Increased Mortality in Depressive Disorders: A Review

Pim Cuijpers, PhD and Robert A. Schoevers, MD*

Address
*Department of Clinical Psychology, Vrije Universiteit, Amsterdam, Van der Boechorststraat 1, 1081 BT Amsterdam, The Netherlands.
E-mail: P.Cuijpers@psy.vu.nl

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Several factors have been proposed to explain the relationship between excess mortality and depressive disorders. These include mechanisms such as increased suicide rates, hazardous health behavior (smoking, alcohol use, unhealthy eating), psychologic reactions to developing a medical illness, biological dysregulations (hyperactivity of the hypothalamic pituitary adrenal, neuro-immune dysregulation, sympathoadrenergic dysregulation), and noncompliance with medical treatment. The evidence supporting the role of each of these mechanisms in excess mortality varies considerably. The causal direction in most of the mechanisms is not clear. It is possible that the explanatory factors, such as smoking, compliance, or biological mechanisms, cause depression, or that depression causes these factors, or that both are explained by a third, underlying factor. We will summarize the evidence supporting these mechanisms, and propose options for possible interventions aimed at reducing the increased risk of dying.

Introduction

The relationship between mental disorder and mortality has been examined in hundreds of studies worldwide in the past few decades, although some of the studies go back at least 150 years [1,2]. One of the mental disorders that has been examined in great depth is depression [3•]. Most of the studies exploring the relationship between depression and mortality have focused on whether mortality rates in people with a mental disorder are higher than in other populations. Relatively few studies have examined the processes through which mental disorders influence mortality risks. This research has resulted in an accumulation of evidence showing that subjects with depression have increased mortality rates. Several hypotheses have been developed to explain this phenomenon. However, the evidence supporting these hypotheses differs greatly for each one.

In this article, we first will summarize the results of epidemiologic research examining the relationship between depression and mortality. We then will describe the hypotheses that have been posed to explain increased mortality in depression and the research supporting these hypotheses.

Are Mortality Rates Increased in Subjects with Depression?

The question of whether depression increases mortality rates has been examined in community studies [4•], in studies comparing patients treated for depression in the general population [3•], and in studies of medical patients, including depressed patients with heart diseases [5–8], patients who have had stroke [9], patients with a life-threatening illness [10], and elderly patients with varying illnesses [11–13].

Recently, we did a meta-analysis of prospective studies examining mortality rates in subjects with depression compared to the rest of the population [4•]. A systematic search of the literature in the most important bibliographic databases resulted in 25 prospective studies, reporting on a random sample from a community and comparing mortality rates in depressed to nondepressed subjects. These studies included 106,628 subjects, of who 6416 were depressed. The overall relative risk (RR) of dying in depressed subjects was found to be 1.81 (95% CI, 1.58–2.07) compared with nondepressed subjects. Because the set of studies was significantly heterogeneous, we excluded the studies that contributed most to the heterogeneity until a homogeneous set of studies was obtained. The relative risk of the resulting set of studies (three studies were excluded) was found to be 1.65 (95% CI, 1.51–1.81).

In our meta-analysis, we included studies examining subjects with major depressive disorder according to diagnostic criteria and studies of subjects with subthreshold forms of depression. Subthreshold depression could be operationalized by scoring above a cut-off point on a self-rated depression questionnaire, by having one or more basic characteristics of depression (mood problems for 2 weeks), or by meeting criteria for minor depression as operationalized in the Diagnostic and Statistical Manual IV, the International Classification of Diseases, 10th Revision, or the Research Diagnostic Criteria. We did not find any indication that the relative risk in subjects with major depression (1.54; 95% CI, 0.96, 2.47) was higher than in subjects with subthreshold forms of depression (1.65; 95% CI, 1.39, 1.96). These results are supported by several other

Table 1. Possible causes of increased mortality in depression

Increased suicide rates in depressed patients
More hazardous health behaviors in depressed patients
Tobacco use
Unhealthy eating habits
Alcohol use
Less physical activity
Hazardous behavior such as dangerous driving
Depression is a psychologic reaction to medical illnesses*
Biological dysregulations
Hyperactivity of the hypothalamic pituitary adrenal
Neuro-immune dysregulation
Sympatho-adrenergic dysregulation
"Vascular" depression (in the elderly)
Less compliance with treatment in depressed patients

*Excess mortality is not caused by depression, but by the illness.

systematic reviews and meta-analyses of studies examining mortality and depression [3•,14,15••,16].

