7 Denollet et al., 1996 (44) Belgium	303 adults, 268/35 (m/f), 55.4 y (31–79), MI, PTCA	Millon Behavioral Health Inventory, cut-off n.s. (depressive symptoms)	Non-adjusted 7 y f/u	Cardiovascular mortality: OR nadj. 2.69 (CI 1.33–5.45)
Study No. 8 Denollet et al., 1998 (45), Belgium	87 adults, 81/6 (m/f), 55.1 y (41–69) MI	Millon Behavioral Health Inventory, cut-off pessimism = 10 and despair = 12 (depressive symptoms)	Non-adjusted 6–10 y f/u (7.9 y)	Cardiovascular mortality: OR nadj 7.46 (CI 1.56–35.80)
Study No. 9 Frasure-Smith et al., Lespérance et al.; 1993 (47), 1995 a (48), b (49), 1996 (50) Frasure-Smith et al., 1999 (51) Canada	222 Canadian adults, 173/49 (m/f), 60 y (24–88), AMI	Beck Depression Inventory (BDI), cut-off = 10 (depressive symptoms)‖ Diagnostic Interview Schedule (DIS, National Institute of Mental Health-modified version) (clinical depression)	Non-adjusted and adjusted: previous MI, Killip class, premature ventricular contractions [PVCs] of ≥10 per hour 6 months f/u 18 months f/u	Cardiovascular mortality: 6 mo (MD): OR nadj. 6.24 (CI 1.88–20.67) 6 mo (MD): HR adj 4.29 (CI 3.14–5.86) 18 mo (MD): OR nadj 3.64 (CI 1.32–10.04)
Study No. 10 Frasure-Smith et al., 1999 (51), Frasure-Smith et al., 2000 (53), Lespérance et al., 2002 (52), Canada	887–896 Canadian adults, 608/279 (m/f) resp. 613/283 (m/f), 59.4 y, MI	Beck Depression Inventory (BDI), cut-off = 10 (depressive symptoms)	Non-adjusted and adjusted: smoking, age, Non-Q-wave MI, LVEF, Killip class 1 y and 5 y f/u	Cardiovascular mortality 1 y: OR nadj 3.22 (CI 1.65–6.31) 5 y: HR adj 3.16 (CI 1.78–5.59)

TABLE 1. (Continued)

Study No., authors, publications, country	Sample characteristics (size, sex, age, CHD)	Definition and assessment of depression, symptoms vs. clinical depression	Statistics, length of follow-up	Results (total mortality, cardiovascular mortality)
Study No. 11 Herrmann et al., 2000 (55), Germany	2432 German adults, 2075/357 (m/f), 53.8 y (41–66.5), CHD	Hospital Anxiety and Depression Scale (HADS), cut-off = 8 on depression subscale (depressive symptoms)	Adjusted: hypertension, age, gender, previous MI, ECG 5–6 y f/u	All cause mortality: HR adj 1.21 (CI 1.04–1.42)
Study No. 12 Irvine et al., 1999 (56), Canada	634 Canadian adults, 525/109 (m/f), 63.8 y (32–89), MI	Beck Depression Inventory (BDI), cut-off = 10 (depressive symptoms)	Adjusted: previous MI or AP, significant biological predictors (n.s.) 2 y f/u	Sudden cardiac death HR adj 2.45 (1.14–5.35)
Study No. 13 Jenkinson et al., 1993 (57), UK	1376 British adults, 1073/303 (m/f), 59 y (25–84), MI	Three items in the psycho-social questionnaire of the ASSET Study, cut-off n.s. (depressive symptoms)	Non-adjusted 6 months f/u 1 y f/u 3 y f/u	All cause mortality 6 mo: OR nadj 1.0 (CI 0.35–2.83) 1 y: OR nadj 1.0 (CI 0.42–2.37) 3 y: OR nadj 0.9 (CI 0.47–1.76)
Study No. 14 Kaufmann et al., 1999 (58), USA	331 US adults, 217/114 (m/f), 65 y (28–92), MI	Diagnostic Interview Schedule (DIS) (clinical depression)	Non-adjusted 6 months f/u 1 y f/u	All cause mortality 6 mo: OR nadj 2.46 (CI 0.86–6.98) 1 y: OR nadj 2.34 (CI 1.18–4.65)
Study No. 15 Ladwig et al., 1991 (59), 1994 (60), Germany	560 German adults, only males, 54 y (29–65), MI	Psychological inventory: Zerssen Self-Rating Scale with 37 items, cut-off n.s. (depressive symptoms)	Non-adjusted and adjusted: age, social class status, recurrent infarction, rehabilitation, cardiac events, helplessness 1 y f/u	Cardiovascular mortality OR nadj 5.3 (CI 1.42–19.69) HR adj 4.9 (CI 1.11–21.59)
Study No. 16 Lane et al., 2001 (61), 2002 (62), UK	288 adults, 215/73 (m/f), 62.7 y (31–89), MI	Beck Depression Inventory (BDI), cut-off = 10 (depressive symptoms)	Non-adjusted 1 y f/u 3 y f/u	Cardiovascular mortality 1 y: OR nadj 1.15 (CI 0.49–2.70) 3 y: OR nadj 0.84 (CI 0.37–1.91)
Study No. 17 Mayou et al., 2000 (63), UK	344 adults, 251/93 (m/f), 63.2 y (30–79), MI	Hospital Anxiety and Depression Scale (HADS), cut-off = 19 (depressive symptoms)	Non-adjusted 6 months f/u 18 months f/u	All cause mortality 6 mo: OR nadj 1.60 (CI 0.43–5.95) 18 mo: OR nadj 1.64 (CI 0.64–4.20)
Study No. 18 Romanelli et al., 2002 (64), USA	153 adults, 85/68 (m/f), 74.5 y (65–93), MI	Beck Depression Inventory (BDI), cut-off = 10 or DSM-III-R (clinical depression)	Non-adjusted 4 months f/u	Cardiovascular mortality OR nadj 4.71 (CI 1.67–13.31)
Study No. 19 Schleifer et al., 1989 (65), USA	283 US adults, 181/102 (m/f), 63.7 y (27–90), MI	Schedule for Affective Disorders and Schizophrenia including patients with minor depression and major depression (clinical depression)	Non-adjusted 3 months f/u	Cardiovascular mortality OR nadj 0.59 (CI 0.20–1.74)
Study No. 20 Welin et al., 2000 (66), Sweden	275 adults, 230/45 (m/f), >65 y (30–65), AMI	Scale (SDS), cut-off = 80 Beck Depression Inventory (BDI), cut-off = 10 (depressive symptoms)	Non-adjusted and adjusted: smoking, hypertension, hypercholesterinemia, low LVEF, gender, social support 10 y f/u	Cardiovascular mortality OR nadj. 3.54 (CI 1.85–6.77) HR adj 3.16 (CI 1.38–7.23)

AMI = acute myocardial infarction; BDI = Beck Depression Inventory (depressive symptoms); BMI = body mass index; CABG = coronary artery bypass graft; CHD = coronary heart disease; CI = Confidence interval; DSM IIIR/IV = Diagnostic and Statistical Manual; f/u = follow-up; HDL = high density lipoprotein; HR = hazard ratio; y = years; LVEF = left ventricular ejection fraction; m/f = males/females; MD = major depression (clinical depression); MI = myocardial infarction; nadj = non-adjusted; n.a. = not available; n.s. = not specified; OR = Odds ratio; PTCA = percutaneous transluminal coronary angioplasty; SCID-NP = Structured Clinical Interview [non-patient version]; SBP = systolic blood pressure.

