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Cardiovascular Disease and Excess Mortality in Depression: Physical Activity as a Game Changer

Herz-Kreislauf-Erkrankungen und überhöhte Sterblichkeit bei Depressionen: Körperliche Aktivität als Game Changer

REVIEW

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Summary

› **Problem:** Depression is a widespread disorder and among the leading causes of disability worldwide. In this article, we perform an umbrella review on the association between depression and excess mortality, cardiovascular disease (CVD), and cardiovascular risk factors. We also provide an overview of mechanisms that explain these associations. Finally, we discuss clinical implications from a general perspective and discuss the potential of physical activity to favorably influence the relationship between depression and premature mortality.

› **Methods:** Meta-analyses were identified via PubMed. Only works on unipolar depression were included.

› **Results:** The association between depression and excess mortality is a robust epidemiological finding. This association can be attributed to the fact that people with depression are at increased risk for CVD and accumulate more cardiovascular risk factors. However, the causal associations are complex. While depression is associated with incident CVD, depression can also be a consequence of cardiac events. Regular physical activity and higher cardiorespiratory fitness levels mitigate the risk of premature mortality associated with depression.

› **Discussion:** More attention should be paid to the physical health of psychiatric patients. High priority should be given to the promotion of physical activity and fitness, as they are beneficial for both physical and mental health.

KEY WORDS:
Fitness, Cardiovascular Disease, Physical Activity, Mortality

Zusammenfassung

› **Problemstellung:** Depressionen sind eine weit verbreitete Erkrankung und gehören weltweit zu den Hauptursachen für gesundheitsbezogene Einschränkungen. In diesem Artikel führen wir eine umfassende Überprüfung des Zusammenhangs zwischen Depression und Übersterblichkeit, Herz-Kreislauf-Erkrankungen und kardiovaskulären Risikofaktoren durch. Zudem geben wir einen Überblick über Mechanismen, die diese Assoziationen erklären können. Schließlich diskutieren wir klinische Implikationen aus einer allgemeinen Perspektive und beleuchten das Potenzial körperlicher Aktivität, die Beziehung zwischen Depression und vorzeitiger Mortalität günstig zu beeinflussen.

› **Methoden:** Existierende Metaanalysen wurden über PubMed identifiziert. Es wurden nur Arbeiten zur unipolaren Depression eingeschlossen.

› **Ergebnisse:** Der Zusammenhang zwischen Depression und Übersterblichkeit stellt einen robusten epidemiologischen Befund dar. Dieser Zusammenhang kann auf die Tatsache zurückgeführt werden, dass Menschen mit Depressionen ein erhöhtes Risiko für Herz-Kreislauf-Erkrankungen aufweisen und mehr kardiovaskuläre Risikofaktoren akkumulieren. Die kausalen Zusammenhänge sind komplex. Während Depressionen zu Herz-Kreislauf-Erkrankungen führen können, können Depressionen auch eine Folge akuter oder chronischer Herz-Kreislauf-Erkrankungen sein. Regelmäßige körperliche Aktivität und eine höhere kardiorespiratorische Fitness verringern das Risiko einer vorzeitigen Sterblichkeit im Zusammenhang mit Depressionen.

› **Diskussion:** Bei psychiatrischen Patienten sollte physischen Gesundheitsproblemen mehr Aufmerksamkeit geschenkt werden. Der Förderung von körperlicher Aktivität und Fitness sollte ein hoher Stellenwert eingeräumt werden, da sie sich sowohl auf die körperliche als auch auf die mentale Gesundheit positiv auswirken können.

SCHLÜSSELWÖRTER:
Fitness, Herz-Kreislauf-Erkrankungen, Körperliche Aktivität, Mortalität

Introduction

The point prevalence of major depressive disorder (MDD) varies between 4-7% in the general population and lifetime prevalence is between 15-20%. MDD is more prevalent among women than men (about 2:1 ratio), and the median age of onset is around 25 years (4, 36). Projections assume that depression will be the leading cause of disability worldwide by 2030 (31). Depression is highly prevalent in cardiac patients with 30-45% of patients with coronary artery disease suffering from clinically relevant symptoms of depression, and 15-20% meeting the diagnostic criteria for MDD (18).

