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Review

Is excess mortality higher in depressed men than in depressed women? A meta-analytic comparison

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ABSTRACT

Background: It is not well-established whether excess mortality associated with depression is higher in men than in women.
Methods: We conducted a meta-analysis of prospective studies in which depression was measured at baseline, where mortality rates were reported at follow-up, and in which separate mortality rates for men and women were reported. We conducted systematic searches in bibliographical databases and calculated relative risks of excess mortality in men and women.
Results: Thirteen studies were included. Among the people with depression, excess mortality in men was higher than in women (RR=1.97; 1.63–2.37). Compared with non-depressed participants, excess mortality was increased in depressed women (RR=1.55; 95% CI: 1.32–1.82), but not as much as in men (RR=2.04; 95% CI: 1.76–2.37), and the difference between excess mortality in men was significantly higher than in women ($p < 0.05$).
Conclusions: Excess mortality related to depression is higher in men than in women. Although the exact mechanisms for this difference are not clear, it may point at differential or more intensified pathways leading from depression to increased mortality in depressed men compared to women.

Contents

Abbreviations: BDI, Beck depression inventory; CES-D, Center for epidemiological studies – depression scale; DIS, Diagnostic interview schedule; DRS, Depression rating scale; FU, Follow-up; GDS, Geriatric depression scale; GMS/AGECAT, Geriatric mental state/automated geriatric examination for computer assisted taxonomy; MDD, Major depressive disorder; mind, Minor depression; MINI, Mini international neuropsychiatry interview; PHQ, Patient health questionnaire; PSE, Present state examination; SDS, Selfrating depression scale

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1. Introduction

Several hundreds of studies have now shown that depressive disorders are associated with excess mortality (Cuijpers et al., 2013). The mortality risk has been found to be independent of disease status (Cuijpers et al., 2013), and has been observed in all kinds of patients and healthy populations including community samples (Cuijpers and Smit, 2002; Saz and Dewey, 2001; Wulsin et al., 1999), heart disease patients (Barth et al., 2004; Nicholson et al., 2006; Sørensen et al., 2005; Van Melle et al., 2004), cancer patients (Chida et al., 2008; Pinquart and Duberstein, 2010), stroke patients (Pan et al., 2011), and diabetes patients (Bruce et al., 2005; Lin et al., 2009). The exact causes for the increased mortality rates in depressed people are not yet known, but may be related to an increased risk for suicide in depressed patients (Botswick and Pankratz, 2000), by hazardous health behaviors, such as physical inactivity (Whooley et al., 2008), increased smoking rates (Dierker et al., 2002), more alcohol consumption (Holahan et al., 2003) and unhealthy eating patterns (Luppino et al., 2009; Penninx et al., 1999), and by biological dysregulation including hyperactivity of the hypothalamic pituitary adrenal axis, neuro-immune dysregulations, and sympathoadrenergic dysregulation (Cesari et al., 2003; Pariante, 2003; Cuijpers and Schoevers, 2004; Penninx et al., 2013). The causal direction of the most of these mechanisms is unclear, however. Depressive disorders may lead to hazardous health behaviors or biological dysregulation, these behaviors and dysregulation may lead to depression, or both may be explained by a third, underlying factor.

It is not yet clear whether excess mortality in depression is higher among men than among women. Some studies have found evidence for such a differential association pointing at higher excess mortality in men than in women (Kopp et al., 2011; Takeida et al., 1997; Ahto et al., 2007), but others have not confirmed this (Faller et al., 2007; Yaffe et al., 2003). Whether or not there is a differential mortality rate in men and women is important because it may point at different causal pathways between men and women with depression. It may also point at more intensified pathways in men or women, which is found for example in suicide where mortality rates in men are higher than in women.

We decided to conduct a meta-analysis of prospective studies in which depression was measured at baseline, mortality rates were reported at follow-up, and in which separate mortality rates for men and women were reported.