‖ The results of this analysis on depressive symptoms were not included due to the more detailed information available in Study 10.

an unfavorable impact of depression or depressive symptoms on mortality. The chi-square value tests for statistically significant heterogeneity among trials; p values lower than .05 indicate heterogeneity; additionally higher I^2 values indicate greater variability among trials than would be expected by chance alone (range, 0–100%) (36). The results are clustered for three follow-up periods: short-term (>3 months and ≤6 months), medium-term (>6 months and ≤2 years), and long-term (>2 years). Funnel plots of all outcome measures can be found in the Appendix (Figures 1a, 2a, and 3a).

RESULTS

Description of the Studies

Twenty-nine papers described details of the 20 primary studies that were included in the meta-analysis (see Table 1 (37–66)). The publications dated from 1988 to 2003 and were all published in English. Table 1 shows the main characteristics of the included studies, which are labeled in the Results section as study 1 to study 20.

Nine studies were performed in the United States (studies 1–5, 14, 18, and 19), and three came from Canada (studies 9–10 and 12). The European studies were performed in the United Kingdom (studies 13, 16, and 17), Belgium (studies 7 and 8), Germany (studies 11 and 15), and Sweden (study 20). The number of participants ranged from 52 (study 4) to 2432 CHD patients (study 11).

Type of Participants

Most of the studies ($n = 15$) included patients with myocardial infarction (studies 3, 5, 8–10, and 12–20). Two studies included patients after coronary bypass surgery (studies 2 and 6), one study included patients after PTCA (study 1), and three studies included patients with a variety of diagnoses (MI, CABG, PTCA) or angiographically validated CHD (studies 4, 7, and 11). Most of the patients in the studies were male. One study reported only on male patients (study 15). The mean age ranged from 53.6 to 74.5 years (the minimum was 19 and the maximum 90).

Measurement of Depression

Four studies measured clinical depression (studies 4–5, 14, and 19), 13 depressive symptoms (studies 1–2, 6–8, 10–13, 15–17, and 20), and two both clinical depression and depressive symptoms (studies 3 and 9). One study assessed depression by way of self-report or clinical diagnostic interview and set up an index for depression (study 18). This study was coded as measuring depressive symptoms.

Three studies used DSM-III-R criteria to assess clinical depression (studies 3–4 and 18) without any specification of the diagnostic procedure. One study assessed clinical depression by using DSM-IV criteria with a specific depression interview developed for this purpose (study 5). The Diagnostic Interview Schedule (DIS) was used in two studies (studies 9 and 14), one study measured clinical depression with the Schedule for Affective Disorders and Schizophrenia (study 19), and another one used a modified SCID (study 3).

The Beck Depression Inventory was used most widely to measure depressive symptoms (studies 3, 6, 9, 12, 16, 18, and 20). Other diagnostic instruments were the Zung Self-Rating Depression Scale (SDS; studies 1 and 20), the Hospital Anxiety and Depression Scale (HADS; studies 11 and 17), and the Millon Behavioral Health Inventory (studies 7 and 8). One study used the Center of Epidemiologic Studies Depression Scale (CES-D; study 2), one used three items from the psychosocial questionnaire of the ASSET Study (study 13), and one used the Zerssen Self-Rating Scale (study 15).

Study Outcome

The outcome of the studies was either cardiovascular mortality, reported in 12 studies (studies 1–2, 6–10, 12, 15–16, 18, and 20), or all-cause mortality, reported in seven studies (studies 3–5, 11, 13–14, and 17). The length of follow up varied from 3 to 4 months (short follow up in studies 1, and 18–19) to 10 years (study 20). Six studies reported data for 5 years or longer (studies 2, 7–8, 10–11, and 20).

Statistics

Eleven studies reported crude ORs (studies 2–4, 7–8, 13–14, and 16–19). In three studies, the authors reported HRs adjusted for known risk factors (smoking, age, sex, hypertension, hyperlipidemia, diabetes mellitus, body mass index) or sociodemographic characteristics and cardiac parameters at baseline (low left ventricular ejection fraction, previous AP, Killip Class, nonQ-wave-MI) (studies 5, 11–12, and 16). Six studies reported crude and adjusted values (studies 1, 6, 9–10, 15, and 20). Multivariate ORs or univariate HRs were not provided in a sufficient number of studies to justify their metaanalytic aggregation.

Effect of Depressive Symptoms

The results are presented as crude estimated effects of depressive symptoms on mortality (Figure 1) and after adjustment for known risk factors (Figure 2). The nonadjusted OR of 2.24 (CI, 1.37–3.60) we found in short- and medium-term follow-up studies supports our hypothesis that depressed patients have higher rates of mortality. The results from long-term follow-up studies also indicate higher mortality but show a lower OR of 1.78 (CI, 1.12–2.83). The effect size for long-term mortality is based on heterogeneous results ($p = .0002$; $I^2 = 71.3\%$), whereas short- and medium-term effects are based on more homogeneous results in primary studies ($p = .09$; $I^2 = 45.7\%$).

After adjustment for known cardiac risk factors, depressive symptoms still show a significant impact on mortality (HR [adj], 1.76; CI, 1.27–2.43). This estimation is also based on heterogeneous results ($p = .002$; $I^2 = 71.4\%$). We were not able to cluster the results depending on follow-up length because of the low number of primary studies.

