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Systematic review and individual patient data meta-analysis of sex differences in depression and prognosis in persons with myocardial infarction: a MINDMAPS study

Running head: Sex differences in depression post-MI

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Abstract

Objective—Using combined individual patient data (IPD) from prospective studies, we explored sex differences in depression and prognosis post-myocardial infarction (MI), and determined whether disease indices could account for found differences.

Methods—Meta-analysis of IPD from 10,175 MI patients who completed diagnostic interviews or depression questionnaires from 16 prospective studies of MI patients, identified by systematic review for the MINDMAPS study. Multilevel logistic and Cox regression models were used to determine sex differences in prevalence of depression and sex-specific effects of depression on **subsequent cardiovascular morbidity and all-cause mortality**.

Results—Combined interview and questionnaire data from observational studies showed that 36% (635/1760) of women and 29% (1575/5526) of men reported elevated levels of depression (age-adjusted OR=0.68, 95% CI 0.60 to 0.77, $p<0.001$). The risk for all-cause mortality associated with depression was higher in men (HR=1.38, 95% CI 1.30 to 1.47, $p<0.001$) than in women (HR=1.22, 95% CI 1.14 to 1.31, $p<0.001$) (**sex*depression interaction $p<0.001$**). Low left ventricular ejection fraction (LVEF) was associated with higher depression scores in men only (sex*LVEF interaction B=0.294, 95% CI 0.090 to 0.498, $p=0.005$), which attenuated the sex difference in the association between depression and prognosis.

Conclusions— The prevalence of depression post-MI was higher in women than men, but the association between depression and cardiac prognosis was worse for men. LVEF was associated with depression in men only, and accounted for the increased risk of all-cause

mortality in depressed men versus women, suggesting that depression in men post-MI may in part reflect cardiovascular disease severity.

Keywords: Depression; myocardial infarction; gender; prognosis; individual data meta-analysis

Acronyms

ACE = angiotensin converting enzyme

BMI – body mass index

CABG = coronary artery bypass graft

CI = confidence interval

CVE – cardiovascular events

HF = heart failure

HR = Hazard ratio

IPD = Individual patient data

LVEF = Left ventricular ejection fraction

MI = myocardial infarction

OR = odds ratio

PTCA = percutaneous transluminal coronary intervention

SD = standard deviation

Introduction

Depression in people with myocardial infarction (MI) has been the source of considerable study. While both clinically diagnosed depression and questionnaire-assessed depressive symptoms have been consistently associated with poorer cardiovascular prognosis in MI patients (1), the treatment of depression has not been demonstrated to reduce morbidity or mortality in randomized trials (2, 3). Recent estimates suggest a prevalence of diagnosed major depressive disorder in the US of 2.1% to 4.9% in adults aged 45 and over (4), with women having a higher prevalence (4.8%) than men (3.3%). Similarly, in adults aged 45 years and above, estimates of elevated depressive symptoms are also more prevalent among women (7-12%) than men (5-7%) (5). Similar findings are available for European countries (6, 7), although the differing methodologies adopted by different countries make overall estimates for major depression more difficult. According to a systematic review of the literature, the prevalence of depression is significantly higher in patients with MI, with 20% having major depression and up to 31% reporting elevated depressive symptoms, although sex differences were not reported (8).

The etiology of depression post-MI has been the subject of considerable debate. While depressive symptoms and trajectories of these symptoms post-MI appear to have similar risk factors to depression in the general population (e.g. stressful life events, personality etc.) (9-13), sex is not always a predictor of depression in these studies. This suggests that there may be a potentially different etiology for depressive symptoms in men and women with MI. Indeed, other researchers have demonstrated that elevated levels of depression, and its subsequent association with cardiovascular prognosis, may be a consequence of

cardiovascular disease severity (14, 15). For example, poor left ventricular ejection fraction (LVEF) has been demonstrated to not only correlate with depression, but also to predict the onset of major depression and depressive symptoms in patients with MI (14). In addition, this study found that poorer LVEF was a stronger predictor of onset of major depression for men than for women (14), again suggesting potentially different etiology for depression between men and women post-MI.

We aimed to establish whether the prevalence of diagnosed depression and elevated depressive symptomatology is similar in men and women with MI, and whether the diagnosed depression or depressive symptoms had a greater impact on prognosis for men than for women. We also investigated the role of LVEF in the etiology of depression and prognosis according to patients' sex. These questions have not been subject to systematic investigation and previous studies were not large enough to detect potential moderating effects. We therefore used data from the MINDMAPS individual patient meta-analytic database of 16 studies (16) to determine the following:

- 1 – whether cardiovascular disease severity indices account for differences in post-MI prevalence of depressive symptoms between men and women; and
- 2 – whether the association between depression and prognosis is stronger in men than in women, and whether disease severity indices (e.g. LVEF) account for these differences.