Depression is accompanied by biological and behavioral features that may be harmful to physical health (3). Since the 1980s, a plethora of studies has appeared around the globe investigating the link between depression, cardiovascular disease (CVD) and mortality. ›

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With this review, we pursue three objectives: First, to perform an umbrella review on the association between depression and (i) excess mortality, (ii) CVD, and (iii) cardiovascular risk factors. Second, to provide an overview of mechanisms that may explain the association between depression, CVD and excess mortality. Third, to discuss clinical implications from a general perspective, and more specifically, shed light on the potential of physical activity to favorably influence the relationship between depression and premature mortality.

Material and Methods

For this umbrella review, meta-analyses were identified via PubMed (for description of search terms see supplementary online material). Various CVD outcomes were considered in this umbrella review including myocardial infarction, coronary heart disease, stroke, and hypertension. Moreover, although a structured clinical interview is the gold standard assessment for a clinical diagnosis of depression, we also included meta-analyses of studies in which depressive symptoms were assessed via self-report questionnaires or a combination of different assessment methods. Finally, we focused on meta-analyses that examined unipolar depression, whereas we did not include meta-analyses on bipolar depression.

Results of Umbrella Review – Association between Depression, Mortalitiy and Cardiovascular Diseases

Excess Mortality

The most important indicators of excess death in people with mental illnesses (used by the American Psychiatric Association as a term to collectively refer to all diagnosable mental disorders involving (a) significant changes in thinking, emotion and/or behavior, and (b) distress and/or problems functioning in social, work of family activities; see https://www.psychiatry.org) are standardized mortality rates, mortality rate ratios, potential years of life lost, average age at death or life expectancy (26). Researchers have estimated that in patients with severe mental illnesses (including those with unipolar depression) all-cause mortality is 2 to 3.5 times higher compared to the general population (13), and that life expectancy is 20% lower than in the general population (47). It has also been estimated that people with severe mental illness die on average 10-25 years earlier than the general population (4, 8, 9, 13, 27). Excess mortality in people with severe mental illnesses is to some extent due to markedly higher death rates from unnatural causes such as suicides, accidents, homicide and alcohol misuse (4, 13, 35, 38). Nevertheless, the absolute number of unnatural deaths is relatively small compared to that of deaths due to natural causes such as circulatory disorders, chronic lung disease, and infectious diseases (25). For instance, in a recent 6-year prospective study, De Mooij et al. (13) showed in people with severe mental illness that death from natural causes accounted for 86% of deaths (versus 14% for unnatural causes of death). Among natural causes, the highest percentage of deaths was due to diseases of the circulatory system (36.6%), followed by disease of the digestive system (16.7%), the respiratory system (6.7%) and neoplasms (6.7%).

Meta-analyses (k=14) that examined the relationship between depression and excess mortality (Table 1) were mainly based on community or population-based samples; some of them focused on special populations such as patients with diabetes, women or elderly people. The meta-analyses uniformly confirm that all-cause and cardiovascular mortality are higher in people with depression compared to the general population, with risk estimates for premature death varying between 33% to 156%. Moreover, few significant moderating influences were observed. An increased relative risk was found for shorter follow-up (Cuijpers et al., 2014b), studies with lower methodological quality (Brandao et al., 2018), and among in-patients compared to out-patients (Walker et al., 2015).

Cardiovascular Diseases

Meta-analyses (k=15) that focused on CVD outcomes (Table 2) mainly included community or population-based samples of initially healthy adults, and all included original studies with a prospective design. A few meta-analyses focused on older adults (k=2) and patients with diabetes (k=2). Some meta-analyses specifically focused on patients with pre-existing CVDs such as stroke to examine whether patients with existing CVD are at increased risk of developing depression later in life (1); however, a summary of this (extensive) literature would be beyond the scope of this review. Therefore, our umbrella review focuses only on meta-analyses that examined whether patients with depression are more likely to develop CVD later in life. The reviewed quantitative syntheses at least partly confirmed that people with depression have a higher risk of incident CVD as risk ratios ranged from 2% to 104%. In some works, the overall effect sizes were not significant (Pan et al., 2011; Eurelings et al., 2018; Lin et al., 2018). Overall, few relevant moderating influences were identified. Nevertheless, in three meta-analyses, clinical depression was associated with a greater risk than symptoms of depressed mood (Rugulies, 2002; van der Kooy et al., 2007; Gan et al., 2014). This might suggest a dose-response effect, but other neurobiological entities (major depression, minor depressive syndrome due to other causes) are also possible.

Cardiovascular Risk Factors

The risk factors considered in this review were metabolic syndrome (MetS) (Table 3), diabetes (Table 4) and overweight/obesity (Table 5), whereas no meta-analyses were identified for dyslipidemia. A distinction is made between cross-sectional and longitudinal evidence. Due to space constraints, Tables 3-5 are presented as supplementary online material.