2. Method

2.1. Selection and inclusion of studies

Studies were traced by means of several methods. First, we conducted comprehensive literature searches (up to April 2013) in three bibliographical databases (Pubmed, Psycinfo and Embase). In these searches we combined words indicating depression (such as major depression, mood disorder, depression, depressive), mortality (death, survival), and prospective design (incidence, follow up studies, longitudinal studies, prospective studies). Both text and key words were used. We also checked the references of included studies, as well as the references of earlier meta-analyses examining the association between depression and mortality (Cuijpers et al., 2013). We retrieved the full-text papers of studies that possibly met inclusion criteria. Full-text papers were examined by two independent raters for possible inclusion. Disagreements were solved by discussion.

In a separate paper we have reported the results of all 293 prospective studies that examined the relative risk (RR) of dying during follow-up in depressed versus non-depressed people (Cuijpers et al., 2013), indicating that depressed people have a significantly increased mortality rate compared to non-depressed people (RR = 1.64; 95% CI: 1.56–1.76). In the current study, we only included studies (–) with a prospective design (–) in which depression was examined at baseline, (–) all-cause mortality was reported at follow-up, and (–) mortality rates were reported separately for men and women. Depression had to be assessed with a standardized depression measure, which could be either a diagnostic interview or a self-report questionnaire. We included studies in any target group (community, patient and any other sample) as well as case-control studies. Studies were excluded when insufficient data were presented to calculate mortality rates at follow-up in the depressed and non-depressed group. We also excluded studies in which the instrument for assessing depression was not standardized (e.g., use of antidepressants, non-standardized interviews, one question), studies based on trials examining the effects of an intervention, and studies in children and adolescents.

2.2. Data extraction and quality assessment

We rated the number of deaths in the groups of men and women with depression, and in the non-depressed control group. For the subgroup (moderator) analyses we rated several characteristics of the included studies: target population (community sample, patient sample, or other sample); and definition of depression (scoring above a cut-off on a self-report measure versus fulfilling diagnostic criteria for a depressive disorder); and follow-up period (< 3 years; 3–5 years; > 5 years).

There is a risk that studies only report differential outcomes for men and women when this difference is significant. In order to examine this we tested for the presence of publication bias (see below), but we also rated the studies on whether the gender difference was the focus of the study. We assumed that when the gender difference was explicitly part of the research question, there would be a risk that this was reported because the authors found the difference to be significant, and that this may not have been published when the difference would not have been significant. When a study reported the gender difference in the title, described this difference explicitly in the Introduction section of the paper, or described it as part of the research question, we considered this study at high risk for publication bias. Other studies were not considered at increased risk for publication bias..

In order to assess the validity of the studies we used a quality rating scale that was based on the instrument developed by Hayden et al., (2006). We adapted the specific items for use with the studies in this field, but retained five of the six basic areas of potential bias that are assessed with this instrument: study

participation (the study sample represents the population of interest on key characteristics); study attrition; adequate outcome measurement; adequate measurement of confounding variables; and adequate statistical analysis. The sixth area of potential bias (the prognostic factor of interest is adequately measured) was not used because an adequate measure of depression (major and subthreshold) was used as an inclusion criterion for this study. Details of the rating instrument are presented elsewhere (Cuijpers et al., 2013). Ratings were conducted by two independent researchers and disagreements were solved by discussion.

2.3. Meta-analyses

In each study we selected the group with depression, and within this group we calculated the relative risk (RR) of dying during the study in the men compared with the women. The RR was based on the percentage of deaths among the (depressed) men, compared with the percentage of deaths among the (depressed) women.

However, we also calculated the RRs of dying in men with depression compared with non-depressed men, as well as the RRs of dying in women with depression compared with non-depressed women. We conducted these analyses to confirm that the association between depression and excess mortality exists in the selected studies, but also to examine whether the RR of dying in depressed women was still significantly higher than in non-depressed women. If we would find that the RR of dying was significantly higher in men than in women, it would be possible that all excess mortality in depressed populations can be attributed to men and consequently, the excess mortality in depressed women would no longer be significant.

Because all studies reported the exact number of deaths in the depressed and non-depressed groups, unadjusted RRs were calculated for all studies. None of the studies reported RRs (comparing the deaths among depressed men and depressed women) that were adjusted for demographics or other variables. Therefore, all analyses were conducted with unadjusted RRs. In the larger meta-analysis of 293 prospective studies we did not find that RRs which were adjusted for demographics (RR=1.45; 95% CI: 1.35–1.55), life style and illness related factors differed very much from unadjusted outcomes (RR=1.64; 95% CI: 1.56∼1.72).