In some community studies, subjects with major depression and subjects with subthreshold depression were examined [17•,18,19], and direct comparisons between these two populations within each of these studies confirm that there is no strong evidence of a significant difference in mortality rates.

Some studies found indications that the increased risk of death especially is present in men, but is not present or is less so in women [17•,19–21]. In our meta-analysis, we also found support for this difference between men and women. The relative risk of dying was 2.25 (95% CI, 1.90, 2.67) in men, compared to 1.62 (95% CI, 1.37, 1.92) in women. In a multivariate metaregression analysis in which we controlled for several possible confounding variables, the difference between men and women remained considerable.

Depressive disorder is not the only mental disorder with increased mortality rates. In a large systematic review of more than 150 studies, evidence showed that mortality rates are increased in all mental disorders, including eating disorders, alcohol and drug dependence and abuse, schizophrenia, bipolar disorders, dysthymia, anxiety disorders, personality disorders, and major depressive disorders [3•]. It also was found in this review that the highest risks for premature deaths were found in substance abuse and eating disorders. However, the risk of death from unnatural causes is especially high in functional disorders, particularly in schizophrenia and major depression.

Possible Causes of Increased Mortality Rates in Depression

On the basis of our meta-analysis, we can calculate the population-attributable risk of depression. This indicates the percentage of deaths that can be avoided if the risk factor (in this case depression) were to be erased altogether. We found the population-attributable risk to be 7.5 %. This is considerable when compared to lifestyle factors [22]. Among these lifestyle factors only tobacco use (18.1%) and poor diet and lack of physical exercise (16.6%) result in more deaths than depressive disorders. Other major lifestyle factors, such as alcohol consumption (3.5%), score considerably lower than depressive disorder.

However, depression cannot be directly compared to these lifestyle factors, as there is much more evidence supporting the causal link between lifestyle factors and increased mortality. A direct causal relation between depression and mortality has not been proven, and it is possible that the increased mortality is not directly caused by depression. We will describe the most important causes of increased mortality in depression that have been proposed, and the supporting evidence. The most important mechanisms explaining the relationship between excess mortality and depression are summarized in Table 1.

Suicide

There are several behavioral causes of the increased mortality in depression and suicide is among the most important. Suicide rates in depressive disorders have been studied for several decades [23]. Although the risk of suicide has long been overestimated in depression, a recent meta-analysis of 47 studies estimated that the lifetime risk of suicide ranges from 2.2% to 8.6% in patients with depression [24], compared with less than 0.5% in nondepressed subjects. The lifetime prevalence was found to be especially large in patients hospitalized for suicidality (8.6%). The lifetime prevalence found in mixed inpatient/outpatients with depression has been found to be 2.2%.

Although suicide is one of the causes of increased mortality in depression, it can explain only a small part of the overall increased mortality because the incidence of suicide is low. Most studies examining the correlation between mortality and depression do not examine differences in actual causes of death between depressed and nondepressed subjects, and most do not have sufficient statistical power to examine these differences. However, there are some exceptions. In a well-designed longitudinal study of elderly people living in the community in the Netherlands, in which 124 subjects with minor or major depression died during 50 months follow-up, only one died because of suicide [17•]. And in a large survey in the United States among almost 46,000 households, it was found that among 223 depressed subjects who died, only two died because of suicide [20].

These figures must be interpreted with caution, because it is known that many suicides are not registered as such in the official statistics. Nonetheless, suicide can never explain more than only a small part of the increased mortality rates in depressed patients.