Methods

MINDMAPS

Details of MINDMAPS are available elsewhere (16). In brief, eligibility for inclusion in the MINDMAPS dataset was determined by a systematic review of published studies on post-MI depression **initiated on 5th January 2011** (within 3 months post-hospitalisation for MI, assessed by validated questionnaire or diagnostic interview) and two prognostic endpoints (all-cause mortality, or major cardiovascular events – CVE: recurrent MI, unstable angina, CABG) (1). Authors of all selected studies were contacted and original data was requested (covering demographics, depression, disease severity [*LVEF*<40%, *Killip class (I vs. II, III, IV), and history of MI*], comorbidities, diabetes, smoking, body mass index [BMI], medication use, and outcomes). Of 30 eligible studies, 16 provided data (16).

Statistical analysis

Stata 11 was used for the main analyses (Statacorp LP, TX, USA). Multilevel logistic regression, adjusting for age, was used to obtain odds ratios (ORs) for differences in depression status between men (1) and women (0), using a binary depression variable (based on interview or recommended scale thresholds). Hazard ratios (HRs) were calculated using multilevel Cox proportional hazards regression analysis, to predict time-to-event (all-cause mortality or CVE), using depression, sex, and the interaction between sex and depression as predictors, adjusting for age. A continuous depression variable was used in these Cox analyses (z-transformed total scale scores). As different studies used different methods and are likely to represent populations with different characteristics (such as date of study, differences in therapies and assessments used, etc.), observations within studies are unlikely to be fully independent. Therefore, a random intercept for

study was included, resulting in a multilevel model. When calculating the prevalence estimates we omitted data from the ENRICHD randomized trial and ancillary studies (2, 17) (which were combined in the original study (16)), as these were enrolled under strict inclusion criteria whereas observational studies would be more inclusive. To demonstrate the random effect variance in respect to the depression prevalence, we displayed the intraclass correlation coefficient, which shows what part of the total variance in prevalence is between studies. To investigate whether cardiovascular disease indices and other risk factors accounted for any sex differences in depression, a linear mixed model with random intercept was used, with depression z-scores as the dependent variable, and sex, disease indices and their interaction as predictors, adjusting for age. For each disease index a separate model was built. A contrast coding of -0.5/0.5 for dichotomous variables was used in the Cox regression analyses to ensure between-study variances between groups were equal (e.g. female vs. male) (18). Separate models were built for each disease and risk factor index. Also, two more multivariate models were built – including all disease and risk factors, but omitting LVEF, together as covariates, and then a final model including all disease and risk factors. To increase confidence interval robustness, and in view of the non-normal distribution of the depression z-scores, bootstrapping with 1000 replications was used in all analyses (19). The handling of the variables used for adjustment and the applied outcomes was identical to that in the main MINDMAPS study (16). All tests were two-tailed.

Results

Sample description

Of 30 eligible studies (16), 16 provided individual patient data (**see supplementary Table S1 for an overview of participating studies**). These studies were from 9 different countries. The description of the combined sample (N=10,175), stratified by sex, is displayed in Table 1:

Insert Table 1 here

Overall, the mean age was 61 years (range 20-97), 71% of participants were men, and mean follow-up time per study was 3.15 years (range 0.96 – 6.65).

Prevalence of depression

Data from four diagnostic interview studies (omitting the ENRICHD data, n=900) showed that 20% (47/240) of women and 12% (76/660) of men had major depression. The age-adjusted multilevel logistic regression showed this to be a significant difference (OR=0.42, 95% CI 0.27 to 0.65, p=0.001). There was little heterogeneity between these interview studies in depression prevalence: the intraclass correlation coefficient was 0.01 (Chi² = 1.4; **p=0.12**).

When using the data from the questionnaire studies, excluding data from the ENRICHD and ancillary studies (fourteen studies; n=7202), the sex differences in prevalence remained significant (age-adjusted OR=0.69, 95% CI 0.61 to 0.77, p<0.001), with a

higher percentage of women scoring above recommended thresholds for “clinically significant” depressive symptoms (38%, 657/1741) than men (30%, 1622/5461). There was some heterogeneity between these questionnaire studies in depression prevalence: the intraclass correlation coefficient was 0.10 ($\text{Chi}^2(1) = 436.3$; $\mathbf{p < 0.001}$). **This implies that 10% of the total variance in depression prevalence is due to differences between studies.**

Combining the interview and questionnaire studies, but omitting the ENRICHHD data (fifteen studies; $n=7286$), resulted in 36% (635/1760) of women and 29% (1575/5526) of men reporting elevated depressive symptoms (age-adjusted $\text{OR}=0.68$, 95% CI 0.60 to 0.77, $\mathbf{p < 0.001}$). The intraclass correlation coefficient was 0.14 ($\text{Chi}^2(1) = 547.7$; $\mathbf{p < 0.001}$), indicating significant, though not large, heterogeneity between studies in depression prevalence.