MetS is defined as a cluster of five conditions (increased blood pressure, high blood sugar, excess abdominal fat, abnormal cholesterol and triglyceride levels) that can lead to heart disease, stroke, or type 2 diabetes. MetS proved to be closely associated with CVD mortality in previous meta-analyses (14). As shown in Table 3, meta-analytic findings (cross-sectional: k=4, longitudinal: k=1) support a close relationship between depression and MetS. Cross-sectional evidence suggests that the risk of MetS is increased by 42% to 57% in people with depression. People with depression were also significantly more likely to develop a MetS, whereas people with MetS had a higher risk to develop a depression. One meta-analysis found that the association between depression and MetS is stronger in men than women (Moradi et al., 2021). Otherwise, few relevant moderators were found.

Diabetes is a chronic disease characterized by an inability of the pancreas to produce insulin or by low insulin sensitivity of target tissues. A close relationship was observed between diabetes and premature cardiovascular mortality in previous meta-analyses (39). Most of the examined meta-analyses (cross-sectional: k=13; longitudinal: k=9) focused on type 2 diabetes, but other forms (type 1, gestational diabetes) were also considered. In total, 11 cross-sectional meta-analyses fully supported a significant relationship between depression and

diabetes. No significant associations were observed by Nouwen et al. (2011). However, these authors did not compare participants with diagnosed diabetes to controls, but focused on people with impaired glucose metabolism or undiagnosed diabetes. When limiting the analyses to patients with a psychiatric diagnosis of MDD, Vancampfort et al. (2016) found that the relative risk of type 2 diabetes was increased by 43% in people with depression (RR=1.43). However, there was a high degree of heterogeneity (95% CI=0.88-2.25) partly explaining why the relationship did not reach significance. Longitudinal studies uniformly confirmed that people with depression are at risk of incident diabetes, and that patients with diabetes have an increased risk of becoming depressed over time. The only exception was the meta-analysis of Tong et al. (2016) where an increased risk of developing depression was only found in people with previously diagnosed diabetes, but not in participants with impaired glucose tolerance or new onset diabetes. Few significant moderators were identified.

Overweight/obesity are associated with a markedly increased risk for premature death (10). Meta-analyses on this outcome (longitudinal: k=5; cross-sectional: k=10) are summarized in Table 5. Overweight/obesity were associated with depression in all meta-analyses that focused on children, adolescents and adults (k=9), whereas an inverse relationship was found in the meta-analysis limited to older people. Among younger populations, the risk estimates were stronger for obesity than overweight, and the increased risk varied between 7% and 147%. Three meta-analyses found that the link between depression and overweight/obesity is stronger among women than men (de Wit et al., 2010, Pereira et al., 2017, Queck et al., 2017). That depression predicts overweight/obesity was supported at least partly in all four available meta-analyses containing longitudinal data. However, depression predicted obesity more strongly than overweight. Finally, all four meta-analyses confirmed that overweight/obesity increase the risk of incident depression, with risk estimates varying between 8% and 57%.

Discussion

Discussion of Meta-Analytic Evidence

Based on the existing meta-analyses, the association between depression and excess mortality can be considered as a robust epidemiological finding (4). This association is (in part) attributable to the fact that people with depression are at increased risk for CVDs and accumulate more cardiovascular risk factors. The present review also suggests that the causal association of depression with CVD and important cardiovascular risk factors is complex and to some extent bidirectional. For instance, while depression is associated with incident CVD, depression can also be a consequence of cardiac events (1, 22) and worsen prognosis (2).

In most meta-analyses, risk estimates were highly heterogeneous. This is due to methodological differences between the original studies. Moreover, risk estimates varied greatly between meta-analyses as a result of different search strategies, inclusion criteria, study populations, study designs, methods and diagnostic criteria to assess depression and risk measures, and duration of follow-up period. While most meta-analyses focused on adult populations, some confirmed that depression is already associated with increased CVD risk in children and adolescents. This is consistent with the American Heart Association's statement that depression might contribute to early CVD and accelerated atherosclerosis already among children and adolescents, independent of other risk factors (16). In most meta-analyses, the assessment of depression was not a relevant moderator, although some evidence exists that depression and CVD outcomes show a stronger link if depression is established via clinical interview.