Tobacco Use

Another mechanism that is assumed to be responsible for increased mortality in depression is hazardous health behavior. It has been established that patients with depression smoke more, stop smoking less easily, have more unhealthy eating habits, drink more alcohol, have less physical activity, and engage in more hazardous behavior, such as dangerous driving.

It has been known for several decades that smokers are more neurotic than nonsmokers [25–27]. These early studies also showed that smokers who ceased smoking were less neurotic, less depressed, and less anxious than those who did not succeed in their attempt to quit. Several more recent studies have shown that there also is a relationship between smoking and depressive disorders that meet rigorous criteria. Compared with nonsmokers, smokers often have had a depressive disorder in their lives [28–30]. This relationship between depressive disorders and smoking has been shown to exist as early as in adolescence [31]. There also is evidence that the likelihood of entering a new episode of major depression is greater among smokers than among nonsmokers [30,32]. Additionally, research has shown smokers with a history of major depression fail their attempts at smoking cessation more often than other smokers [28,30]. When smokers with a history of depression stop, they have a significantly increased risk of developing a new depressive disorder as compared with smokers without a history of depression [32].

Although the evidence clearly points to a strong relationship between tobacco use and depression, there is little evidence about the exact nature of this relationship and causal directions. It has been suggested that depression may be caused by smoking through neurochemical changes [33••], that depression leads to smoking by increasing the likelihood that individuals will self-medicate negative feelings with nicotine [27], and that depression and smoking are caused by common physical or psychologic factors that independently increase the risk of both conditions [33••].

Other Hazardous Health Behaviors

Tobacco use is only one of the unhealthy lifestyle factors that are more prevalent in patients with depressive disorder than in other subjects. It has been shown repeatedly that patients with depression more often drink too much alcohol [34–37], although there are indications that this is not true in elderly subjects [17•,38]. There also is some evidence that problem drinking has a negative effect on prognosis of depressive disorder.

Several other studies found that depressive disorder is associated with body mass index [39,40] and obesity [41], especially among subjects with severe obesity. Depressive disorders also have been found to be associated with lower physical activity [17•], and with a larger number of fatal accidents [42].

The relationship between these lifestyle factors and depression also can work in the three directions cited earlier: lifestyle factors may cause depression, depression may cause differences in lifestyle, or both may be the result of one or more independent factors.

Mortality in Depressed Patients With General Medical Illnesses

As indicated previously, depression has been shown to be more prevalent in several general medical illnesses, including diabetes [43], heart diseases [5–8], cancer [44,45], stroke [9], arthritis, osteoporosis, Alzheimer's disease [46•], and life-threatening illness in general [10]. It has been concluded that the prevalence rates of depression increase from 2% to 5% in community settings, to 5% to 10% in primary care, and to 6% to 14% or greater in medical and/or surgical patients [47–49].

It has been suggested that some patients develop depressive symptoms as a psychologic reaction to these illnesses, and that the increased risk of mortality is not caused by depression, but because of the illnesses that also cause the depressive symptoms [50]. In these cases, getting an illness is considered to be an important life event. These psychologic reactions to illnesses cannot explain all increased mortality. It also has been shown that subjects with depression also have an increased risk of developing new general medical illnesses, and this has been shown especially for cardiovascular disease [51–53] and diabetes [54,55].

Additionally, there is evidence that the prognosis of patients with depression is in many cases worse than the prognosis of patients without depression, such as in patients with myocardial infarction [6]. However, this could be explained by the phenomenon that illnesses with a poor prognosis are more depressing than less serious conditions [56••].

Depression and Biological Dysregulations

Another possible explanation for the association between depression and excess mortality is biological, occurring through neuroendocrine and autonomic dysregulation.