We also checked whether the sex difference in depression prevalence varied with age. We did so by including an interaction term $\text{sex} * \text{age}$ in the above analysis. The interaction was not significant ($\text{OR}=1.00$, 95% CI 0.99 to 1.01, $\mathbf{p} = 0.91$). So, the sex difference in depression prevalence did not vary with age. **The main effect of age on the prevalence of depression, adjusted for sex, was small and not significant ($\text{OR}=0.99$, 95% CI = 0.99 to 1.00, $\mathbf{p} = 0.069$).**

Disease severity

Various disease indices and risk factors were analysed to determine if these accounted for sex differences in depression scores. Interactions between sex and history of MI, Killip class, diabetes, smoking or BMI were not associated with depression z-scores (**Supplementary Table S2**). However, an interaction between sex and left ventricular ejection fraction was observed (see the upper panel of Table 2):

Insert Table 2 here

This interaction remained significant when adjusting for all other disease factors and risk indices (see the lower panel of Table 2). The results suggest that for men only, low LVEF was associated with higher levels of depression.

Moderation effects of sex in the association between depression and prognosis

Survival curves for all-cause mortality and depression status, and cardiovascular events and depression status are shown in Fig 1:

Insert Fig 1 about here

The survival curves show that depression was related to poorer prognosis, in both men and women, and that the effect is more important in men. This is further investigated in Table 3:

Insert Table 3 here

The Cox regression analyses for all-cause mortality showed that the interaction between sex and depression was statistically significant (HR for interaction=1.12; 95% CI: 1.05 to 1.19, **p<0.001**), suggesting that the association between depression and mortality was indeed stronger for men than for women. The HR associated with depression was 12% higher in men compared to women (men, HR=1.38, 95% CI 1.30 to 1.47, p<0.001; women, HR=1.22, 95% CI 1.14 to 1.31, p<0.001). Omitting data from the ENRICHHD studies had little effect on the interaction term (HR for interaction=1.10, 95% CI 1.02 to 1.19, p=0.014). The interaction effect for CVE pointed into the same direction, but did not reach significance.

We also checked whether the sex difference in the impact of depression on cardiovascular outcomes varied with age. We did so by including an interaction term sex*age*depression in the above analyses. The interaction was not significant (all-cause mortality HR =1.00. 95% CI 0.99 to 1.01, p = 0.92; CVE: HR =1.00. 95% CI 0.99 to 1.00, p = 0.59; **Supplementary Table S2**). So, the sex difference in the impact of

depression on cardiovascular outcomes did not vary with age. **The sex*depression interaction now did reach significance also in the CVE model (p = 0.038).**

Because sex differences between depression and cardiac prognosis may be dependent on post-menopausal status (20, 21), we did a sensitivity analysis repeating the analysis of Table 3 but now separately for individuals aged younger and older than 55 years. This did not yield different results. The sex*depression interaction in the prediction of all-cause mortality was significant in both age groups (age<=55, HR=1.20, 95% CI 1.01 to 1.43, p=0.038; age>55, HR=1.11, 95% CI 1.03 to 1.20, p=0.005). The HR for the sex*depression interaction in the prediction of CVE pointed in the same direction but was non-significant in both age groups (age<=55, HR=1.15, 95% CI 0.94 to 1.41, p=0.18; age>55, HR=1.05, 95% CI 0.90 to 1.23, p=0.51).

Finally, we determined if the moderating effect of sex in the association between depression and all-cause mortality could be explained by the cardiovascular disease indices or risk factors. The same multilevel Cox regression analyses were used, predicting all-cause mortality by age, depression, sex, and sex*depression. Then, the size of the change in the estimate for the interaction sex*depression was determined when each of the disease variables was included in these separate models, and in two multivariate models. Results are shown in Table 4:

Insert Table 4 here

In the separate models, LVEF accounted for the largest reduction in the size of the sex*depression interaction, and inclusion of this variable resulted in a non-significant interaction. History of MI also accounted for a substantial reduction in the interaction, but most other factors *increased* instead of reduced the size of the interaction. These differences could be the result of differences between studies or sample sizes, therefore, the analyses were repeated with only those participants who had data on all six cardiovascular disease variables and risk indices (History of MI, LVEF, and Killip class, diabetes, smoking, BMI). The last rows of Table 4 show the results of the multivariate models. While adjusting for all covariates except LVEF (5172 participants in 5 studies) resulted in an 8% increase in the sex*depression interaction, inclusion of all six covariates (2226 participants in 3 studies) resulted in a 32.5% reduction of the sex*depression interaction effect, and resulted in a non-significant interaction. Together, these results suggest that the moderating effect of sex on the association between depression and all-cause mortality can partially be explained by differences in LVEF and history of MI among depressed men and women, and that LVEF explained the largest part **of the sex*depression interaction**.