To calculate pooled RRs, we used the computer program Comprehensive Meta-Analysis (version 2.2.021). As we expected considerable heterogeneity among the studies, the pooled RR was calculated using a random effects model.

In order to examine heterogeneity, we calculated the I^2-statistic, which is an indicator of heterogeneity in percentages. A value of 0% indicates no observed heterogeneity, and larger values show increasing heterogeneity, with 25% as low, 50% as moderate, and 75% as high heterogeneity (Higgins et al., 2003). We calculated 95% confidence intervals around I^2 (Ioannidis et al., 2007), using the non-central chi-squared-based approach within the heterogi module for Stata (Orsini et al., 2005). In order to test for significant heterogeneity, we also calculated the Q-statistic, but only report whether this was significant or not.

Subgroup analyses were conducted according to the mixed effect model. In the mixed effects model, studies within subgroups are pooled with the random effects model, while tests for significant differences in RRs between subgroups are conducted with the fixed effects model. Publication bias was tested by inspecting the funnel plot and by Duval and Tweedie's trim and fill procedure (Duval and Tweedie, 2000), which yields an estimate of the effect size after the publication bias has been taken into account (as implemented in Comprehensive Meta-analysis, version 2.2.021). We also conducted Egger's test of the intercept to quantify the bias captured by the funnel plot and tested whether it was significant.

3. Results

3.1. Selection and inclusion of studies

Having examined a total of 8275 abstracts (6252 after removal of duplicates), we retrieved 1178 full-text papers for further consideration. We excluded 895 of the retrieved papers (reasons for exclusion are given in Fig. 1). Among the 293 studies reporting excess mortality for depressed people versus non-depressed people, 13 studies reported separate data for men and women and these were included in the current meta-analysis (Table 1). Fig. 1 presents a flowchart describing the inclusion process.

3.2. Characteristics of included studies

Selected characteristics of the 13 included studies are presented in Table 1. The 13 studies included 41,331 respondents (16,998 men of whom 1556 had a depression; and 24,333 women of whom 3949 had a depression). Eight studies were conducted among community samples, four among patient samples (mixed admissions to a hospital or nursing home) and one was a case-control study among psychiatric patients. In five studies the presence of depression was established with a diagnostic interview, while the other eight used a cut-off on a self-report depression measure to define depression. Five studies had a follow-up period of less than 4 years, in five studies a follow-up period of 4–5 years was examined, and in three studies follow-up was more than 5 years. Six studies scored positive on at least four of the five quality criteria, while the remaining seven studies scored lower (Table 1).

In six studies the gender difference in mortality was explicitly mentioned in the title, introduction or research question, in the other seven studies the gender difference was not specifically mentioned as goal of the study.Fig. 2

3.3. Mortality rates in depressed men compared with depressed women

Among the depressed subjects the RR of dying was significantly higher in men than in women (RR=1.97; 95% CI: 1.63∼2.37). Heterogeneity was moderate to high (I^2=67; 95% CI: 40∼81), and significant ($p<0.001$).

In order to examine possible sources of heterogeneity, we conducted a series of subgroup analyses (Table 2). We found no indication that the RR differed significantly in studies in which depression was established with a diagnostic interview compared with a self-report measure; in studies with different follow-up periods; and in studies with higher versus lower quality. We did find a significant difference between studies among community samples and other (mostly mixed patient) populations. The difference between men and women was significantly larger in community samples ($p<0.01$). In the mixed patient samples the differential mortality rate between depressed men and women was considerably smaller (RR=1.34; 95% CI: 1.00–1.79).

The studies in which the gender difference was explicitly mentioned in the title, introduction or research question, did not differ significantly from the studies in which the gender difference was not specifically mentioned as goal of the study ($p=0.86$).