Effect of Clinical Depression

The effect of clinical depression was assessed predominantly in the short and medium term with unadjusted ORs. Only three studies reported an adjusted HR. Figure 3 shows a nonsignificant short-term effect of clinical depression on mortality (OR, 2.07; CI, 0.82–5.26; $I^2 = 64.8\%$). The OR resulting from medium-term studies is significant (OR, 2.61; CI, 1.53–4.47). The result for the medium-term follow-up period is based on homogenous effects in the primary studies ($p = .89$; $I^2 = 0\%$). Contrary to the hypothesis

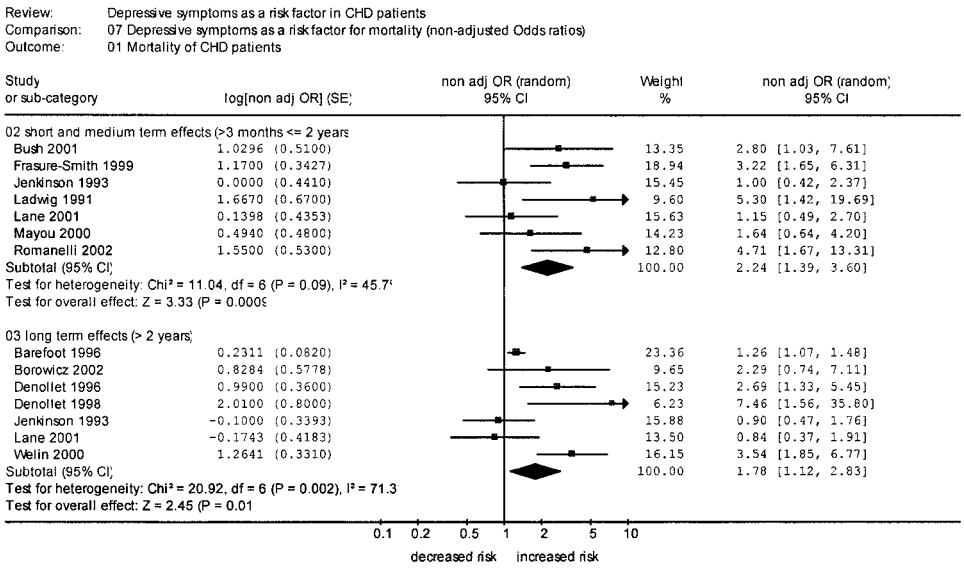

Figure 1. Depressive symptoms as a risk factor for mortality (univariate risk estimates using odds ratios).

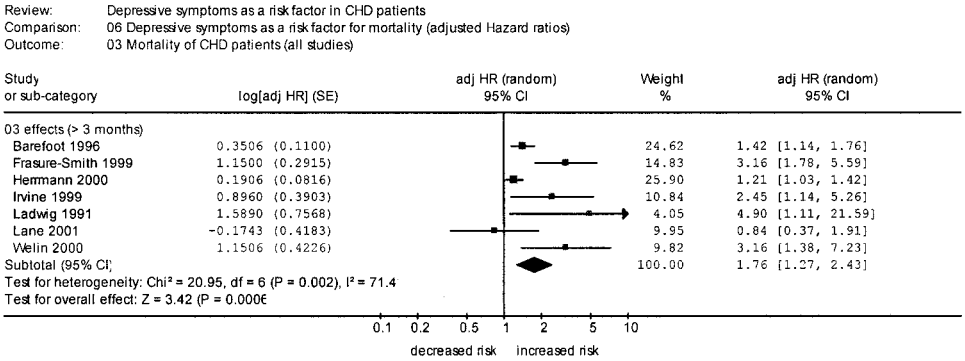

Figure 2. Depressive symptoms as a risk factor for mortality (adjusted risk estimates using hazard ratios).

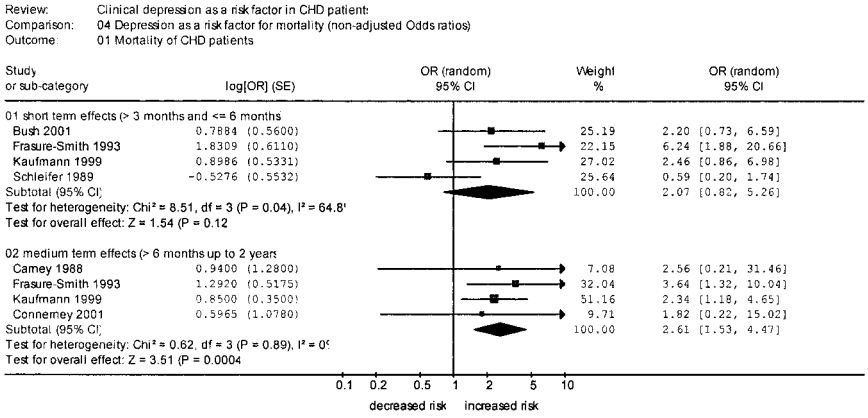

Figure 3. Clinical depression as a risk factor for mortality (univariate risk estimates using odds ratios).

that the prognostic impact of initial depression declines over time, we find a higher OR in studies with longer follow-up periods. As mentioned previously, only three studies performed an adjusted risk analysis. In the short term, such an analysis results in an adjusted HR of 4.29 (CI, 3.14–5.86) (47). Connerney et al. (43) also reported a significant adjusted HR of 2.31 (CI, 1.17–4.56) after 12 months. In the only published study with a follow-up period of more than 2 years, Carney et al. (42) reported an adjusted HR of 2.4 (CI, 1.2–4.7).

Sensitivity Analysis

A sensitivity analysis can be performed to look for moderating factors on the effects in the various studies. We tried

to reduce heterogeneity by limiting our meta-analysis to studies with specific characteristics. One factor that may confound effect sizes is the diversity of end points in the studies. We therefore focused on studies with cardiac mortality as the end point of sensitivity analyses and excluded studies with all-cause mortality (studies 3–5, 11, 13–14, and 17). For depressive symptoms, this led to no exclusion of studies reporting crude ORs in the long term. In the other analyses, only one or two primary studies were excluded.

In short- and medium-term follow-up studies, the effect sizes of the adverse impact of depressive symptoms were slightly higher for cardiac mortality (OR, 2.88; CI, 1.47–5.63) than for total mortality, as shown in Figure 1. The pooled estimate was still homogeneous ($p = .10$; $I^2 = 51.7\%$). The effect sizes of the adjusted model were also slightly stronger (HR [adj], 2.07; CI, 1.31–3.27) than the results shown in Figure 2. The fact that we limited the data set to studies with an outcome of cardiac mortality contributed only marginally to the homogeneity of the underlying results. On the whole, the data set was still heterogeneous ($p = .01$; $I^2 = 66.4\%$).

In the sensitivity analysis that tested the effects of clinical depression on cardiac mortality, only two studies with a short-term follow up remained in the data set. One of these studies found a nonsignificant negative result (study 19), and the other showed a very strong influence (study 9). For studies with a medium-term follow up, the OR remained almost the same (OR, 2.62; 1.51–4.53), even after the exclusion of one study (study 4); this pooled effect size is based on homogenous results ($p = .73$; $I^2 = 0\%$).

DISCUSSION

The results of this meta-analysis indicate that depressive symptoms have a strong adverse effect on cardiac and total mortality in CHD patients. This result is not limited to short-term follow-up studies; the negative effect also holds for long-term studies. Even in the long term, the mortality rate is higher for CHD patients who report depressive symptoms. However, the latter findings are based on heterogeneous results, and the average estimate of 1.78 must thus be interpreted with caution. Although a different set of studies is included in the analysis of adjusted HRs, the relative risk of mortality in depressed patients is nearly the same as in studies reporting nonadjusted results. We found heterogeneity in these results as well.

