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## Review article

# Cardiovascular risk in individuals with depression<sup>☆</sup>

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## ABSTRACT

Depression and cardiovascular diseases (CVD) are both common illnesses. Several studies demonstrated that depressed individuals have higher mortality compared to age- and gender-matched population, with an excess of cardiovascular deaths. There is a bidirectional association between depression and CVD. Several factors can interact and influence this relationship: poverty and social inequality, reduced accessibility to health care, biological alterations (as reduced heart rate variability, endothelial dysfunction, increased inflammation and platelet function, and hyperactivity of hypothalamic-pituitary-adrenal axis), side effects of psychiatric medication, lower adherence to medical treatments, and higher frequency of cardiovascular risk factors (higher tobacco use, physical inactivity, obesity, diabetes mellitus). This article aims to update the current evidence of the possible mechanisms involved in the association between depression and CVD.

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## Risco cardiovascular em indivíduos com depressão

### RESUMO

A depressão e as doenças cardiovasculares (DCV) são patologias frequentes. Estudos demonstram que indivíduos deprimidos têm maior mortalidade quando comparados a indivíduos do mesmo sexo e faixa etária, com um excesso de mortes por doenças cardiovasculares. Há uma associação bidirecional entre depressão e doenças cardiovasculares. Vários fatores podem interagir e influenciar esta relação: a pobreza e a desigualdade social, dificuldade de acesso a cuidados de saúde, alterações biológicas (menor variabilidade da frequência cardíaca, disfunção endotelial, atividade inflamatória e função plaquetária aumentadas, hiperatividade do eixo hipotálamo-hipófise-adrenal), efeitos colaterais de medicações psiquiátricas, menor adesão aos tratamentos e maior frequência de fatores de risco

### Palavras chave:

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<sup>☆</sup> Study conducted at Centro de Saúde Escola Barra Funda “Dr. Alexandre Vranjac”, Irmandade da Santa Casa de Misericórdia de São Paulo, São Paulo, SP, Brazil.

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cardiovasculares (pior estilo de vida, maior frequência de tabagismo e inatividade física e maior prevalência de obesidade e diabetes mellitus). O objetivo deste artigo é revisar as evidências sobre a associação entre depressão e doenças cardiovasculares.

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## Introduction

Depression is the leading cause of disability (measured by years lived with disability), and the fourth leading cause of disease burden worldwide.<sup>1</sup> It is a common disorder; the World Mental Health Survey found a lifetime prevalence of depression of 14.6% in developed countries and of 11.1% in developing countries. The same study found a lifetime prevalence of depression in the metropolitan region of São Paulo of 18.4%.<sup>2</sup>

Several studies point to a higher mortality in individuals with psychiatric disorders, including depressive subjects.<sup>3-8</sup> This is partly explained by a high suicide rate, but these individuals also present high all-cause and cardiovascular mortality.<sup>5,9,10</sup> Cardiovascular disease (CVD) is the leading cause of death worldwide, and also in Brazil.<sup>1,11</sup> As described above, the impact of CVD among people with mental disorders (including depression) is higher than observed in general population.

There are several mechanisms that can influence this association: psychotropic medication side effects, poor lifestyle, reduced access to health care, increased frequency of smoking, and association with cardiovascular risk factors. The aim of this article is to review the evidence on the different factors that can influence the increased cardiovascular risk in individuals previously diagnosed with depression.