Inspection of the funnel plot nor Duval and Tweedie's trim and fill procedure pointed at any potential publication bias (the effect size after adjusted for possible publication bias was exactly the

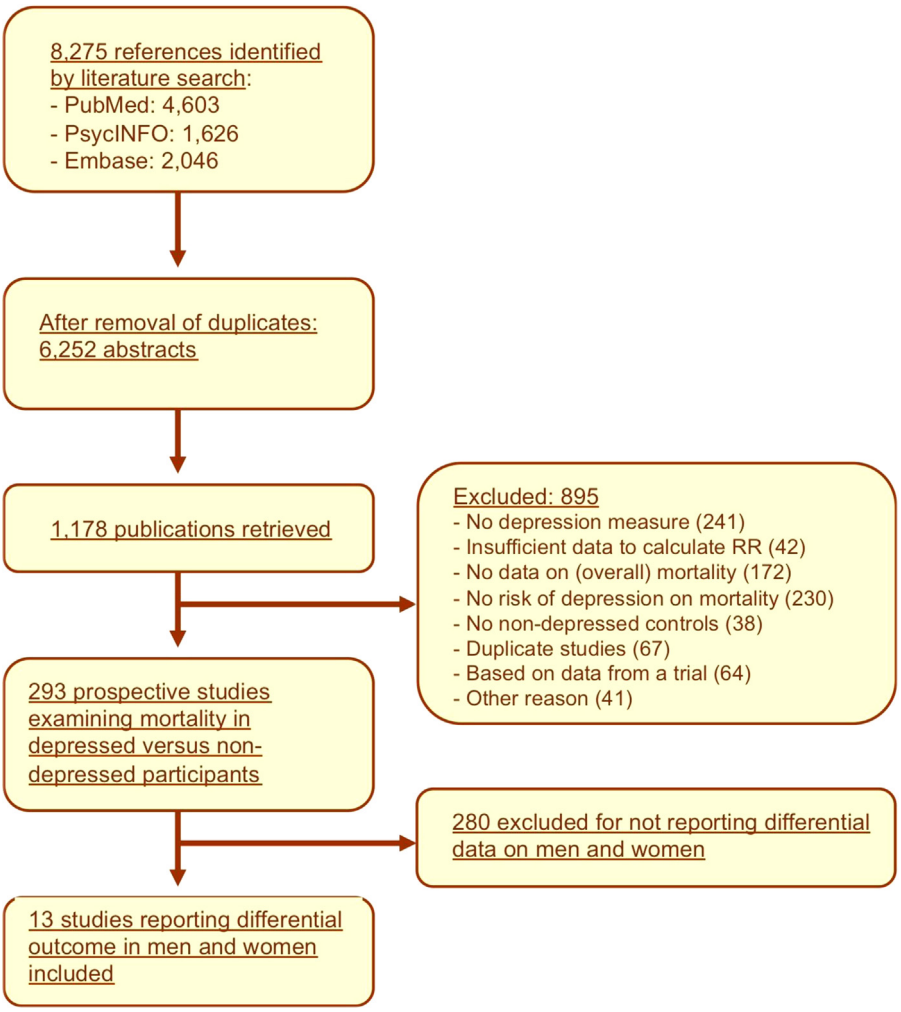

Fig. 1. Flowchart of inclusion of studies.

same as the unadjusted effect size and the number of imputed studies was zero). Egger's test was not significant either ($p > 0.1$).

We also examined whether the studies included in this meta-analysis differed from the larger sample of 238 out of 293 studies in which the unadjusted RR for excess mortality in depressed versus non-depressed people was reported. We found that the RR in the 225 studies not included in the current meta-analysis (RR=1.63; 95% CI: 1.55∼1.71) did not significantly differ ($p > 0.1$) from the studies in the current meta-analysis (RR=1.69; 95% CI: 1.47–1.94).

3.4. Mortality rates in depressed men and women compared with non-depressed controls

Comparisons of depressed men with non-depressed men indicated that the mortality rates were significantly higher in depressed men (RR=2.04; 95% CI: 1.76∼2.37). Heterogeneity was high, however, in this comparison (I^2=80; 95% CI: 66–88). In depressed women the mortality rate was also significantly higher than in non-depressed women, although it was not as high as in men (RR=1.55; 95% CI: 1.32–1.82). Heterogeneity was low in this analysis (I^2=15), but the 95% CI was broad (0–57). A subgroup analysis in which the RRs between men and women were compared with each other, indicated that the RR in men was significantly higher than in women ($p < 0.05$).