The risk of mortality is at least two times higher in the short and medium term for patients suffering from CHD and comorbid clinical depression. These results were based on bivariate statistics. Analyses with adjusted Cox regression models confirmed these effect sizes.

Heterogeneity in primary studies was quite an issue in this meta-analysis, especially for studies that looked at depressive symptoms rather than clinical depression. Interestingly, even when depressive symptoms were measured with the same instrument (eg, BDI), different effects emerged. Not even the length of the follow-up period seemed to contribute to making the basis of the underlying studies more homogeneous. It was not sufficient to limit the analysis to cardiac mortality as an outcome to reduce heterogeneity either. One possible explanation for the heterogeneity of the adjusted analyses may be the selection of risk factors, which varied greatly from study to study. One possible solution to this problem would be to pool and reanalyze the original data of all included studies.

A closer look at the studies with negative or null effects (studies 13, 16, and 19), which were the ones that contradicted the total effect, revealed no shared study characteristics. There was not any indication that methodologic biases could have affected the results of these three studies either. This is at least true of two of the three studies (studies 16 and 19). In the study by Jenkinson et al. (study 13), only the assessment of depressive symptoms by three unvalidated self-report items is quite questionable and may explain the null result.

Likewise, the closer inspection of the four studies with large effect sizes indicated no lack of methodologic quality (studies 8–9, 15, and 18). Although the assessment of depressive symptoms in the study by Denollet et al. may be questioned (study 8), the other studies used widely accepted scales for measuring depressive symptoms. The use of a clinical interview or self-report to index depression in the study by Romanelli et al. was certainly a disadvantage, but it does not explain the high ORs.

As mentioned previously, our meta-analysis found that depression has an adverse effect after a first manifestation of CHD. This raises the question as to whether patients who are depressed after a cardiac event already had more depressive symptoms before the event. The data in our analysis cannot answer this question. Retrospective data from CHD patients about earlier episodes of major depression showed that one of four patients had a lifetime diagnosis (50). Ongoing research is investigating the effect of affectivity before the clinical manifestation of CHD (32), which would confirm the unfavorable effect.

In this meta-analysis, we differentiated between studies with self-report measures and those with clinical interviews. Self-report measures are very useful for screening patients, planning, and evaluating psychotherapeutic or drug interventions in clinical practice. Additionally, we know that clinical depression and depressive symptoms (eg, BDI $\geq$10) share 60% to 80% of common variance (50,67). A clinical diagnosis cannot be made by self-report questionnaires, and this may be a disadvantage. On the other hand, self-rating scales may be more sensitive in detecting subthreshold disorders, and we found that the low cutoff of 10 in the BDI is sufficient for indicating an increased mortality risk. Hence, for epidemiologic purposes, it is difficult to demonstrate the superiority of one or the other measure of depression. Accordingly, we found no clear prognostic difference between studies that defined depression through self-report and those that did so with a clinical interview.

Limitations

Our review included only published studies with sufficient data. We did not include abstracts because they cannot give reliable information on inclusion and outcome criteria. The adjusted OR reported in one publication of the EPPI study

(48) could not be included in our analysis, because it appeared inappropriate to mix results of logistic regression and Cox regression models in one meta-analysis. Like in every meta-analysis, we have to take into account a publication bias. We found some hints for a publication bias in studies assessing depressive symptoms (see funnel plots in the Appendix, Figures 1a, 2b, and 3a). The funnel plot of studies assessing the impact of depressive disorders seems appropriate. It is possible that small nonsignificant studies of depressive symptoms are not submitted because they have lower chances of being accepted. We did not assess the quality characteristics of each study as recommended for randomized, controlled studies (68). Therefore, we did not use a sum score for study quality either (for limitations of sum scores, see (69)). Some results of this meta-analysis are based on heterogeneous effects of the primary studies. Therefore, the pooled estimates were not an accurate summary estimate in all reported results.

Future Research

Missing Studies

There are sufficient data on the influence of depressive symptoms on total or cardiac mortality in the long term. Results on the long-term impact of clinical depression are rather limited. Data from the ENRICHD trial (study 5) give initial hints on this topic, but further research is necessary to obtain more stable effects on the impact of depressive disorders on mortality in CHD patients.

Heterogeneity of End Points

Further research should report cardiac events, cardiac mortality, and total mortality as end points. Many studies mixed these criteria by reporting results on cardiac prognosis. An aggregated index is a good way to deal with insufficient statistical power. On the other hand, the comparison, reanalysis, and aggregation of these studies are problematic because of heterogeneity in the end points.

Adjustment of Risk Factors

In reporting data, it would be helpful to get results of nonadjusted ORs and adjusted HRs. Some results might reach the level of significance only before or after adjustment. For transparency, it would be helpful to obtain both results. Another point is the selection of risk factors. Authors focused mainly on somatic parameters that may increase physical distress and decrease cardiac functioning. On the other hand, established risk factors like smoking or lipids should also be controlled for the prognosis of the CHD. Initial cessation of smoking is quite common in CHD patients. However, on the other hand, approximately 50% of those who stop smoking begin smoking again within 1 year after the event. Recent epidemiologic studies show evidence for a link between smoking behavior and depression (70). To get more reliable information on the impact of depression on CHD, it would be helpful to adjust the analysis for risk factor information, not only in the initial phase, but also during the follow up.

CONCLUSIONS

This meta-analysis showed evidence that depression has an unfavorable effect on mortality in CHD patients. Depression, like smoking or lipids, seems to be a highly relevant risk factor in patients with CHD. Standardized treatment strategies have been established for these known risk factors. It is unknown at the moment how best to treat comorbid depressive patients with CHD because of the limited efficacy of psychotherapeutic (71) or psychopharmacologic interventions (72). Psychotherapy has failed to reduce cardiac or total mortality (71). On the other hand, the legitimacy of psychotherapeutic or psychopharmacologic interventions is based not only on mortality rates. The reduction of the depressive symptoms in these patients is also an ethical principle. In the coming years, it will be necessary to develop more feasible intervention strategies designed for the specific needs of these patients and based on their predominantly somatic illness concepts. The motivation for psychotherapeutic treatment in primarily medically ill patients especially needs further research. The question as to when intervention should be provided must also be discussed. This may lead to an integrated treatment strategy that may reverse the increased risk of mortality in depressed CHD patients.