Furthermore, despite there being no statistically significant sex*depression interaction **in the cardiac disease and risk factor-adjusted models** for predicting CVE, the percentage reduction **of the interaction term** was again largest for LVEF, showing a consistency across outcomes (results not shown).

Discussion

In this largest study to date, we found a number of results that are important in interpreting the association between post-MI depression and prognosis. Firstly, low LVEF was associated with depressive symptoms, but only in men. Secondly, the association between depression and prognosis was stronger in men than in women, which could partly be explained by depressive symptoms being a reflection of low LVEF more often for men than for women. LVEF attenuated the interaction effect between depression and sex in the prediction of prognosis.

In general, the prevalence of depression by diagnostic interview and questionnaire studies are similar to that previously reported (8), with higher proportions of women having depression according to both diagnostic interview and questionnaire studies. This higher prevalence of depression in women, added to the fact that depression was associated with disease severity in men only, demonstrates how depression in this population mimics depression in the general population. Other studies have also demonstrated how psychosocial risk factors for depression are predictors not only of elevated post-MI depressive symptomatology, but also of trajectories of depression post-discharge (9-13, 22), suggesting that depressive symptoms cannot be attributed solely to coronary disease severity. However, the higher prevalence of depression reported using scale thresholds rather than interview techniques again provides evidence that psychometric scales overestimate the prevalence of depression in this population, with our findings

demonstrating 2.5- to 3-fold higher prevalence, as found previously (8). This higher prevalence by questionnaire probably represents confounding between somatic symptoms of depression and symptoms of coronary disease (14, 15, 23), which cannot easily be thoroughly investigated as may happen during a diagnostic interview. Conversely, it has been demonstrated that even low levels of depression predict cardiovascular prognosis (24), thus relying on diagnostic interviews may actually underestimate meaningful levels of depression. Furthermore, while it has previously been suggested that the higher prevalence of depression in women might lead to poorer cardiovascular prognosis (25), we have found no evidence for this. Indeed, depression was more strongly related to a worse cardiac prognosis in men than in women. Single studies may not have had the power to detect such effects.

Depression was associated with a poor LVEF in men but not in women. Poor LVEF has been associated with depression in patients with coronary disease (26, 27). Previously, van Melle et al. (14) have shown that in 1989 post-MI patients LVEF was inversely correlated with depression status (from diagnostic interviews) and depression scale scores at several time points in the year post-MI, even in those who did not demonstrate depression at baseline. Furthermore, men demonstrated a trend towards a stronger increase in rates of depression across more severe LVEF categories, which was confirmed in the present findings. The data from that sample were included in the present analyses. However, that was a single study, while the present analyses are from 16 studies. That depression was more strongly related to prognosis for men may be explained by the differential nature of MI in women and men. Women with MI tend to be

older by approximately 10 years, have more diffuse coronary disease, have non-ST-elevation MI thereby not being eligible for emergency primary percutaneous coronary intervention (21, 28) which is protective of subsequent lowering of LVEF (29-31), and therefore have worse hospital outcomes (28, 29). Men tend to have more focal lesions that result in ST-elevation MI. In the current data, women were less likely to receive percutaneous coronary intervention. As a result, women are more likely to end up with heart failure with preserved ejection fraction while men end up with heart failure with reduced ejection fraction (29-31). Thus, the differential attenuation by LVEF of the association of depression with outcomes may be partly explained by the fact that women are less likely to have the type of MI that results in a low LVEF. Further research is needed to clarify this possibility. Alternatively, the etiology of depression in post-MI patients may differ in women and men. Men may be more likely to have depression as a result of coronary disease severity, while women may more often have pre-existing depression (32). These sex differences are perhaps unlikely to be mediated by other biological (e.g. reduced cardiac autonomic tone, increased platelet aggregation, increased inflammatory processes) (33, 34) or behavioral (e.g. smoking, physical inactivity etc.) (34-36) mechanisms linking depression to MI, as no consistent links with men or women have been reported. Recent research also suggests that fetal exposure may have increased the risk of both depression and cardiovascular disease, and that this effect is stronger in women (37), although this requires further investigation. **The lack of variation in results in the sensitivity analysis was perhaps surprising given that younger women have consistently been shown to have poorer prognosis than younger men (21). This may be due to the fact that there were relatively few young women in each study included**

here, and that these studies took place over a large timeframe, perhaps making them less representative than larger registry studies, or that using age thresholds is too crude to represent actual menopausal status. It is unclear why there was not a significant moderating effect of sex in the association between depression and CVE. One reason may be that CVE is a less well-defined endpoint across the studies, and this may lead to measurement error, or that there were different numbers and types of studies and participants analysed for this outcome.