4. Discussion

In this study we could confirm that excess mortality is significantly higher in depressed men than in depressed women, and this was true in studies in which depression was established with a diagnostic interview as well as in studies in which a self-report measure was used to define depression. The mortality rate in depressed women is significantly higher than in non-depressed women, but it is also significantly lower than in depressed men.

It is not clear why excess mortality is higher in depressed men than in depressed women, and a broad range of cultural, social, behavioral, and biological differences between men and women could be responsible for this difference. Because the exact pathways leading from depression to increased mortality are not yet known, a broad range of differential pathways between men and women may explain these differences (Penninx et al., 1999; Ryan et al., 2008). For example, the physiological and behavioral reactions to stress of women may differ from those of men (Penninx et al., 1999). Or, the appraisal of psychosocial functioning may differ between men and women. There is some evidence showing that men report fewer depressive symptoms than women at the same degree of impairment of psychosocial functioning, thereby possibly causing an artifactual female preponderance (Penninx et al., 1999; Angst and Dobler-Mikola, 1984). Another explanation could be that depression is often not recognized in men (Crawford et al., 1998; Ryan et al., 2008), and when it is detected it may reflect a more severe condition.

Table 1
Selected characteristics of included studies.

Study	*Recruitment*	*Patient group*	*Definition of depression*	*G*[a]	*Total N*	*Men*	*Women*	*% depressed*	*FU period*	*Country*	*Quality* [b]
Ahto et al. (2007)	All residents of community	Community residents	SDS ⩾ 45	Y	660	282	378	15.2	12	Finland	+++ − − 6
Enzell (1984)	Community sample	People born in 1905	Positive response to 5 questions indicating depression	N	6663	2724	3939	9.7	9	Sweden	± −+− − 3
Evans (1993)	Acute admissions to a geriatric medical ward	Physically ill older inpatients	Depressive disorder (GMS/AGECAT)	N	72	27	45	31.9	1	UK	− ± ± − − 2
Faller et al. (2007)	Consecutive patients to university hospital	Patients with chronic heart failure	Probable MDD and minD (based on PHQ-9)	Y	231	163	68	MDD: 13.4 minD: 16.5 any: 29.9	2.8	Germany	± ++ ± + 8
Fuhrer et al. (1999)	Community sample	Older adults (65 and older)	CES-D ⩾ 17 in men and ⩾ 23 in women	N	3777	1576	2201	13.9	5	France	+++++ 10
Hjaltadóttir et al. (2011)	Patients admitted to nursing home	Nursing home residents	DRS > 14	N	2194	883	1311	2.4%	3	Iceland	± ++ ± + 8
Kopp et al. (2011)	Community sample	Adults (40–69)	BDI-9 ⩾ 25	Y	2659	1130	1529	16,5	3,5	Hungary	+ −+ ± +7
Murphy et al. (1988)	Patients referred to psychiatric services	Older depressed patients compared with community controls	Depressive disorder (PSE)	Y	310	100	210	47.1	4	UK	± ++ ± − 6
Penninx et al. (1999)	Community sample (LASA)	Older adults (55–85 years)	MDD (DIS; DSM-III); CES-D⩾16	N	3056	1478	1578	MDD: 2.0 CES-D⩾16: 12.8	4.2	Netherlands	+ −+++8
Ryan et al. (2008)	Community sample (3C study)	Older adults (⩾ 65 years)	MDD (MINI; DSM-IV) or CES-D⩾23	Y	7363	2885	4478	10.2	4	France	+ ± ± ++ 8
Schoevers et al. (2000)	Community sample	Older adults (⩾ 65 years)	Neurotic / psychotic depression (GMS / AGECAT)	Y	4051	1523	2528	12.9	6	Netherlands	+ ± + ± + 8
Takeida et al. (1997)	Community sample	Older adults (60–74 years)	SDS ⩾ 2,4	N	2166	1023	1143	11.5	4	Japan	± −++ − 5
Yaffe et al. (2003)	Patients eligible for nursing home	Frail elderly living in the community	GDS ⩾ 6	N	252	73	179	29.2	1.5	USA	+ − ± ± +6