Several limitations should be considered when interpreting the meta-analytic findings. First, in most prospective studies, depression was only measured once, although the course of depression can take various forms (7). Second, depression is linked to other CVD risk factors such as smoking or physical inactivity. Since many original studies did not assess these lifestyle-related factors, they were not always adequately controlled for in the meta-analyses (7). Moreover, many risk estimates became weaker in more extensively adjusted models (e.g., adjusted for sex, age, socioeconomic status, other health behaviors), which points towards some confounding. However, the associations mostly remained significant even after adjustment. Finally, while publication bias can inflate meta-analytic risk estimates, controlling for this factor did not change the findings significantly.

Mechanisms Linking Depression and Cardiovascular Disease

The underlying pathophysiological mechanisms linking depression and CVD are complex and still not well understood (9). Currently, multiple plausible biological mechanism are proposed (4, 7, 17, 18, 31, 36, 47, 49). Possible pathways include (i) changes in cardiac rhythm and cardiac autonomic tone (e.g., higher risks for ventricular tachycardia, increased resting heart rates, decreased heart rate variability, increased heart rate responses after exposure to stress, reduced baroreflex sensitivity, increased heart rate turbulence), (ii) hemorheological alterations (e.g., changes in blood viscosity and hemoconcentration), (iii) increased platelet aggregation and blood coagulation, (iv) neurohormonal changes, dysregulations of the autonomic nervous system and alterations of the hypothalamic-pituitary-adrenal axis (e.g., higher levels of plasma and urinary catecholamines, hypercortisolism and glucocorticoid resistance), or (v) alterations in the activity of the immune system and inflammation (e.g., increased levels of tumor necrosis factors and other pro-inflammatory cytokines/markers, shifts in the relative distribution of T and B lymphocytes). Further potential mechanisms include endothelial dysfunction (7, 17, 18, 36), oxidative stress (9), mitochondrial dysfunction (9), and higher risk for obstructive sleep apnea (43). Some researchers suggest that depression and CVD share common underlying processes. Hence, depression and CVDs might result from a disseminated vascular disease, which may lead to lesions of brain and heart structures. Plasminogen activator inhibitor-1, tissue plasminogen activator and brain-derived neurotrophic factor could be such underlying processes that are linked to both diseases (3, 4, 17, 18, 31, 36).

Another reason why people with depression have higher risks for CVDs might be that primary and secondary prevention is much less successful in people with mental illnesses (9). For instance, previous research has shown that people with depression are less likely to receive adequate medical care because physical conditions are overseen and/or not treated. Physicians may wrongly assume that physical conditions are psychological and/or psychiatric patients may be less able or likely to communicate their physical health needs (25, 33, 35, 47). It is also assumed that some physicians feel uncomfortable dealing with psychiatric patients (due to stereotypes), and that such negative attitudes can result in poor communication and delays in diagnostic procedures or treatment (33, 35, 47). ›

Research also revealed that people with mental illnesses engage in more unhealthy behaviors (e.g., unbalanced diet, higher alcohol consumption, tobacco smoking) and that depression acts as a barrier towards a necessary change of health behaviors (4, 17, 25, 27, 33, 36). Moreover, treatment adherence to CVD-risk-lowering medication (e.g., statins, antiplatelet drugs, angiotensin-converting-enzyme inhibitors, anti-hypertensive medication) is lower in people with depression compared to healthy controls (4, 17, 33, 36). Increased CVD morbidity may also be the result of the side effects associated with specific treatments of mental illnesses (e.g., psychotropic medication), either directly or through weight gain (25, 27, 36). Socioeconomic disadvantage is more frequently observed among people with mental illnesses, which in turn is associated with more health-risk behaviors and reduced access to health care (26). Finally, adverse childhood experiences might act as a common potent risk factor for both depression and CVD (45).

In summary, the relationship between depression and CVD reflects a complex multifactorial problem (26, 47). However, mediation studies show that none of the above influences account for more than a small proportion of the associated risk (7). Some researchers therefore proposed a "perfect storm" model, suggesting that multiple factors and environmental events are needed to activate critical pathophysiological processes (36).

Clinical Implications

Given the high worldwide prevalence of depression and the fact that the mortality gap between people with and without mental illnesses has not narrowed over the past years (26), even in countries with the highest-quality and most equitably distributed healthcare systems in the world (47), people with depression should become a priority target population for public health strategies (4).