Hyperactivity of the hypothalamic pituitary adrenal (HPA) axis frequently has been established in patients with depression [57,58]. Through insufficient negative feedback of the glucocorticoid receptors in the hippocampus and the hypothalamic paraventricular nucleus [58], excess production of hypothalamic CRH leads to higher hypophysial adrenocorticotropic hormone release, which in turn causes higher blood cortisol levels [59]. Hypercortisolemia is associated with insulin resistance and accumulation of intra-abdominal fat [60]. The combination of "upper-body obesity," diabetes, hypertension and dyslipidemia, also called "deadly quartet," is associated with a significantly higher risk of myocardial infarction and stroke [61]. Through lower bone density, hypercortisolemia also is associated with an increased likelihood of

bone fracture [62]. There has been debate on whether these PHA axis abnormalities precede affective disorder, or result from chronic stress, traumatization, and depression. Genetic studies have shown that polymorphisms in the glucocorticoid receptors are associated with the occurrence of affective disorders, [58,63,64] and healthy family members of patients with depression have been shown to have HPA axis overactivity [64]. Therefore, HPA axis abnormalities may participate in the development of depressive symptoms and in the occurrence of numerous medical conditions.

A second pathogenetic mechanism, possibly explaining the association between depression and excess mortality, is neuro-immune dysregulation. Patients with depression show higher levels of pro-inflammatory cytokines such as interleukins (IL) IL-1 and IL-6, C-reactive protein, and α-1 antichymotrypsin [65,66]. These are associated with hypercortisolemia, [67] myocardial infarction, and stroke [68–71]. The temporal associations between depression and neuro-immune dysregulation still must be elucidated because low doses of endotoxins have been shown to cause symptoms of depression, anxiety, and cognitive disturbances in healthy volunteers [72,73].

A third mechanism is sympathoadrenergic dysregulation. Depression is associated with increased noradrenaline levels [68], and autonomic hyperactivity leading to reduced heart rate variability and an increase in coronary events [74,75•] Through autonomic dysregulation, upregulation of platelet serotonin receptors and increased intracellular calcium mobilization, platelet aggregation and thrombo-embolic processes also are enhanced [75•].

In the elderly, a specific subtype of vascular depression is distinguished with psychomotor retardation, loss of interest, a decrease in functional abilities, and vegetative symptoms. Patients are found to have cerebral (frontostriatal) white matter lesions most likely related to microvascular pathology, which also may affect longevity [76,77].

All of these biological mechanisms are linked to depression and are associated with various somatic disorders. However, the direction of these mechanisms is unclear. Again, it may be possible that these mechanisms cause the depression directly, that depression causes these mechanisms, or that the depression and the mechanisms are caused by a third factor.

Compliance with Medical Treatment

Another possible explanation for the increased mortality in depressed patients with general medical disorders is that compliance with treatment is less optimal than in other patients. There is ample support for this hypothesis in various patient groups such as patients with HIV [78], patients with cancer [79], and elderly patients with coronary artery disease [80]. A recent meta-analysis of the literature concluded that, compared with nondepressed patients, the odds are three times greater that patients with depression will be noncompliant with medical treatment recommendations [81].

Why depression affects adherence is unclear. It has been suggested that reduced adherence is related to other factors, such as poor social support, increased functional impairment, heightened sensitivity to physical discomforts, and impaired attention span, concentration, and memory. Each of these factors has been shown to be related to depression and to reduced compliance [80]. However, the most obvious explanation is that the depression reduces the motivation to adhere to a medical treatment.

It also has been suggested that it is not depression that causes poor adherence, but the behavior of noncompliance preceding the mood state [82]. More research is needed to clarify the causal link between depression and compliance.

Does Treatment of Depression Affect Survival?

In the preceding paragraphs, we have described the mechanisms that may explain excess mortality rates in depression. Because there are several mechanisms that may be interlinked, excess mortality probably is caused by several different pathways. Theoretically, there are several different methods to intervene in these pathways. Although it is beyond the scope of this article to describe them all, we will describe some major possible interventions.

First, as most suicides are committed by subjects with depression, effective suicide prevention programs may reduce mortality rates in depressed subjects. Generally, there is little evidence that suicide prevention programs are effective, mostly because of a lack of randomized controlled trials and small sample sizes [83]. However, there are some promising interventions, such as long-term lithium treatment [84], and some recent studies show promising effects of psychosocial interventions [85–87].