[a] In this column a "Y" indicates that the study was specifically aimed at examining gender differences in excess mortality, the studies with "N" are not specifically aimed at examining this gender difference.
[b] Quality was scored on the following 5 domains: (−) Study participation; (−) Study attrition; (−) Outcome measurement; (−) Confounding measurement and account; (−) Analysis. Each item was scored as positive (+), partly (±) or negative (−). We also report the total sum of the quality score (with 2 for positive, 1 for partly, and 0 for negative; range: 0–10).

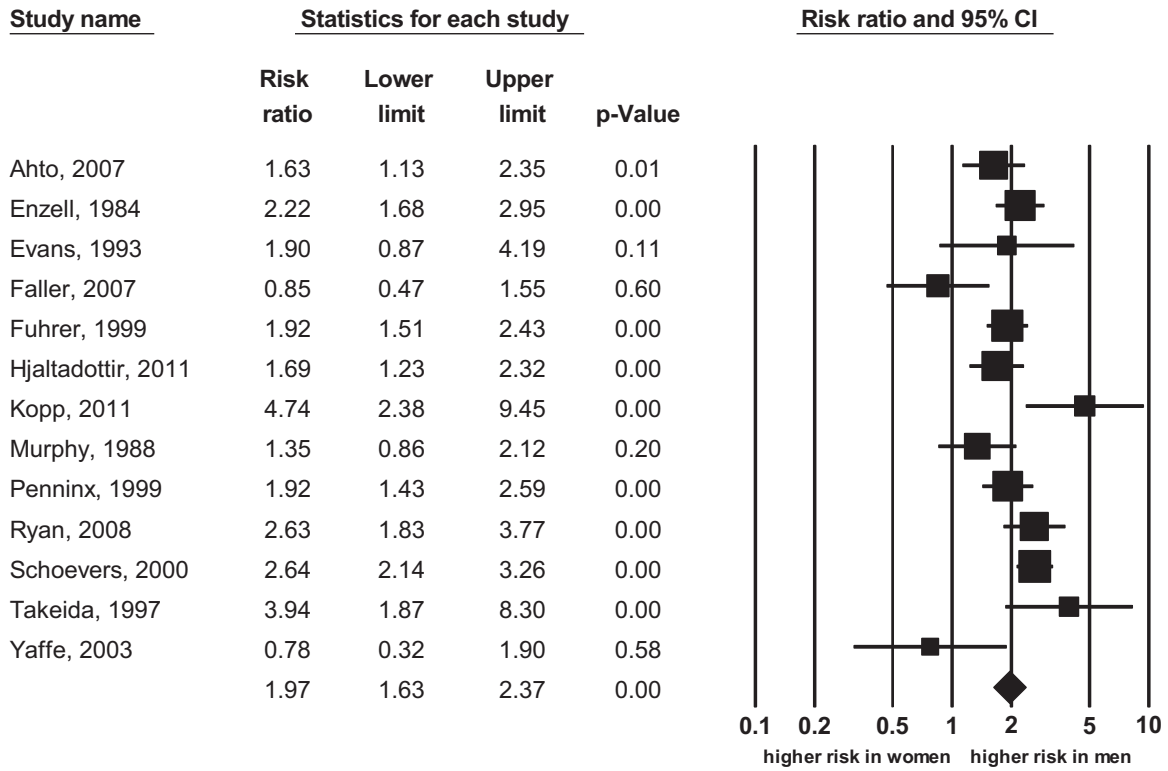

Fig. 2. Studies directly comparing excess mortality in men and women with depression: relative risks.

Table 2
Meta-analyses of studies directly comparing excess mortality in men and women with depression: relative risks [a].