APPENDIX

Barth, Schumacher, Herrmann-Lingen (Depression and Coronary Heart Disease)

Search History in* Medline, Premedline, BIOSIS, and *Journals@Ovid (1980–2003)

#1 coronary disease (58,450 records)
#2 myocardial infarction (205,412 records)
#3 angina pectoris (37,630 records)
#4, #1, or #2 or #3 (267,536 records)
#5 affective disorder (11,517 records)
#6 depression (256,320 records)
#7 depressive mood (1533 records)
#8 depressive symptoms (19,577 records)
#9, #5, or #6 or #7, or #8 (265,290 records) #10, #4, and #9 (16,683 records) #11 mortality (491,759 records) #12, #10, or #11 (6038 records) → 6038 hits in Medline, Premedline, BIOSIS, and Journals@Ovid

Search History in* PsycInfo *(1980–2003)

#1 TI CHD or AB CHD or MJ CHD (1531 records)
#2 TI myocardial infarction or AB myocardial infarction or MJ myocardial infarction (1531 records)
#3 TI angina pectoris or AB angina pectoris or MJ angina pectoris (247 records)
#4 (S1 or S2 or S3) (3048 records)
#5 TI affective disorder or AB affective disorder or MJ affective disorder (12,235 records)
#6 TI depression or AB depression or MJ depression (89,077 records)
#7 TI depressive mood or AB depressive mood or MJ depressive mood (611 records)
#8 TI depressive symptoms or AB depressive symptoms or MJ depressive symptoms (7176 records)

Table of Excluded Studies

Citation	Reasons for Exclusion
Abramson J, Berger A, Krumholz HM, et al. Depression and risk of heart failure among older persons with isolated systolic hypertension. Arch Intern Med 2001; 161:1725–30.	The authors analyze to what extent depression is to be regarded as a risk factor for heart insufficiency in the case of preexisting isolated systolic hypertension. The outcome of this study is not mortality, but the rate of heart failure.
Ahern DK, Gorkin L, Anderson JL, et al. Biobehavioral variables and mortality or cardiac arrest in the cardiac arrhythmia pilot study (CAPS). Am J Cardiol 1990; 66:59–62.	This article does not contain sufficient data to calculate OR or HR. The study reports BDI means regarding survivors vs. nonsurvivors of a cardiac arrest and *p* values only.
Aromaa A, Raitasalo R, Reunanen A, et al. Depression and cardiovascular disease. Acta Psychiatr Scand 1994; 377:77–82.	Epidemiologic study on the impact of depression in patients with mixed diagnosis.
Blumenthal JA, Lett HS, Babyak MA, et al. Depression as a risk factor for mortality after coronary artery bypass surgery. Lancet 2003; 362:604–9.	This study analyzes patients undergoing elective CABG before surgery. Hazard ratios were only available for mixed subgroups of initially depressed patients and/or depressed patients at 6-month followup.
Burg MM, Benedetto C, Soufer R. Depressive symptoms and mortality two years after coronary artery bypass graft surgery (CABG) in men. Psychosom Med 2003; 65:508–10.	This study analyzes patients undergoing elective CABG and assessed depressive symptoms before this procedure.
Carinci F, Nicolucci A, Ciampi A, et al. Role of interactions between psychological and clinical factors determinating 6-month mortality among patients with acute myocardial infarction. Eur Heart J 1997; 18:835–45.	In this study, multiple criteria of depression, vital exhaustion, and anxiety are used as predictors.
Dankner R, Goldbourt U, Boyko V, et al. Predictors of cardiac and noncardiac mortality among 14,697 patients with coronary heart disease. Am J Cardiol 2003; 91:121–7.	This study does not analyze psychologic predictors (depressive symptoms or depression), but rather clinical–organic and biochemical factors, eg, heart rate, previous infarctions, diabetes mellitus, and so on.
Denollet J, Brutsaert DL. Reducing emotional distress improves prognosis in coronary heart disease: 9-year mortality in a clinical trial of rehabilitation. Circulation 2001; 104:2018–23.	This study evaluates the effects of rehabilitation interventions. Only improvement and worsening of depressive symptoms was reported.
Denollet J. Type D personality: a potential risk factor refined. J Psychosom Res 2000; 49:255–66.	Several factors are analyzed, but the factor "negative affectivity" is not related explicitly to depressive symptoms. Data on the calculation of OR is also missing.
Frasure-Smith N, Lespérance F, Gravel G, et al. Depression and health-care costs during the first year following myocardial infarction. J Psychosom Res 2000; 48:471–8.	Outcome parameters are healthcare costs, which the study relates to the patients' BDI scores. The sample data was integrated into the meta-analysis of other publications of this research group.
Glassman AH, O'Connor CM, Califf RM, et al. Sertraline treatment of major depression in patients with acute MI or unstable angina. JAMA 2002; 288:701–9.	Only patients with major depression are included in this study. Therefore, no comparison with nondepressed patients is possible.
Gonzalez MB, Snyderman TB, Colket JT, et al. Depression in patients with coronary artery disease. Depression 1996; 4:57–62.	The authors only report mean values and standard deviation of the depression scores, and thus no cell frequencies for a fourfold table could be gathered from the article, nor could OR be calculated.
Herlitz J, Brandrup-Wognsen G, Haglid M, et al. Predictors of death during 5 years after coronary artery bypass grafting. Int J Cardiol 1998; 64:15–23.	Does not analyze psychologic predictors, but rather only medical–biologic parameters.
Hippisley-Cox J, Fielding K, Pringle M. Depression as a risk factor for ischaemic heart disease in men: population based case–control study. BMJ 1998; 316:1714–9.	Case–control study.
Horsten M, Mittleman MA, Wamala SP, et al. Depressive symptoms and lack of social integration in relation to prognosis of CHD in middle-aged women. Eur Heart J 2000; 21:1072–80.	The authors measure depressive symptoms with an assessment scale with quite low correlation to a BDI (.71). In the results section, the sample was divided into quartiles. Inclusion of this data in the meta-analysis would be arbitrary because the study includes no information about clinical relevance.
Jiang W, Alexander J, Christopher E, et al. Relationship of depression to increased risk of mortality and rehospitalization in patients with congestive heart failure. Arch Intern Med 2001; 161:1849–56.	Patients with congestive heart failure.
Kop WJ, Appels PW, Mendes de Leon CF, et al. Vital exhaustion predicts new cardiac events after successful coronary angioplasty. Psychosom Med 1994; 56:281–87.	Study assessed only vital exhaustion as predictor.
Kulik JA, Mahler HIM. Emotional support as a moderator of adjustment and compliance after coronary artery bypass surgery: a longitudinal study. J Behav Med 1992; 16:45–63.	Calculation of OR impossible because cell frequencies for a two-by-two table could not be ascertained from the text.