## Depression, mortality, and cardiovascular events

Despite the known impact of depression on quality of life, the association between increased mortality and depression may be usually unrecognized by physicians. The first study that showed higher mortality in psychiatric patients was published in 1841, conducted by the British epidemiologist William Farr.<sup>12,13</sup> According to that study, inpatients with mental illness in London had three to 14 times higher all-cause mortality compared to the general population. Recent studies support these results, considering either individuals with severe psychiatric disorders or only those with depression. Most studies observed that CVD was the main cause of death.<sup>3,8,14-23</sup>

An English cohort of mental health service users with a three-year follow-up was conducted between 2007 and 2009, and included 11,697 individuals with depressive disorders. It was found a standardized mortality ratio of 1.53 (95% CI: 1.36 to 1.72) in men and 1.18 (95% CI: 1.06 to 1.31) in women.<sup>6</sup> The National Health Interview Survey evaluated 57,897 white individuals in the United States aged 25 years or older in 1989, and their vital status in the National Death Index after two years. A total of 615 individuals were depressed in that survey. The relative risk for death by all causes in men was 2.4 (95% CI:

1.4 to 4.2). However, no difference was found for depressive women.<sup>4</sup>

A Danish register-based cohort with 5,558,959 individuals verified cause-specific mortality and its association with hospital admission for psychiatric conditions. Patients admitted with unipolar depressive disorder had higher mortality rates in all age groups. There were higher mortality rate ratios (MRR) for cardiovascular causes in both men (MRR 1.59; 95% CI: 1.53 to 1.65) and women (MRR 1.47; 95% CI: 1.43 to 1.52).<sup>20</sup> Most studies support these findings, with higher mortality and higher proportion of cardiovascular deaths in depressed individuals (Table 1).<sup>3,8,14-21,24</sup>

There is also consistent evidence on the association between depression and non-fatal cardiovascular events (myocardial infarction and coronary artery disease). This association is bidirectional: individuals with depression have a higher incidence of CVD and individuals with CVD (mainly acute events) have a higher incidence of depression.<sup>25-27</sup> Two systematic reviews have studied the impact of depression on the incidence of cardiovascular events. Hemingway et al. observed an increased incidence of CVD in individuals with depression. The relative risk (RR) in the included studies ranged from 1.23 to 5.4.<sup>26</sup> Wulsin et al. found a combined RR for cardiovascular events in patients with depression of 1.64 (95% CI: 1.41 to 1.90).<sup>25</sup>

## Mechanisms of association

The association between depressive disorders and the incidence of cardiovascular events is explained by several factors, detailed below. Table 2 shows the known possible mechanisms of association between depressive disorders and the incidence of CVDs.

### Vulnerability and accessibility

According to the World Health Organization (WHO), people with mental health conditions, including depression, should be considered a vulnerable group, ensuring their inclusion in development programs and strategies of promotion and protection of their rights. Vulnerable individuals share common challenges in the exercise of their civil and political rights; have higher rates of stigma, discrimination, and decreased employment and educational opportunities; suffer violence and abuse; and have reduced access to health and social services.<sup>28</sup> The International Guidelines for Biomedical Research Ethics defines vulnerability as the inability to protect one's own interests, including any group or individual characteristic that could reduce the ability of self-determination.<sup>29</sup>

There is substantial evidence to support that people with mental disorders have experienced more physical or sexual violence than the general population. They are more often stigmatized, resulting in barriers in finding employment, and

**Table 1 – Studies evaluating all-cause and cardiovascular mortality in individuals previously diagnosed with depression.**