Limitations and strengths

The heterogeneity of study populations, depression, cardiovascular risk factor measurements, and endpoint assessments may be problematic, although the inclusion of the random intercept accounts for study differences. Measures of distress have been shown to demonstrate measurement invariance across sex and ethnic groups in a large cross-sectional study (38). All-cause mortality includes non-cardiac deaths, and may bias the results. The heterogeneity of cardiovascular risk factors reported in individual studies meant that full adjustment could not be made in the overall sample. Inclusion of variables such as New York Heart Association categorisation, diastolic function, blood pressure, and cholesterol were not included in the dataset, but might have changed the results. Similarly, psychiatric history was unavailable, as was alcohol abuse, and other non-cardiac co-morbidities or their treatments may also impact on the findings. Not all relevant studies were available for analysis (16), which may have biased the results, although most did not report sex differences or did not find any differences in prognosis.

Another major limitation of the present research, and indeed other studies in this area, is the lack of a plausible model that could explain the effects seen in this study. Other researchers have rightly called for more conceptual and theoretical clarity in the analysis of observational studies which investigate risk factors in disease etiology (39, 40). To establish any single variable as a true independent risk factor, confounder or mediator for a given outcome, knowledge of temporal precedence of variables is required (39, 40). This is extremely difficult in the case of cardiovascular disease and depression. In the present analyses we cannot, for example, assume that depression precedes LVEF, or vice versa, as this data simply was not available to us. We have therefore avoided the terms ‘mediate’ or ‘confound’, etc. Further research with repeated measures of important variables is required before true risk factors and mediators of sex differences in depression and prognosis post-MI are elucidated.

The major strength of the study is the use of individual patient data, which allows for time-to-event analysis, and adjustment for potentially confounding variables systematically across studies, which cannot be done in summary meta-analyses, resulting in more accurate estimates of effect sizes, increased statistical power, generalizability and reliability of results (41). The inclusion of the random intercept term allows important between-study differences to be accounted for statistically, such as changing acute treatments (percutaneous coronary intervention has superseded thrombolysis in the timeframe spanned by the present studies) (29, 30), or differential assessment of LVEF –

which may impact on its prognostic ability (42, 43). The ability to analyse both interview and questionnaire studies is a strength, and the results demonstrated consistent patterns across these methods.

Conclusions

Using IPD from a large sample, the present study revealed significant differences in the prevalence, possible etiology and consequences of depression post-MI in men versus women. The prevalence of depression post-MI was higher in women than men, but the association between depression and cardiac prognosis was worse for men. LVEF was associated with depression in men only, and accounted for the increased risk of all-cause mortality in depressed men, suggesting that depression in men post-MI may in part reflect cardiovascular disease severity. Future studies, including intervention studies, should account for these sex differences.

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Table 1: Baseline characteristics by sex

	Men (n=7200)	Women (n=2975)	p-value	N measured
Demographic characteristics				
Age (mean, (SD))	59.7 (11.5)	64.1 (12.2)	<0.001***	10,171
Employment status (% employed)	53.6	27.0	<0.001***	6,528
Partner status (% with partner)	77.5	51.4	<0.001***	6,412
Cardiac disease severity				
History of MI (% yes)	19.2	18.0	<0.001***	9,646
LVEF (% of patients <40%)	22.6	22.4	0.56	3,505
Killip class (% poor)	16.1	22.9	<0.001***	7,532
PTCA (%)	47.2	42.1	<0.001***	7,679
History of PTCA (%)	11.4	11.0	0.11	4,830
CABG (%)	9.8	9.3	<0.001***	8,139
History of CABG (%)	10.8	7.9	<0.001***	4,849
Thrombolysis (%)	33.8	34.0	0.061	8,065
Congestive HF (%)	17.2	24.3	0.013*	6,104
Other risk factors				
Diabetes (%)	18.0	29.8	<0.001***	10,060
Smoking (%)	49.5	32.8	<0.001***	9,942
BMI (mean, (SD))	26.8 (4.5)	27.8 (6.0)	0.002**	7,188
Hyperlipidemia / hypercholesterolemia (%)	45.3	50.2	<0.001***	8,405