Table of Excluded Studies (Continued)

Citation	Reasons for Exclusion
Löwel H, Lewis M, Härtel U, et al. Herzinfarkt-Patienten ein Jahr nach dem Ereignis. Münchner medizinische Wochenzeitschrift 1994; 136:29–38.	This study evaluates the effectiveness of postacute inpatient rehabilitation measures with regard to smoking, return to work, and so on.
Macleod J, Smith GD, Heslop P, et al. Psychological stress and cardiovascular disease: empirical demonstration of bias in a prospective observational study of Scottish men. BMJ 2002; 324:1247–53.	The authors of this study do not analyze depression or depressive symptoms as predictors; instead, they examine patients' mental states with the aid of the four statements of the "Reeder Stress Inventory."
McKhann GM, Borowicz LM, Goldborough MA, et al. Depression and cognitive decline after coronary artery bypass grafting. Lancet 1997; 349: 1282–4.	The outcome parameter of this study is cognitive decline in patients with depressive disorders, not cardiac morbidity or mortality.
Milani RV, Lavie CJ. Prevalence and effects of cardiac rehabilitation on depression in elderly with coronary heart disease. Am J Cardiol 1998; 81: 1233–6.	Morbidity or mortality are no outcome parameters in this study.
Murberg TA, Bru E, Svebak S, et al. Depressed mood and subjective health symptoms as predictors of mortality in patients with congestive heart failure: a two-year follow-up study. Int J Psychiatry Med 1999; 29:311–26.	Patients with congestive heart failure were studied.
Ruberman W, Weinblatt E, Goldberg JD, et al. Psychosocial influences on mortality after myocardial infarction. N Engl J Med 1984; 311:552–9.	The confidence interval for the calculation of HR is not specified. An OR could not be calculated from the data.
Sheps DS, McMahon RP, Becker L, et al. Mental stress-induced ischemia and all-cause mortality in patients with coronary artery disease. Circulation 2002; 105:1780–4.	The authors report associations between depressive symptom scores and mortality without specifying cutoff scores.
Silverstone PH. Depression and outcome in acute myocardial infarction. Med J Clin Res 1987; 294:219–20.	Length of followup is unclear.
Söderman E, Lisspers J, Sundin Ö. Depression as a predictor of return to work in patients with coronary artery disease. Soc Sci Med 2003: 56:193–202.	The outcome criterion is "return to work" and not cardiac morbidity or mortality.
Sullivan M, LaCroix A, Russo J, et al. Depression in coronary heart disease: what is the appropriate diagnostic threshold? Psychosomatics 1999; 40:286–92.	The strength of effect estimates reported in this study are correlations and not OR, making it impossible to calculate OR from raw data.
Sullivan MD, LaCroix AZ, Russo JE, et al. Depression and self-reported physical health in patients with coronary disease: mediating and moderating factors. Psychosom Med 2001; 63:248–56.	
Sullivan MD, LaCroix AZ, Spertus JA, et al. Five-year prospective study of the effects of anxiety and depression in patients with coronary artery disease. Am J Cardiol 2000; 86:1135–8.	
Takeshita J, Masaki K, Ahmed I, et al. Are depression symptoms a risk factor for mortality in elderly Japanese American men? The Honolulu-Asia aging study. Am J Psychiatry 2002; 159:1127–32.	Outcome (mortality) is only stated for several physical disorders together and was not specified for cardiac disorders only.
Thomas SA, Friedmann E, Wimbush F, et al. Psychosocial factors and survival in the cardiac arrhythmia suppression trial (CAST): a reexamination. Am J Crit Care 1997; 6:116–26.	The study only contains mean values and standard deviation; OR cannot be calculated from the raw data.
Silverstone PH. Depression and outcome in acute myocardial infarction. Med J Clin Res 1987; 294:219–20.	Length of followup is unclear (only <6 months is reported).

#8 (S5 or S6 or S7 or S8) (97,783 records)
#9 TI mortality or AB mortality or MJ mortality (7053 records)
#10 (S8 and S9) (81 records)
→ 81 hits in PsycInfo

Search History in* PSYNDEXplus–Lit.& AV *(1980–2003)
#1 coronary heart disease (99 records)
#2 myocardial infarction (249 records)
#3 angina pectoris (41 records)
#4, #1, or #2 or #3 (368 records)
#5 affective disorder (159 records)
#6 depression (7031 records)
#7 depressive mood (112 records)
#8 depressive symptoms (291 records)
#9, #5, or #6, or #7, or #8 (7171 records)
#10 mortality (461 records)
#11, #4, and #9 (43 records)
#12, #10, and #11 (2 records) → 2 hits in PSYNDEX

ACKNOWLEGDMENTS

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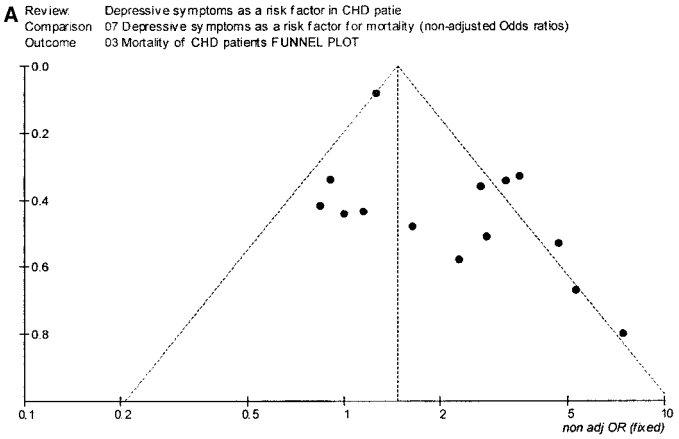
CONFLICT OF INTEREST

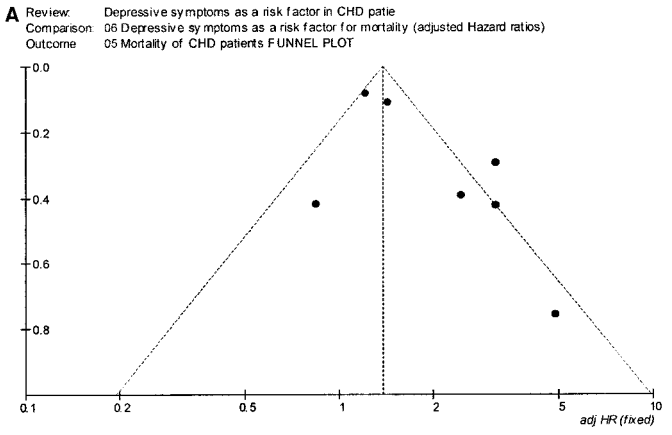
J.B. is a principal investigator in an intervention study on depressed CHD patients. C.H.L. did epidemiologic research on the topic of this review. One study was included in the meta-analysis.



x-axis: Odds ratio

y-axis: standard error of the Odds ratio

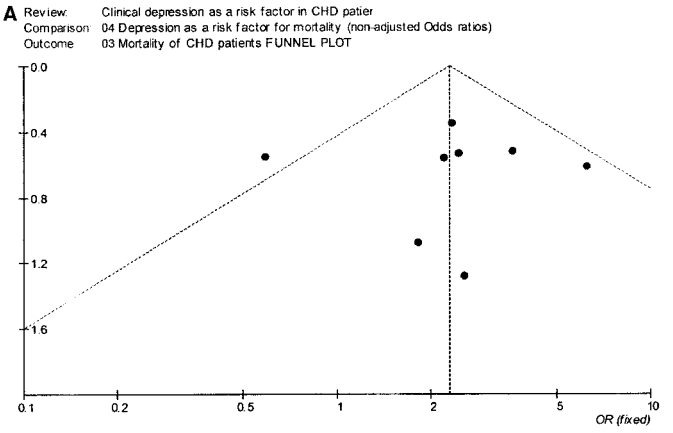
Figure 1a. Funnel plot of trials studying depressive symptoms as a risk factor for mortality (univariate risk estimates using odds ratios) with lines of 95% confidence interval.



x-axis: adjusted Hazard ratio

y-axis: standard error of the adjusted Hazard ratio

Figure 2a. Funnel plot of trials using depressive symptoms as a risk factor for mortality (adjusted risk estimates using hazard ratios) with lines of 95% confidence interval.



x-axis: Odds ratio

y-axis: standard error of the Odds ratio

Figure 3a. Funnel plot of trials using clinical depression as risk factor for mortality (univariate risk estimates using odds ratios) with lines of 95% confidence interval.