Author and year of publication	Study design and population	Sample size	Results
Zheng D, 1997 <sup>4</sup>	Cohort in the United States	57,897 white individuals 615 depressed individuals	Death from all causes RR 2.4 (95% CI: 1.4 to 4.2) in male subjects No higher mortality in women (RR 1.0; 95% CI: 0.4 to 2.6)
Whooley M, 1998 <sup>7</sup>	Cohort (Study of Osteoporotic Fractures)	7,518 elderly white women 473 depressed women	RR 2.14 (95% CI: 1.75 to 2.61) for all-cause mortality and RR 1.8 (95% CI: 1.2 to 2.5) from cardiovascular diseases
Laursen TM, 2007 <sup>20</sup>	Register-based cohort in Denmark	5,558,959 individuals Subjects with hospital admissions 72,165 individuals admitted with unipolar depression	Mortality rate ratio for cardiovascular causes 1.59 (95% CI: 1.53 to 1.65) in men and 1.47 (95% CI: 1.43 to 1.52) in women
Lin EHB, 2009 <sup>57</sup>	Cohort in the United States	4,184 diabetic subjects 493 depressed individuals	Hazard ratio 1.52 (95% CI: 1.19 to 1.95) for all-cause mortality, but no higher mortality for cardiovascular diseases (HR 1.25; 95% CI: 0.83 to 1.86)
Chang CK, 2010 <sup>6</sup>	Register-based cohort in Southeast London	11,697 subjects with depressive disorders	Standardized mortality ratio 1.53 (95% CI: 1.36 to 1.72) in men and 1.18 (95% CI: 1.06 to 1.31) in women
Almeida OP, 2010 <sup>5</sup>	Cohort in Perth, Australia	5,276 non-institutionalized elderly men and 297 depressed men	Standardized mortality ratio 1.98 (95% CI: 1.61 to 2.43) for all-cause mortality and 2.69 (95% CI: 2.01 to 3.59) for cardiovascular causes
Laan W, 2011 <sup>22</sup>	Register-based cohort in Netherlands	103,824 individuals without psychiatric diagnosis and 14,778 depressed individuals	1.83 (95% CI: 1.72 to 1.95) for all-cause mortality and 1.63 (95% CI: 1.45 to 1.83) from circulatory diseases
Patten SB, 2011 <sup>24</sup>	Cohort in Canada	17,276 individuals	No higher mortality Hazard ratio 1.1 (95% CI: 0.7 to 1.7)
Pan A, 2011 <sup>23</sup>	Cohort in the United States (Nurses' Health Study)	78,282 women aged 54 to 79 years 11,120 depressed women	RR 1.76 (95% CI: 1.64 to 1.89) for all-cause mortality and RR 1.81 (95% CI: 1.54 to 2.13) for cardiovascular diseases
Gale C, 2012 <sup>19</sup>	Register-based cohort in Sweden	1,095,338 men and 9,237 depressed individuals	Hazard ratio for all-cause mortality 1.51 (95% CI: 1.26 to 1.81)

are restricted in their ability to access essential health care and social care.<sup>28</sup>

People with mental health conditions are largely overlooked by government policies and programs around the world, also resulting in reduced access and low quantity and quality of health and social services. WHO estimates that 75% to 85% of individuals with mental disorders living in low and middle income countries do not have access to mental health treatment.<sup>28</sup>

There is considerable data showing that part of CVD burden in individuals with psychiatric disorders could be explained by lower accessibility to effective health services and poorer quality of health care.<sup>9,10,14</sup> Accessibility is a complex concept defined as "the features of health services and resources that favor or limit the utilization by potential users".<sup>30</sup> Accessibility also reflects patients' characteristics (such as empowerment, social support, educational level) and health system features (such as barriers to health care, and quality and quantity of health services).

Kisely et al. evaluated data on health insurance users in Nova Scotia (Canada) between 1995 and 2001, and found that cardiovascular mortality in psychiatric patients was greater than in the general population. However, they found that the odds ratio (OR) of undergoing cardiac catheterization was significantly smaller (OR 0.92; 95% CI: 0.86 to 0.98) for individuals with psychiatric conditions. Additionally, rates of percutaneous angioplasty and open revascularization also had a non-significant trend to be smaller (OR 0.97, 95% CI: 0.86 to 1.09; and OR 0.92, 95% CI: 0.83 to 1.02, respectively) in that group.<sup>10</sup>

Druss et al. evaluated 88,241 elderly patients with previous myocardial infarction included in the Cooperative Cardiovascular Project, and observed that patients with psychiatric diseases other than depression or delirium were less likely to undergo myocardial reperfusion therapy (RR 0.87; 95% CI: 0.79 to 0.95), even in the absence of any contraindication to the procedure.<sup>9</sup> The authors found higher rates of acute myocardial infarction mortality (RR 1.11; 95% CI: 1.02 to 1.20) in