Hypertension (%)	31.6	38.6	<0.001***	8,301
History of hypertension (%)	43.1	62.2	<0.001***	5,348
Medication use				
Hypolipidemics (%)	43.5	44.1	0.29	4,004
Beta-blockers (%)	72.3	71.2	0.003**	8,833
Aspirin (%)	87.2	87.2	0.49	7,561
Calcium-channel blockers / antagonists (%)	14.5	21.3	<0.001***	7,056
ACE-inhibitors (%)	48.7	49.8	0.26	8,550
Antidepressant use (%)	5.8	8.1	0.013*	5,507
Study type				
Diagnostic interview (n)	660	240		900
Questionnaire (n)	7108	2942		10,050

ACE: angiotensin converting-enzyme; BMI: body mass index; CABG: coronary artery bypass graft; HF: heart failure;

LVEF: left ventricular ejection fraction; MI: myocardial infarction; PTCA: percutaneous transluminal coronary angioplasty; SD: standard deviation

***p < 0.001; **p < 0.01; *p < 0.05

Table 2: Linear mixed model with random intercept for study, predicting depression z-score (n=3115, 5 studies)

	B	Bootstrapped 95% CI	p
Adjusted for age (n=3115, 5 studies)			
Age	-0.001	-0.004 – 0.002	0.57
LVEF	-0.015	-0.191 – 0.161	0.87
Sex	-0.371	-0.476 – -0.265	<0.001***
Sex*LVEF	0.294	0.090 – 0.498	0.005**
Adjusted for all confounders (n=2226, 3 studies)			
Age	-0.002	-0.008 – 0.003	0.36
History of MI	0.148	0.064 – 0.233	0.001**
Killip class	0.132	0.029 – 0.235	0.012*
Diabetes	0.145	0.059 – 0.231	0.001**
Smoking	0.057	0.024 – 0.090	0.001**
BMI	-0.011	-0.028 – 0.006	0.21
LVEF	-0.019	-0.089 – 0.052	0.61
Sex	-0.348	-0.426 – -0.269	<0.001***
Sex*LVEF	0.274	0.061 – 0.488	0.012*

***p < 0.001; **p < 0.01; *p < 0.05. Sex (0=female, 1=male)

Table 3: Multilevel Cox proportional hazards regression assessing sex differences in the association between depression and cardiovascular prognosis

	All-cause mortality (n=7628, 10 studies)			Cardiovascular events (CVE) (n=6556, 7 studies)		
	HR	Bootstrapped 95% CI	P	HR	Bootstrapped 95% CI	P
Age	1.07	1.06 – 1.08	< 0.001***	1.01	1.01 – 1.02	< 0.001***
Depression z-score	1.30	1.24 – 1.37	< 0.001***	1.17	1.13 – 1.22	< 0.001***
Sex	1.07	0.90 – 1.28	0.44	0.93	0.78 – 1.11	0.42
Sex * depression z-score	1.12	1.05 – 1.19	< 0.001***	1.07	0.98 – 1.17	0.118

***p < 0.001; **p < 0.01; *p < 0.05. Sex (-0.5=female, 0.5=male)

Table 4: Percentage change in sex*depression interaction effects in the prediction of all-cause mortality by additional disease indices or risk factors

Factor	HR for interaction sex*depression	Adjusted HR for interaction sex*depression	% change	N/n studies
History of MI	1.097***	1.088**	-8.9%	7543/10
LVEF	1.126*	1.086	-30.5%	3115/5
Killip class	1.137***	1.162***	+16.9%	5924/6
Diabetes	1.107***	1.130***	+20.2%	7587/10
Smoking	1.118**	1.119**	+0.8%	7485/10
BMI	1.128**	1.125**	-2.2%	6133/7
Adjusting for all covariates except LVEF	1.140***	1.152**	+8.0%	5172/5
Adjusting for all covariates	1.107**	1.071	-32.5%	2226/3

Adjusted for age, depression z-score, and sex, with study as a random factor

Note: The percentage change was estimated by using the log HR for the sex*depression interaction effect.

***p < 0.001; **p < 0.01; *p < 0.05

Figure Legends

Figure 1: Survival curves for all-cause mortality (ACM) and cardiovascular events (CVE), by depression category and sex (adjusted for age). depr = depression. Depression categories are based on a split-half of the continuous depression z-scores on self-report questionnaires. (Note: In all Cox regression analyses, the continuous depression z-score is used.)

