

A reassessment of the relationship between depression and all-cause mortality in 3,604,005 participants from 293 studies

As reported in the February issue of this journal¹, over three decades of research suggest that depression is associated with an increased risk of all-cause mortality, although some large recent studies have found negative or null associations^{2,3}. To better inform clinical decision making and evidence-based service provision, it is crucial to resolve this discrepancy.

Here we summarize the principal findings of the largest ever investigation of the relationship between depression and all-cause mortality, comprising 3,604,005 participants and over 417,901 deaths, based on a reassessment of 293 studies derived from 15 systematic reviews. We observed that several factors moderate the relationship between depression and mortality, and found no evidence of an association when controlling for comorbid mental disorders and health behaviors (see <https://osf.io/svywu/> for the complete report and the extracted data).

The purpose of this reassessment was to better understand the features of studies that have sought to address the depression-mortality relationship, to delineate some methodological reasons for heterogeneity between studies (sample size and characteristics, number of deaths and follow-up periods, and adjustment for mental disorders and health behaviors), and to explore whether estimates of the relationship between depression and mortality on the basis of the methodologically most rigorous studies differed from those of previous meta-analyses. The three main results of the study are as follows.

First, there was a pronounced publication bias⁴, as indicated by the positive intercept (1.02; 95% CI: 0.72-1.31) of effect estimates on their standard errors favoring imprecise studies with large positive associations. The largest estimates consistently came from studies with small samples, low number of deaths, and brief follow-up periods.

Second, only 16 (~5%) of the included studies adjusted for at least one comorbid mental condition. This is surprising, given that more than half of individuals diagnosed with major depressive disorder suffer from at least one additional comorbid mental disorder in their lifetime⁵. The pooled relative risk (RR) of these 16 estimates (1.08; 95% CI: 0.98-1.18) was smaller than the RR of the 266 estimates that were unadjusted for comorbid mental disorders (1.33; 95% CI: 1.29-1.37). Additionally, there was no evidence of an association between depression and all-cause mortality among the fraction of eight of these estimates that also adjusted for health behaviors (smoking, drinking or physical inactivity) (1.04; 95% CI: 0.87-1.21).

Third, apart from sample size, follow-up duration, and lack of adjustment for important variables, other substantial sources of heterogeneity between studies emerged. Over two-thirds of the estimates comprised respondents who were pre-selected on the basis of medical conditions. This is problematic, because many symptoms of major depression (e.g., insomnia, fatigue) are shared with various physical conditions⁶, or may arise as

side effects of medications used to treat existing pathologies. Pre-selecting participants on the basis of medical conditions could therefore result in confounding by reverse causality among those who are physically unwell at baseline. Given that somatic symptoms that are not confounded by physical conditions are integral to a diagnosis of major depression, studies based on medical samples that use rating scales (instead of diagnostic interviews that query the source of these somatic symptoms) may be particularly likely to misclassify individuals who are of relatively poorer health as depressed. Furthermore, we found that over forty different instruments were used to measure depressive symptoms, which is problematic due to the considerable content heterogeneity among commonly used instruments⁷. Even studies that used the same questionnaire frequently adopted different cutoff scores for a probable diagnosis of major depressive disorder. The interaction of three of the aforementioned points – the use of scales encompassing physical symptoms that may indicate comorbid medical conditions; the use of samples pre-selected based on medical conditions; the lack of adjustment for comorbidities when estimating the effect of major depressive disorder on mortality – points to significant weaknesses in the literature.

We therefore estimated the association of depression and mortality among studies that used DSM-based structured interviews requiring the presence of core depressive symptoms (sad mood or anhedonia) prior to assessing for more general physical, somatic and cognitive symptoms, in community-based samples and based on survival analysis methodology. Only four estimates (1% of all studies) met these criteria, among which the pooled hazard ratio was 1.17 (95% CI: 0.75-1.60).

Given the overall poor quality of the available evidence, we are unable to draw strong conclusions about the relationship between depression and mortality. Studies with large samples, extensive follow-up periods, adjustment for mental disorders and health behaviors, and time-to-event outcomes assessed using survival analysis methodology are especially needed.

More work of a higher quality is also required to examine which variables related to depression and mortality may modify this relationship. For example, the subsequent onset of health behaviors such as smoking, drinking and physical inactivity appear to play an important role in mediating the risk of adverse cardiovascular outcomes among depressed individuals⁸. This could account for a variety of adverse health outcomes that are not limited to cardiovascular disorders. Moreover, the risk of depression and mortality are both influenced by a subset of common variables. For example, smoking at baseline is associated with increased risk of depression onset at follow-up⁹, and smoking is associated with many causes of death¹⁰.

More rigorous research is needed to better understand whether depression does, in fact, pose an increased risk of all-cause mortality. We hope that our work will encourage such efforts.

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DOI:10.1002/wps.20439

Correction

It has been brought to our attention that the Acknowledgements section of the paper “Disorders related to sexuality and gender identity in the ICD-11: revising the ICD-10 classification based on current scientific evidence, best clinical practices, and human rights considerations”, by Reed et al, published in the October 2016 issue of *World Psychiatry*, should contain the following additional statement: “The authors are grateful to the other members of the 2011-2013 ICD-11 Working Group on Sexual Disorders and Sexual Health, including R. Coates, J. Cottingham, S. Krishnamurti, A. Marais, E. Meloni Vieira, S. Winter and A. Giami, for their contributions to the proposals discussed in this article”.