**Table 2 – Possible mechanisms of association between depressive disorders and the incidence of cardiovascular diseases.**

a) Social inequality and poverty <sup>28</sup>
b) Side effects of psychiatric medication <sup>45</sup>
c) Lower adherence to medical treatments <sup>33</sup>
d) Biological alterations <sup>27,34-37</sup>
Increased platelet activation
Increased endothelial dysfunction
Elevated C-reactive protein
Elevated interleukin-6
Elevated tumor necrosis factor
Increased resting heart rate
Reduced heart rate variability
Greater QT interval variability
e) Genetic mechanisms <sup>40</sup>
f) Reduced accessibility to health care <sup>9,10,14,28</sup>
g) Higher frequency of cardiovascular risk factors <sup>41-57</sup>
Tobacco smoking
Sedentary lifestyle
Diabetes mellitus
Obesity and metabolic syndrome (in depressed women)

patients with mood disorders. After adjustment for variables associated with the quality of medical care in this scenario (frequency of prescribed reperfusion therapy, aspirin, beta-blockers, and angiotensin-converting enzyme inhibitors at hospital discharge whenever indicated), this difference disappears (RR 1.05; 95% CI: 0.87 to 1.23). This suggests that the association of myocardial infarction mortality in patients with mood disorders is mediated by health care access, an indirect evidence that people with mental health conditions may also suffer prejudice and discrimination by mental health care workers.<sup>28</sup>

In order to enhance the universality of access and quality of care, the WHO suggests that mental health care should be provided in primary care settings, integrated with general health services.<sup>28</sup> It is necessary to coordinate between medical and mental facilities, removing boundaries in order to improve communication and facilitate the development of common goals between medical and mental care providers.<sup>31</sup>

### Adherence

Adherence to medical treatment is another mechanism of association between the presence of depressive disorders and onset of CVD. Four main interacting elements can influence patients' adherence: health care team and health care system (costs of treatment, availability of treatment in health system, easily accessibility of medical services and procedures); condition-related factors (features of the disease that can contribute to the adherence, such as memory disturbances, as seen in depression); therapy characteristics (side effects, medications that have to be used several times a day); and patient-related issues (ideas and feelings about the disease and treatment, expectations, resiliency, confidence in the health professional).<sup>32</sup>

Depressed patients have lower adherence to treatment, resulting in greater impact of chronic medical comorbidities. DiMatteo et al. found an OR of 3.03 (95% CI: 1.96 to 4.89) for non-adherence to treatment recommendations in people with

depression.<sup>33</sup> Both condition- and patient-related factors can interact and reduce adherence in depressed patients. Some of the features of depressive disorders can reduce adherence, such as diminished memory, anhedonia, negative thoughts, and depressed mood.

### Biological alterations

Several biological changes influence the incidence of CVD in depressed individuals. Hypothalamus-hypophysis-adrenal axis hyperactivity has been described.<sup>27,34-37</sup> Increased resting heart rate, reduced heart rate variability, and greater QT interval variability on the electrocardiogram may lead to ventricular arrhythmias and sudden death.<sup>34</sup> There are reports of increased platelet activation associated with depression, increased inflammatory activity, and endothelial dysfunction.<sup>34,36,37</sup> There are studies showing higher levels of inflammatory markers such as C-reactive protein, interleukin-6, and tumor necrosis factor, which may all have a role in triggering an acute coronary event.<sup>37-39</sup>

Genetic-based theories for this association have also been raised. Vaccarino et al. evaluated 289 monozygotic and dizygotic twins where only one of the siblings had the diagnosis of depression. No differences were observed for signs of myocardial ischemia between twins with and without a diagnosis of depression. However, a difference in coronary computerized tomography was observed among dizygotic twins, with the worst function in those individuals with a history of depression. In monozygotic twins, this difference was not found, suggesting a role for genetic mechanisms.<sup>40</sup>