To minimize morbidity and mortality, it is essential to understand that depression and CVD are often comorbid and that both conditions should be treated simultaneously (37). More specifically, the following public health measures are proposed: First, to overcome systemic barriers to healthcare provision, integrated care models, such as collaborative care (48), seem necessary (e.g., through co-location of physical and mental health services, use of case managers or other liaison staff, facilitated sharing of electronic health records) (12, 26, 27). This seems relevant as "major improvements in health outcomes for people with mental illnesses are unlikely without system wide commitment to achieving equality in health service delivery and access" (26, p. 5). Second, additional incentives for identifying physical health problems in people with depression are required (e.g., through increasing funding models allowing general practitioners to spend more time with patients with more complex problems, routine screening and follow-up for CVD risk in psychiatric institutions) (9, 12, 35). Third, more systematic efforts to educate and increase health literacy among patients are needed. This can be achieved through lifestyle interventions (e.g., promotion of healthy behavior via counselling), enhanced smoking cessation efforts, or technology-based tools to improve adherence to medication (11, 12, 27, 31, 33). Fourth, among patients with existing CVDs, depression often remains underdiagnosed and untreated (18), especially because many general practitioners and cardiologist do not believe that their role includes the detection of depression in their patients (17, 30). Routine screening of cardiac patients with a short screening tool is one possible solution (17, 18, 30, 37). After a positive screening, however, confirmatory psychiatric interviews are required and further treatment should be provided. According to Carney et al. (7), different treatments for depression have been tested in patients with CVD including antidepressant medication, cognitive behavioral therapy (CBT), interpersonal psychotherapy, stepped care and exercise training. In summary, studies show that these interventions were associated with a stronger reduction of depressive symptoms compared to the control conditions. Large intervention trials have also tested whether treatment for depression has positive effects on cardiac outcomes. The findings of these studies were not fully conclusive, but evidence suggests that if depression improves, positive effects might be found for survival (7). With regard to psychopharmacological treatment, selective serotonin reuptake inhibitors are preferred for patients with coronary heart disease (50) and could even improve cardiac outcome (20). However, the "benefits of improved psychiatric status with antipsychotics and psychotropic agents other than selective serotonin reuptake inhibitors, which may increase risk of bleeding and QT prolongation, need to be carefully weighed against their potential for elevated cardiometabolic risk, which differs across available agents" (9, p. 176).

In summary, reducing CVD risk in patients with mental illnesses is a complex endeavor, requiring concerted action on different levels as well as cooperation between different stakeholders and professional groups (11). The fact that the mortality gap between people with versus without mental illnesses stubbornly persists is a clear indication that national strategies need to be improved, and that without the development of alternative approaches to promoting and treating the physical health of people with mental illness, it will be difficult to successfully address the disparity in mortality outcomes (8, 25).

Depression, Mortality and Physical Activity

The final objective of our review is to discuss the potential of physical activity as a "game changer" when it comes to reducing the mortality gap between people with and without mental illnesses. We therefore review original studies in which researchers investigated whether physical activity (or cardiorespiratory fitness [CRF]) can buffer some of the cardiovascular health risks associated with depression.

From general population studies, it is well known that regular physical activity reduces the risk of premature death even if doses are small (23). The same is true for adequate CRF (21). However, people with depression are less likely to accumulate sufficient amounts of physical activity, engage in more sedentary activities and have lower CRF than (mentally) healthy counterparts (4, 5). By contrast, previous studies with people with depression demonstrate that regular exercise training leads to clinically meaningful improvements in CRF (24, 42), already after short periods of time (29).

Research on whether physical activity can contribute to a reduction of the mortality risk of people with mental illnesses is still in an early stage, but first indications for the plausibility of this assumption are emerging. For instance, a longitudinal study with 5'888 individuals from US communities showed that both individuals with depressive symptoms and with physical inactivity were at greater risk for premature cardiovascular mortality, with the highest probability found in those who combined both risk factors. After adjustment for further confounders, physical activity was associated with a 26% reduction in cardiovascular mortality. This rate was similar in people with and without established coronary heart disease (52). Similar findings were observed in the Finland, Italy, and the Netherlands Elderly (FINE) study with 909 elderly men (70-90 years) who were free of CVD and diabetes at baseline. During the 10-year

follow-up, both depressive symptoms and lower physical activity levels were significantly associated with an increased cardiovascular mortality risk. Adjustment for physical activity led to a 9% decrease in mortality risk in people with depression (19).