REFERENCES

1. Sans S, Kesteloot H, Kromhout D. The burden of cardiovascular diseases mortality in Europe: Task force of the European Society of Cardiology on cardiovascular mortality and morbidity statistics in Europe. Eur Heart J 1997;18:1231–48.
2. Watson R. Heart disease rising in central and eastern Europe. BMJ 2000;320:467.
3. National Heart Lung and Blood Institute. NHLBI Morbidity and Mortality Chartbook; 2002.
4. Vaccarino V, Krumholz HM, Yarzebski J, Gore JM, Goldberg RJ. Sex differences in 2 year mortality after hospital discharge for myocardial infarction. Ann Intern Med 2001;134:239–41.
5. Rugulies R. Depression as a predictor for coronary heart disease: a review and meta-analysis. Am J Prev Med 2002;23:51–61.
6. Wulsin LR, Singal BM. Do depressive symptoms increase the risk for the onset of coronary disease? A systematic quantitative review. Psychosom Med 2003;65:201–10.
7. 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.
8. Katon W, Chiechanowski P. Impact of major depression on chronic medical illness. Psychosom Med 2002;53:859–63.
9. Musselman DL, Evans DL, Nemeroff CB. The relationship of depression to cardiovascular disease. Arch Gen Psychiatry 1998;55:580–92.
10. Appels A, Bär FW, Bär J, Bruggeman C, De Beats M. Inflammation, depressive symptomatology, and coronary artery disease. Psychosom Med 2000;62:601–5.
11. Kiecolt-Glaser JK, Glaser R. Depression and immune function: central pathways to morbidity and mortality. J Psychosom Res 2002;53:873–6.
12. Danesh J, Whincup P, Walker M, Lennon L, Thomson A, Appleby P, Gallimore JR, Pepys MB. Low grade inflammation and coronary heart disease: prospective study and update meta-analyses. BMJ 2000;321:199–203.
13. Nemeroff CB, Musselman DL. Are platelets the link between depression and ischemic heart disease? Am Heart J 2000;140:57–62.
14. Laghrissi-Thode F, Wagner WR, Pollock BG, Johnson PC, Finkel MS. Elevated platelet factor 4 and β-thromboglobin plasma levels in depressed patients with ischemic heart disease. Biol Psychiatry 1997;42:290–5.
15. O'Connor CM, Gurbel PA, Serebrunany VL. Depression and ischemic heart disease. Am Heart J 2000;140:63–9.
16. Rozanski A, Blumenthal JA, Kaplan J. Impact of psychological factors on the pathogenesis of cardiovascular disease and implications for therapy. Circulation 1999;99:2192–217.
17. DiMatteo MR, Lepper HS, Croghan TW. Depression is a risk factor for noncompliance with medical treatment. Meta-analysis of the effects of anxiety and depression on patient adherence. Arch Intern Med 2000;160:2101–7.
18. 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 myocardial infarction. Arch Intern Med 2000;160:1818–23.
19. Kaplan GA, Keil JE. Socioeconomic factors and cardiovascular disease: a review of the literature. Circulation 1993;88:1973–98.
20. Tennant C. Life stress, social support and coronary heart disease. Aust N Z J Psychiatry 1999;33:636–41.
21. Segrin C. Social skills deficits associated with depression. Clin Psychol Rev 2000;20:379–403.
22. Hemmingway H, Marmot M. Psychosocial factors in aetiology and prognosis of coronary heart disease: systematic review of prospective cohort studies. BMJ 1999;318:1460–7.
23. Krishnan KR, George LK, Pieper CF, Jiang W, Arias R, Look A, O'Connor C. Depression and social support in elderly patients with cardiac disease. Am Heart J 1998;136:491–5.
24. Smith TW, Ruiz JM. Psychosocial influences on the development and course of coronary heart disease: current status and implications for research and practice. J Consult Clin Psychol 2002;70:548–68.
25. Stewart RAH, North FM, West TM, Sharples KJ, Simes R, Colquhoun