Systematic review and individual patient data meta-analysis of sex differences in depression and prognosis in persons with myocardial infarction: a MINDMAPS study

Supplementary Table S1: Overview of participating studies

PI, study name, country	Start of study	N ³ / % Women (n women)	Inclusion criteria	Exclusion criteria	Mean age (SD)	Depression measurement ¹ instrument ¹ and cut-off score	N / % depressed	Mean depression score (SD)	Mean follow-up time (days)	No. of events ACM / CVE
R. Carney, J. A. Blumenthal ENRICHD and ancillary HRV study ² USA (1-3)	1996 / 1997	2848 / 42% (1196)	standardized criteria for MI; low social support or depression ancillary study: no depression or social isolation, otherwise eligible for ENRICHD	other life-threat. med. illn.; cogn. impairm.; too ill; other major psych. disord.; unable/refused to participate	61 (12.3)	BDI-1A ≥ 10	1951 / 69%	14.13 (8.87)	ACM: 834 CVE: 609	ACM: 350 CVE: 1151
J. Ormel, P. de Jonge, MIND-IT The Netherlands (4)	1999	1814 / 23% (417)	standardized criteria for MI age ≥ 18	other life-threat. med. illn.; MI during hosp. for other reason; psych. depr. treatm; part. in conflicting clin. trial	61 (11.6)	BDI 1-A ≥ 10	BDI: 474 / 26%	6.77 (6.18)	ACM: 2167 CVE: 1517	ACM: 278 CVE: 784
J. Ormel, P. de Jonge DepreMI The Netherlands (5)	1997	528 / 19% (100)	standardized criteria for MI	other life-threat. med. illn.; cogn. impairm.; too ill; unable to communicate; MI	61 (11.7)	modified Dutch version of CIDI 2.1 BDI 1A ≥ 10	CIDI: 73 / 15% BDI:	6.80 (6.12)	ACM: 2663 CVE: 1851	ACM: 116 CVE: 237

				during hosp. for other reason				117 / 23%			
J. Denollet The Netherlands (6)	2003	501 / 22% (110)	Standardized criteria for MI; Age > 30	other life-threat. med. illn.; cogn. Impairm.	60 (11.6)	BDI-1A \geq 10	132 / 26%	7.03 (6.18)	ACM: 1374 CVE: 1284	ACM: 38 CVE: 82	
F. Doyle, H. M. McGee Ireland(7)	2003	433 / 25% (108)	standardized criteria for ACS (only MI patients were included in the IPD meta-analysis)	nr	63 (12.3)	HADS-D > 7 BDI-FS > 3	HADS- D or BDI- FS: 75 / 17%	HADS-D: 4,14 (3,26) BDI-FS: 1.88 (2.69)	ACM: 356 CVE: na	ACM: 17 CVE: na	
F. Doyle, H.M. McGee Ireland(8)	2006	285 / 20% (57)	standardized criteria for ACS (only MI patients were included in the IPD meta-analysis)	patient too distressed	61 (10.9)	HADS-D > 7 BDI-FS (6- item) > 3	either HADS- D or BDI- FS: 78 / 27% HADS- D: 33 / 12%; BDI-FS 69 / 24%	HADS-D: 3,52 (3,07) BDI-FS: 2.15 (2.84)	ACM: 427 CVE: 427	ACM: 19 CVE: 67	
S. Bergerone Italy(9)	1999	98 / 22% (22)	standardized criteria for MI	in-hosp. mort.; other major psych. disord.; alcoholism; antidepr. therapy	62 (12.6)	struct. int. based on DSM-IV criteria BDI 1A \geq 10	MDD: 14 / 14% BDI: 35 / 34%	BDI: 8.34 (8.48)	ACM: 1485 CVE: 1485	ACM: 6 CVE: 29	