In the Cooper Center Longitudinal study, comparable effects were reported for CRF. One publication placed a specific focus on men (N=5'240, aged 20-86 years) with emotional distress including depression, anxiety, suicidal ideation, and a history of psychiatric or psychological counselling. The results revealed that, if compared to participants with low CRF, the risk of premature death was considerably lower among men with moderate or high CRF (46% and 53% reduced risk, respectively), even after controlling for other relevant mortality predictors (46). In a second publication, Rethorst et al. (41) tested the impact of depression, MetS, and cardiorespiratory fitness on mortality. In total, 47'702 adults (aged 20-75 years) were included in the analyses. In summary, findings revealed that history of depression and MetS were independent risk factors of increased mortality, with the highest risk found in individuals combining both conditions. By contrast, moderate or high CRF were associated with a 36% and 50% reduced mortality risk, respectively. Moderate or high CRF were also associated with lower mortality in individuals with a history of depression and/or MetS, which suggests that interventions to promote CRF could reduce the health burden of those with depression, independent of the presence of MetS. Lastly, Willis et al. (51) examined whether fitness assessed in midlife buffers the relationship between depression in later life (≥65 years) and mortality in 17'989 men and women (M=50 years). The findings showed that participants with high CRF had a 16% lower risk of developing depression later in life. Moreover, in participants without depression, high CRF was associated with a 61% lower mortality risk compared to low CRF. Most importantly, after a depression diagnosis, participants with high CRF still had a 56% lower risk of premature death compared to people with low CRF. Based on these findings, the authors emphasized the importance of midlife fitness in primary prevention of depression and subsequent CVD mortality, and claimed that physical activity can play an important role in the promotion of healthy aging, also among people who develop a mental illness. Regarding secondary prevention, in a study with 522 patients with coronary heart disease participating in cardiac rehabilitation, improved CRF was related to a decrease in depressive symptoms and its associated mortality after a mean follow-up of 3.5 years (28).

In summary, emerging evidence exists that physical activity has the potential to moderate the relationship between depression, CVD and mortality. Currently, research is still at an early stage and more insight is needed into the causal relationships and mechanisms that link these constructs. It is also important to note that physical activity not only has the potential to mitigate the effects of depression on future CVD and mortality, but also plays and important role in reducing depressive symptoms in cardiac rehabilitation (53) or the mortality risk of cardiac patients with existing depression (28).

Conclusions

The present review highlights that it is essential to pay more attention to the poor physical health of psychiatric patients. "Despite numerous calls to take their physical health seriously, psychiatric patients still suffer excess morbidity and mortality from physical causes, and they receive inferior physical health care" (35, p.331). It was also seen that in the treatment of people with depression, high priority should be given to the promotion of physical activity and fitness, as they are beneficial for both physical and mental health. Nevertheless, Belvederi Murri et al. (4) observed that the importance of physical activity is still downplayed in clinical practice, and exercise therefore remains under-prescribed (6). Reasons could be lack of awareness and knowledge of clinicians regarding how to deliver physical activity to people with depression, prejudice that patients will not adhere to prescribed physical activity and therefore not achieve their goals, and reluctance to cooperate with different professionals such as clinical exercise physiologists, health coaches, wellness specialists, and/or physical therapists (4). Despite this, it is encouraging that several clinical guidelines have meanwhile included physical activity as a treatment for depression (32, 44), hereby providing concrete prescriptions for the implementation of physical activity programs (34, 40, 44). Physicians and psychiatrists willing to introduce exercise as a standard treatment for depression can be seen as the starting point of a collaborative approach (3). At this point, however, sustained efforts and well-coordinated action is needed on regional and national levels to establish structures and environments that are conducive to more systematically assess physical activity status and promote physically active lifestyles among people with mental illnesses (15). Importantly, the main focus should be placed on those who might benefit most: namely those who are chronically inactive, have very poor fitness, and/or multiple CVD risk factors.

Conflict of Interest

The authors have no conflict of interest.

Table 1

Meta-analyses on the association between depression and excess mortality. RR=Relative risk, OR=Odds ratio, HR=Hazard ratio, LMICs=Low-to-middle income countries. *Full references are shown in supplementary online material. **The most extensively controlled risk estimates are reported if meta-analyses provided risk estimates for uncontrolled and controlled models. ***The lowest and highest risk estimates are highlighted with bold font.