DM, White HD, Tonkin AM. Depression and cardiovascular morbidity and mortality: cause or consequence? Eur Heart J 2003;24:2027–37.
26. Fielding R. Depression and acute myocardial infarction: A review and reinterpretation. Soc Sci Med 1991;32:1017–27.
27. Lespérance F, Frasure-Smith N. Depression in patients with cardiac disease: a practical review. J Psychosom Res 2000;48:379–91.
28. Januzzi JL, Stern TA, Pasternak RC, De Sanctis RW. The influence of anxiety and depression on outcomes of patients with coronary artery disease. Arch Intern Med 2000;160:1913–21.
29. Barrick C, Barrett TU. Sad, glad, or mad hearts? Epidemiological evidence for a causal relationship between mood disorders and coronary artery disease. J Affect Disord 1999;53:183–201.
30. Sirois BC, Burg M. Negative emotion and coronary heart disease: a review. Behav Modif 2003;27:83–102.
31. Blumenthal JA, Lett HS, Babyak MA, White W, Smith PK, Mark DB, Jones R, Mathew JP, Newman MF. Depression as a risk factor for mortality after coronary artery bypass surgery. Lancet 2003;362:604–9.
32. Burg MM, Benedetto C, Soufer R. Depressive symptoms and mortality two years after coronary artery bypass graft surgery (CABG) in men. Psychosom Med 2003;65:508–10.
33. Aromaa A, Raitasalo R, Reunanen A, Impivaara O, Heliövaara M, Knekt P. Depression and cardiovascular disease. Acta Psychiatr Scand 1994; 377:77–82.
34. Herrmann-Lingen C, Buss U. Angst und Depressivität im Verlauf der koronaren Herzkrankheit. Frankfurt (Main): VAS—Verlag für Akademische Schriften; 2002.
35. Lipsey MW, Wilson DB. Practical Meta-analysis. Thousand Oaks, CA: Sage Publications; 2001.
36. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60.
37. Barefoot JC, Helms MJ, Mark DB, Blumenthal JA, Califf RM, Haney TL, O'Connor CM, Siegler IC, Williams RB. Depression and long term mortality risk in patients with coronary artery disease. Am J Cardiol 1996;78:613–7.
38. Barefoot JC, Brummet BH, Helms MJ, Mark DB, Siegler IC, Williams RB. Depressive symptoms and survival of patients with coronary artery disease. Psychosom Med 2000;62:790–5.
39. Borowicz L, Royall R, Grega M, Selnes O, Lyketsos C, McKhann G. Depression and cardiac morbidity 5 years after coronary artery bypass surgery. Psychosomatics 2002;43:464–71.
40. Bush DE, Ziegelstein RC, Tayback M, Richter D, Stevens S, Zahalsky H. Even minimal symptoms of depression increase mortality risk after acute myocardial infarction. Am J Cardiol 2001;88:337–41.
41. Carney RM, Rich MW, Freedland KE, Saini J, Tevelde A, Clark CS. Major depressive disorder predicts cardiac events in patients with coronary artery disease. Psychosom Med 1988;50:627–33.
42. Carney RM, Blumenthal JA, Catellier D, Freedland KE, Berkman LF, Watkins L, Czajkowski SM, Hayano J, Jaffe AS. Depression as a risk factor for mortality after acute myocardial infarction. Am J Cardiol 2003;92:1277–81.
43. Connerney I, Shapiro PA, McLaughlin JS, Bagiella E, Sloan RP. Relations between depression after coronary artery bypass surgery and 12-month outcome: a prospective study. Lancet 2001;358:1766–71.
44. Denollet J, Sys SU, Stroobant N, Rombouts H, Gillebert TC, Brutsaert DL. Personality as independent predictor of longterm mortality in patients with coronary heart disease. Lancet 1996;347:417–21.
45. Denollet J, Brutsaert DL. Personality, disease severity, and risk of long-term cardiac events in patients with decreased ejection fraction after myocardial infarction. Circulation 1998;97:167–73.
46. Denollet J, Vaes J, Brutsaert DL. Inadequate response to treatment in coronary heart disease. Circulation 2000;102:630–5.
47. Frasure-Smith N, Lespérance F, Talajic M. Depression following myocardial infarction: impact on 6-month survival. JAMA 1993;270:1819–25.
48. Frasure-Smith N, Lespérance F, Talajic M. Depression and 18-month prognosis after myocardial infarction. Circulation 1995;91:999–1005.
49. Frasure-Smith N, Lespérance F, Talajic M. The impact of negative emotions on prognosis following myocardial infarction: is it more than depression? Health Psychol 1995;14:388–98.
50. Lespérance FNF-S, Talajic M. Major depression before and after myocardial infarction: its nature and consequences. Psychosom Med 1996;58:99–110.
51. Frasure-Smith N, Lespérance F, Juneau M, Talajic M, Bourassa MG. Gender depression and one-year prognosis after myocardial infarction. Psychosom Med 1999;61:26–37.
52. Lespérance F, Frasure-Smith N, Talajic M, Bourassa MG. Five-year risk of cardiac mortality in relation to initial severity and one-year changes in depression symptoms after myocardial infarction. Circulation 2002;105:1049–53.
53. Frasure-Smith N, Lespérance F, Gravel G, Masson A, Juneau M, Talajic M, Bourassa MG. Social support, depression, and mortality during the first year after myocardial infarction. Circulation 2000;101:1919–24.
54. Herrmann C, Brand-Driehorst S, Kaminsky B, Leibing E, Staats H, Rüger U. Diagnostic groups and depressed mood as predictors of 22-month mortality in medical inpatients. Psychosom Med 1998;60:570–7.
55. Herrmann C, Brand-Driehorst S, Buss U, Rüger U. Effects of anxiety and depression on 5-year mortality in 5057 patients referred for exercise testing. J Psychosom Res 2000;48:455–62.
56. Irvine J, Basinski A, Baker B, Jandciu S, Paquette M, Cairns J. Depression and risk of sudden cardiac death after acute myocardial infarction: Testing for the confounding effects of fatigue. Psychosom Med 1999;61:729–37.
57. Jenkinson CM, Madelay RJ, Mitchell JRA, Turner ID. The influence of psychosocial factors on survival after myocardial infarction. Public Health 1993;7:305–17.
58. Kaufmann MW, Fitzgibbons JP, Sussman EJ, Reed JF, Einfalt JM, Rodgers JK. Relation between myocardial infarction, depression, hostility, and death. Am Heart J 1999;138:549–54.
59. Ladwig KH, Kieser M, Knig J, Breithardt G, Borggrefe M. Affective disorders and survival after acute myocardial infarction. Eur Heart J 1991;12:959–64.
60. Ladwig KH, Roll G, Breithardt G, et al. Post-infarction depression and incomplete recovery 6 months after acute myocardial infarction. Lancet 1994;343:20–3.
61. Lane D, Carroll D, Ring C, Beevers DG, Lip YH. Mortality and quality of life 12 months after myocardial infarction: effects of depression and anxiety. Psychosom Med 2001;63:221–30.
62. Lane D, Carroll D, Ring C, Beevers DG, Lip YH. In-hospital symptoms of depression do not predict mortality 3 years after myocardial infarction. Int J Epidemiol 2002;31:1179–82.
63. Mayou RA, Gill DM, Thompson DR, Hicks N, Volmink J, Neil A. Depression and anxiety as predictors of outcome after myocardial infarction. Psychosom Med 2000;62:212–9.
64. Romanelli J, Fauerbach JA, Bush DE, Ziegelstein RC. The significance of depression in older patients after myocardial infarction. J Am Geriatr Soc 2002;50:817–22.
65. Schleifer SJ, Macari-Hinson MM, Coyle DA, Slater WR, Kahn M, Gorlin R, Zucker HD. The nature and course of depression following myocardial infarction. Arch Intern Med 1989;140:1785–9.
66. Welin C, Lappas G, Wilhelmsen L. Independent importance of psychosocial factors for prognosis after myocardial infarction. J Intern Med 2000;247.
67. Wunsch A, Rundel M, Härter M, Bengel J. Screening psychischer Störungen in der kardiologischen und orthopädischen Rehabilitation. Rehabilitation (Stuttg) 2002;41:375–81.
68. Jüni P, Altman G, Egger M. Assessing the quality of controlled clinical trials. BMJ 2001;323:42–6.
69. Jüni P, Witschi A, Bloch R, Egger M. The hazards of scoring the quality of clinical trials for meta-analysis. JAMA 1999;282:1054–600.
70. Schmitz N, Kruse J, Kugler J. Disabilities, quality of life, and mental disorders associated with smoking and nicotine dependence. Am J Psychiatry 2003;160:1670–6.
71. ENRICHD Investigators. Effects of treating depression and low perceived social support on clinical events after myocardial infarction: the enhancing. JAMA 2003;289:3106–16.
72. Glassman AH, O'Connor CM, Califf RM, Swedberg K, Schwartz P, Bigger JT. Sertraline treatment of major depression in patients with acute MI or unstable angina. JAMA 2002;288:701–9.