Another possibility is to improve lifestyle factors in patients with depression. Most research in this area has focused on tobacco use. Several trials have examined the effects of cognitive behavior therapy in smokers with a lifetime history of major depression [88–91]. Most of these studies show positive results, although most of the sample sizes are small and more research in this area is needed. Comparable approaches could be possible, focusing on other lifestyle factors.

A recent meta-analysis of studies examining the effects of interventions aimed at the improvement of medication adherence showed that this type of intervention has small to moderate effects [92]. However, only one of the studies examined by this meta-analysis was aimed at subjects with depression, and the effect size for this study was small.

Another important research question is whether adequate treatment of depression may affect the risk of mortality. Theoretically, treatment with antidepressant medication could result in better survival and excess mortality. Tricyclic antidepressants may cause ventricular arrhythmias and orthostatic hypotension. In medical (cardio) and elderly patients these side effects may have substantial negative consequences [93,94]. However, it is

unlikely that this could be responsible for the excess mortality in depression. Sparsely available earlier studies suggest that adequate treatment of depression may reduce mortality [95,96]. Antidepressants have been shown to affect event-free interval in patients who have had MI [97]. One placebo-controlled trial found that 9-year survival after stroke was significantly better if patients had been given antidepressants for some time soon after their stroke, regardless of the presence or absence of depression [98]. Research has shown that antidepressant medication may directly affect numerous biological parameters. Selective serotonin re-uptake inhibitors have been shown to normalize platelet aggregation, and may influence cardiovascular risk patterns [99]. Recent research indicates that antidepressants may help to restore normal functioning of the HPA axis in individuals with depression [100,101]. However, possible effects on survival have not been shown consistently. Recently, this idea was investigated more thoroughly in two large randomized placebo-controlled trials. One study of 369 cardiac patients found that sertraline could safely and effectively be used to treat depression in patients with acute MI or unstable angina, although it did not show an improvement in cardiologic parameters [102]. Another study specifically investigated the impact of treatment on 6-months survival in 2481 patients after MI and found that cognitive behavior therapy, with the addition of SSRI improved severe depression and social isolation, but not event-free interval [103].

Psychotherapy or psychosocial interventions aimed at reducing depression also may influence survival. A meta-analysis of psychosocial interventions showed that the addition of psychosocial treatments to standard cardiac rehabilitation regimens reduced mortality and morbidity, psychologic distress, and some biological risk factors during the first 2 years [104]. Providing psychosocial support reduces depression, anxiety, and pain in patients with cancer, but studies are divided on whether this also increases survival time [44].

Overall, it can be concluded that interventions aimed at either of the pathways linking depression and excess mortality have beneficial effects on a number of clinically relevant biological and psychologic parameters, but currently it is not an established fact that survival of patients with depression can be improved substantially by these measures.

Conclusions

There is little doubt that there is a relationship between depression and excess mortality. However, the mechanisms explaining this relationship are less clear. Several behavioral and physical mechanisms have been proposed. The evidence supporting the role of each of these mechanisms in excess mortality varies greatly. The causal direction in most of the mechanisms is not clear. It is possible that the explanatory factors, such as smoking, compliance, or neurobiological dysregulation cause depression. It also is possible that depression causes these factors, or that both are explained by a third, underlying factor.

The mechanisms explaining excess mortality in depression may be interlinked with each other in complex ways. For example, lifestyle factors may trigger biological vulnerability and psychologic reactions to getting an illness and may increase suicide risk. It also is possible that underlying pathogenetic mechanisms and genetic polymorphisms may constitute higher vulnerability for depression and medical illnesses.

This suggests that excess mortality is a result of complex interactions between different factors, and depression may lead to mortality through different pathways.

We must conclude that the relationship between depression and excess mortality is not yet well understood, and although several possible mechanisms explaining this relationship are suggested, more research is needed before interventions will become available to reduce this increased risk of death in patients with depression.

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Dr. Schoevers is affiliated with Metrum Mental Health Care Amsterdam and the Department of Psychiatry, VU Medical Centre, Amsterdam, The Netherlands.

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