AUTHORS, YEAR*	STUDY POPULATION	DEFINITION OF DEPRESSION	OUTCOME	NUMBER OF STUDIES	NUMBER OF PARTICIPANTS	RISK ESTIMATE**,***
Cuijpers et al. (2002)	General population	Dichotomous measures (yes/no) or with a cut-off point indicating severe depressive symptoms	All-cause mortality	25	Total: 106,628 Depression: 6,416	RR=1.81 (1.58-2.07)
Baxter et al. (2011)	General population	Clinical diagnosis based on ICD or DSM diagnostic criteria	All-cause mortality	21	153,965	RR=1.67 (1.48-1.90) (total) RR=1.92 (1.65-2.23) (major depression)
Cuijpers et al. (2013)	General population	Major depressive disorder and sub-threshold depression (measured via clinical interview or questionnaire)	All-cause mortality	22	Total: 18,705 Subthreshold: 3,238 Major: 1,147	OR=1.58 (1.31-1.89) (major vs. non-depressed) **OR=1.33 (1.11-1.61) (subthreshold vs. non-depressed)**
Hofmann et al. (2013)	People with diabetes	Depression measured by self-reports versus clinical interview	All-cause and cardiovascular mortality	16	Total: 107,944 Depression: 19,589	**HR=2.56 (1.89-3.47) (self-reported symptoms)** HR=1.49 (1.15-1.93) (clinical interview)
Park et al. (2013)	People with diabetes	Depression measured by clinical interview, self-report or antidepressant prescription	All-cause mortality	10	Total: 42,363 Depression: 5,325	HR=1.50 (1.35-1.66)
van Dooren et al. (2013)	People with diabetes	Depression measured by yes/no, clinical interview or self-report	All-cause and cardiovascular mortality	16	Total: 109,046 Depression: 21,443	HR=1.46 (1.29-1.66) (all-cause) HR=1.39 (1.11-1.73) (cardiovascular)
Cuijpers et al. (2014a)	Women	Depression measured by self-reports or clinical interview	All-cause mortality	13	Total: 41,331 Depression: 5,505	OR=1.97 (1.63-2.37 (depressed men vs. depressed women) OR=2.04 (1.76-2.37) (depressed vs. non-depressed men) OR=1.55 (1.32-1.82) (depressed vs. non-depressed women)
Cuijpers et al. (2014b)	General community vs. patients with specific illnesses	Depression measured by self-reports or clinical interview	All-cause mortality	293	Total: 1,813,733 Depression: 135,007	OR=1.52 (1.45-1.59) (depressed vs. non-depressed) OR=1.59 (1.47-1.71) (community samples)
Walker et al. (2015)	General population	Diagnosed depression	All-cause mortality	43	Information not available	OR=1.71 (1.54-1.90)
Correll et al. (2017)	General population	Diagnosed depression	Cardiovascular mortality	7	465,311	HR=1.63 (1.25-2.13)
Brandao et al. (2018)	Elderly people living in LMICs	Depression measured by self-reports or clinical interview	All-cause mortality	10	Total: 13,828 Depression: 2,402	RR=1.60 (1.37-1.86)
Eurelings et al. (2018)	Older community-dwelling populations	Depression measured with the Geriatric Depression Scale	All-cause mortality	21	46,859	HR=1.44 (1.35-1.53) (all-cause) HR=1.50 (1.35-1.66) (non-cardiovascular) HR=1.33 (1.18-1.51) (cardiovascular)
Wei et al. (2019)	Older community-dwelling populations	Clinically relevant depression measured by self-reports, clinical interview or use of anti-depressant medication	Cardiovascular and all-cause mortality	61	198,589	RR=1.34 (1.27-1.42) (all-cause) RR=1.31 (1.20-1.43) (cardiovascular)
Inoue et al. (2020)	People with diabetes	Depression measured by self-reports or clinical interview	Cardiovascular mortality	8	20,930	RR=1.47 (1.21-1.77)

Table 2

Meta-analyses on the association between depression and cardiovascular diseases. RR=Relative risk, OR=Odds ratio, HR=Hazard ratio, MI=Myocardial infarction, CHD=Coronary heart disease, CVD=Cardiovascular disease, RFS=Risk factor score, HT=Hypertension, CED=Cerebrovascular disease, CD=Coronary death. *Full references are shown in supplementary online material. **The most extensively controlled risk estimates are reported if meta-analyses provided risk estimates for uncontrolled and controlled models.***The lowest and highest risk estimates are highlighted with bold font.