Comparison	*N*	*RR*	*95% CI*	I^2 [b]	*95% CI*	*p*[c]
Men vs. women	13	1.97	1.63–2.37	67***	40–81	
Subgroup analyses [d]						
Diagnosis						
Yes	5	2.10	1.56–2.82	56	0–84	0.57
No	8	1.87	1.46–2.41	70**	39–86	
Follow-up						
< 4 years	5	1.62	1.12–2.35	76**	41–90	0.49
4–5 years	5	2.08	1.54–2.82	53	0–83	
> 5 years	3	2.16	1.52–3.09	61	0–89	
Quality						
4 or higher	6	1.93	1.48–2.52	71**	34–88	0.86
lower than 4	7	2.01	1.49–2.70	67**	26–85	
Gender was goal of study						
Yes	6	2.00	1.50–2.66	80***	57–91	0.86
No	7	1.93	1.47–2.53	35	0–72	
Depressed vs non-depressed						
Men	13	2.04	1.76–2.37	80***	66–88	*0.015*
Women	13	1.55	1.32–1.82	15	0–54	

** $p < 0.01$.
*** $p < 0.001$.
[a] All reported results are based on the random effects model.
[b] The p-values in this column indicate whether the Q-statistic is significant.
[c] The p-values in this column indicate whether the subgroups differed significantly from each other.
[d] All subgroup analyses were conducted according to the mixed effects model.

It is not known whether excess mortality is associated with specific causes of death. It is well-known that suicides are more common among men than among women and this may explain part of the difference in excess mortality in men and women. However, in most of the included studies, suicide is not very common and not the main factor driving the excess mortality. Consequently, it is also very likely that other causes of death are also related to the differential excess mortality in men and women, but more research is needed to explore this.

It is also possible that differences between men and women in lifestyle, behavioral and illness-related factors cause the difference in excess mortality. For example, inflammation and abdominal obesity are associated with depression in men but not in women (Vogelzangs et al., 2010; 2012). Other research has found that

social risk factors, such as life events may be a stronger risk factor for depression in women than in men (Kendler et al., 2005; Maciejewski et al., 2001). Such factors may also be associated with differences in excess mortality.

Our finding that the differential RR in excess mortality among men and women was significantly different in community samples compared to patient populations was unexpected. Because of the correlational nature, this association has to be interpreted with caution and may very well be a chance finding. In our larger meta-analysis of 293 studies, we did not find that excess mortality rates in community samples differed from those in patient samples, nor did we find large differences between different patient samples. The finding in the current meta-analysis was, therefore, unexpected.

It was remarkable that the only study among patients with chronic heart failure did not result in an increased relative risk among men (Faller et al., 2007). This study was also an outlier in the sense that the confidence interval of the relative risk did not overlap with the pooled relative risk of all studies together. It is not clear what caused this. It may be a chance finding, but it may also be somehow related to the fact that these were heart disease patients and could potentially indicate that in a diseased sample, the excess mortality among men is not as prominent.

This study has several limitations. First, the number of studies was small and especially in the subgroup analyses, statistical power may have been too small to find significant differences between subgroups. A second limitation is that the quality of the studies was not optimal in all cases. This may have influenced our results, although we did not find significant differences between higher and lower-quality studies. Third, we were only capable of examining unadjusted associations between excess mortality and gender, and as we indicated above the association between depression and excess mortality in men and women may be explained by differences in lifestyle, behavioral and illness-related factors between men and women. Nonetheless, we think that the difference between men and women is important, even when this may be explained by such factors.

An important possible source of bias in this study is that authors only report differences between men and women when they find that these are significant. Only 13 of almost 300 prospective studies on excess mortality reported differential outcomes for men and women. However, we could differentiate between studies in which the differential mortality rate in men and women was part of the research question of the study, and studies that did not specifically focus on this difference but still reported it. We did not find a significant difference between these two groups of studies, and the differential mortality rate among depressed men and women was still significant in the studies that did not specifically focus on this difference. We also did not find that the overall excess mortality in our study differed from the larger meta-analysis of almost 300 prospective studies. This cannot be seen as a guarantee that this possible source of bias did not affect the results of this study, but it does give confidence that the difference between men and women is a robust outcome. However, because of this and the other limitations of this study, the results have to be considered with caution.

Despite these limitations this study suggests that excess mortality in depression is higher in men than in women, although the mortality risk is increased compared to non-depressed controls in both men and women.

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Conflict of interest

None

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