S.H. Hosseini	2004	540 / 31% (167)	standardized criteria for MI	other life-threat. med. illn.; MI result of CABG or angiogr.; too ill	58 (12.0)	BDI 1A \geq 10	355 / 66%	14.20 (9.80)	na (24 months)	ACM: na CVE: 55
Iran(10)										
D.A. Lane	1997	288 / 25% (72)	standardized criteria for MI	other life-threat. med. illn.; cogn. impairm.; MI result of CABG or angiogr.; unable to communicate; too ill	63 (11.5)	BDI 1A \geq 10	89 / 31%	7.72 (6.26)	ACM: 976 CVE:na	ACM: 38 CVE: na
UK(11, 12)										
L. Pilote	1996	553 / 19% (105)	acute MI; surv. up to 24 hours after hosp. adm.; adm. through emergency dept.	phys. unable to respond to quest.; unable to communicate	60 (12.2)	BDI 1 \geq 10	193 / 35%	9.07 (7.93)	ACM: 350 CVE: 205	ACM: 32 CVE: 222
Canada(13)										
K. Parakh, R.C. Ziegelstein	1995	284 / 43% (122)	standardized criteria for MI	other life-threat. med. illn.; cogn. impairm.; too ill	65 (12.1)	SCID BDI 1A \geq 10	MDD: 29 / 10% BDI: 56 / 20%	BDI: 5.76 (6.15)	ACM: 2428 CVE: na	ACM: 153 CVE: na
USA (14)										
C. Rafanelli	1995	61 / 15% (9)	standardized criteria for MI; first MI	nr	59 (9.9)	modified SCID (minor and major depression	7 / 11%	na	na (24 months)	ACM: 4 CVE: 22
Italy(15)										
H. Sato OACIS Japan(16)	1998	1042 / 20% (208)	standardized criteria for MI	in-hosp. mort.; other major psych. disord.; unable to communicate	63 (11.2)	ZSDS \geq 40	438 / 42%	38.03 (9.07)	na (12 months)	ACM: na CVE: 283
R.P. Steeds	1999	131 / 67%	MI; age < 75	nr	60	BDI-II \geq 14	52 /	12.42 (9.09)	ACM: 457	ACM: 11

UK(17)		(88)			(9.4)		40%		CVE: na	CVE: na
S.L. Grace	1997	468 / 28%	confirmed MI; age ≥ 18	too ill; unable to communicate	61 (12.2)	BDI 1A ≥ 10	136 / 28%	7.93 (7.22)	na (12 months)	ACM: 29 CVE: 101
Canada(18)		(131)								
C. Welin	1985	270 / 16%	standardized criteria for MI; first MI; age <	nr	56 (7.0)	ZSDS ≥ 40	96/ 36%	36.76 (8.58)	na (120 months)	ACM: 65 CVE: 73
Sweden(19)		(43)	65							

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

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

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

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

Note: Most data in Supplementary Table 1 has been reproduced with permission from the original MINDMAPS study published in the British Journal of Psychiatry (Meijer A, Conradi HJ, Bos EH, Anselmino M, Carney R, Denollet J, Doyle F, Freedland KE, Grace SL, Hosseini SH, Lane DA, Pilote L, Parakh K, Rafanelli C, Sato H, Steeds RP, Welin C, de Jonge P. Adjusted prognostic association of post-myocardial infarction depression with mortality and cardiovascular events: an

individual patient data meta-analysis. Br J Psychiat. 2013;203:90-102. <http://bjp.rcpsych.org/content/203/2/90.short>). The authors gratefully acknowledge this permission.

Supplementary Table S2: Interactions between sex and disease indices and other risk factors in the prediction of depression z-scores

	B	Bootstrapped 95% CI	p	N/n studies
Sex*History of MI	0.080	-0.051 – 0.212	0.23	7543/10
Sex*LVEF	0.294	0.090 – 0.498	0.005**	3115/5
Sex*Killip class	0.066	-0.210 – 0.078	0.37	5924/6
Sex*Diabetes	-0.045	-0.166 – 0.075	0.46	7587/10
Sex*Smoking	0.002	-0.101 – 0.105	0.97	7485/10
Sex*BDI	-0.008	-0.018 – 0.002	0.13	6133/7

Linear mixed models with random intercept, with z-depression scores as dependent variable, and sex, disease index/risk factor, and their interaction as predictors, adjusting for age. **p<0.01. Sex (0=female, 1=male)

Supplementary Table S3: Multilevel Cox proportional hazards regression assessing sex and age differences in the association between depression and cardiovascular prognosis

	All-cause mortality (n=7628, 10 studies)			Cardiovascular events (CVE) (n=6556, 7 studies)		
	HR	Bootstrapped 95% CI	P	HR	Bootstrapped 95% CI	P
Age	1.07	1.07 – 1.08	< 0.001***	1.01	1.01 – 1.02	< 0.001***
Depression z-score	1.32	1.21 – 1.43	< 0.001***	1.19	1.13 – 1.26	< 0.001***
Sex	0.89	0.77 – 1.04	0.44	0.53	0.23 – 1.22	0.14
Sex * depression z-score	1.14	1.05 – 1.24	< 0.001***	1.09	1.00 – 1.17	0.038*
Age * depression z-score	1.00	1.00 – 1.01	0.58	1.00	1.00 – 1.00	0.50
Sex * age	1.02	1.01 – 1.03	< 0.001***	1.01	1.00 – 1.02	0.17
Sex * age * depression z-score	1.00	0.99 – 1.01	0.92	1.00	0.99 – 1.00	0.59

***p < 0.001; **p < 0.01; *p < 0.05.

Note. Age and sex are grand-mean centered in this analysis, to facilitate interpretation of the main effects

References for supplementary Table S1

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