AUTHORS, YEAR*	STUDY POPULATION	DEFINITION OF DEPRESSION	OUTCOME	NUMBER OF STUDIES	NUMBER OF PARTICIPANTS	RISK ESTIMATE**,***
Rugulies (2002)	Initially healthy subjects	Clinical depression or depressive symptoms	Myocardial infarction or coronary death	11	36,549	RR=1.64 (1.29-2.08)
Nicholson et al. (2006)	Healthy populations	Depression or depressive symptoms	Fatal CHD or incident myocardial infarction (fatal and nonfatal)	21	124,509	RR=1.90 (1.48-2.42)
van der Kooy et al. (2007)	Adults/elderly people, community dwelling or general practice samples	Depression or depressive symptoms	Fatal or non-fatal CVD	MI: 8 CHD: 16 Stroke: 10 CVD: 7	Information not available	OR=1.60 (1.34-1.92) (MI) OR=1.48 (1.29-1.69) (CHD) OR=1.43 (1.17-1.75) (stroke) OR=1.63 (1.26-2.12) (CVD)
Pan et al. (2011)	Non-institutionalized adults (≥18 years)	Depression or depressive symptoms	Stroke morbidity and mortality, broad definition (fatal, nonfatal, ischemic, hemorrhagic)	28	317,540	HR=1.55 (1.25-1.93) (fatal stroke) HR=1.25 (1.11-1.40) (ischemic stroke) HR=1.21 (0.91-1.62) (non-fatal) HR=1.16 (0.80-1.70) (hemorrhagic)
Dong et al. (2012)	Community or population-based samples	Depression or depressive symptoms	Fatal or non-fatal stroke incidence	17	206,641	RR=1.34 (1.17-1.54)
Meng et al. (2012)	Apparently healthy normotensive individuals	Depression or depressive symptoms	Hypertension determined in interview, use of antihypertensive medications, or self-reported or recorded diagnosed hypertension)	9	22,367	RR=1.42 (1.09-1.86)
Valkanova et al. (2013)	Elderly people (aged ≥50 years)	Depression or depressive symptoms	Vascular risk factor composite score, cardiovascular disease, stroke	RFS: 18 CVD: 10 Stroke: 10	RFS: 17,899 CVD: 2,184 Stroke: 16,221	OR=1.15 (1.02-1.28) (RFS) OR=1.40 (1.08-1.80) (CVD) OR=1.80 (1.24-2.62) (stroke)
Gan et al. (2014)	Community or population-based samples, free of CHD at entry	Depression or depressive symptoms	Coronary heart disease or myocardial infarction	CHD: 39 MI: 12	893,850	RR=1.30 (1.22-1.40) (coronary heart disease) RR=1.30 (1.18-1.44) (myocardial infarction)
Barlinn et al. (2015)	Community-, population-, or registry-based samples without history of stroke or transient ischemic attack	Depression or depressive symptoms	First-ever stroke during the follow-up period, including fatal and non-fatal ischemic stroke and intracerebral hemorrhage	28	68,139	OR=1.43 (1.19-1.72)
Wu et al. (2016)	Community or population-based samples	Depression or depressive symptoms	Myocardial infarction or coronary death	MI: 9 CD: 8		HR=1.22 (1.13-1.32) (total) HR=1.31 (1.09-1.57) (MI) HR=1.36 (1.14-1.63) (CD)
Correll et al. (2017)	People without prior subclinical CVD	Diagnosed depression	Cardiovascular disease, coronary heart disease, cerebrovascular disease	CVD: 13 CHD: 6 CED: 4	CVD: 964,666 CHD: 491,238 CED: 45,899	HR=1.72 (1.48-2.00) (CVD) HR=1.63 (1.33-2.00) (CHD) **HR=2.04 (1.02-3.96) (CED)**
Eurelings et al. (2018)	Community-dwelling elderly people	Depression (Geriatric Depression Scale)	Stroke and myocardial infarction	Stroke: 10 MI: 8	Stroke: 23.337 MI: 21,377	HR=1.36 (1.18-1.56) (stroke) HR=1.08 (0.91-1.29) (MI)
Lin et al. (2018)	Adults	Depression or depressive symptoms	CAC score measured with computed tomography and quantified using the Agatston method	15	32,884	OR=1.15 (1.04-1.28) (diagnosed depression) **OR=1.02 (0.97-1.07) (depressive symptoms)**
Farooqi et al. (2019)	People with diabetes type 2	Depression or depressive symptoms	Coronary heart disease, stroke, cardiovascular mortality	9	960,611	OR=1.48 (1.19-1.85) (cardiovascular mortality) OR=1.37 (1.17-1.61) (CHD) OR=1.33 (1.21-1.37) (stroke)
Inoue et al. (2020)	People with diabetes	Depression or depressive symptoms	Non-fatal cardiovascular disease events	11	1,017,628	RR=1.35 (1.20-1.53)

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