### Classic risk factors for CVD

Several studies showed a higher frequency of some cardiovascular risk factors among individuals with depressive disorders, which can also explain the higher incidence of cardiovascular events. There is consistent evidence that associates poorer lifestyle and depression. Strine et al., evaluating 217,379 participants in a phone-based depression survey, found that individuals with a current episode of depression were more frequently smokers (OR 2.2; 95% CI: 2.0 to 2.3) and sedentary (OR 2.1; 95% CI: 1.9 to 2.3). Similar results were found in individuals with prior diagnosis of depression (OR 1.9; 95% CI: 1.8 to 2.1 for smoking and OR 1.3; 95% CI: 1.2 to 1.4 for sedentarism).<sup>41</sup>

The association between obesity and depression is consistent for the female gender.<sup>42,43</sup> Simon et al. evaluated 9,125 individuals in a population prevalence study (National Comorbidity Survey Replication) and observed that obesity was associated with a lifetime diagnosis of depression (OR 1.21; 95% CI: 1.09 to 1.35). However, when the analysis was stratified by gender, the difference occurred only in women (OR 1.29; 95% CI: 1.11 to 1.50).<sup>42</sup> This association may be partially mediated by the use of antidepressants, which could cause weight gain as side effect.<sup>44</sup>

There is an association between the presence of depression and the incidence of diabetes mellitus. In a systematic review of nine cohort studies, Knol et al. found a combined RR of 1.37 (95% CI: 1.14 to 1.63) for the development of diabetes mellitus in depressive subjects.<sup>45</sup> Similar results were found

by Mezuk et al. (combined RR 1.60; 95% CI: 1.37 to 1.88).<sup>46</sup> Part of this effect may be caused by the use of antidepressants. Andersohn et al., in a nested case-control study, found that individuals who used antidepressants in moderate to high doses for periods greater than 24 months had higher risk of incident diabetes (OR 1.84; 95% CI: 1.35 to 2.52). It is noticeable that this is not fully explained by the use of tricyclic antidepressants and their associated weight gain. Higher diabetes incidence was also found among depressive individuals treated with selective serotonin reuptake inhibitors.<sup>47</sup> Conversely, diabetes may also precede the onset of depression. Mezuk et al. also found a combined RR of 1.15 (95% CI: 1.02 to 1.30) for depression in individuals with diabetes, reinforcing the positive link between these two conditions.<sup>46</sup>

Metabolic syndrome is also more frequent in depressed women. Raikkonen et al. followed 432 premenopausal women in the Healthy Women Study cohort for 15 years. Depressive symptoms were associated with higher incidence of metabolic syndrome with a RR of 1.29 (95% CI: 1.04 to 1.60).<sup>48</sup> Kinder et al. published a study of cross-sectional data from the National Health and Nutrition Examination Survey III (NHANES III) with 6,189 individuals aged between 17 and 39 years, and observed a positive association between the presence of metabolic syndrome and lifetime history of major depression in women, with an OR of 1.96 (95% CI: 1.03 to 3.73). No association was found in men.<sup>49</sup>

Regarding the association between depression and hypertension or dyslipidemia, data are contradictory and suggest that there is no significant link.<sup>50-56</sup>

## Final considerations

The increased all-cause and cardiovascular mortality in individuals with depression demonstrated in most studies could be affected by several factors. Studies evaluating these factors, however, have some limitations. There is heterogeneity in the criteria used to define depression, as several different questionnaires were used. Additionally, some instruments are validated only for depressive symptoms, but not for definitive diagnosis. Few studies used psychiatric evaluation or semi-structured interviews, which have better reliability. Another limitation is that some cohorts did not assess confounding variables related to clinical comorbidity, adherence, and accessibility.

Increased cardiovascular risk among individuals with depression is multifactorial and requires several strategies towards cardiovascular risk reduction. Development of antidepressant treatments targeted to less weight gain and less insulin resistance may also lower cardiovascular risks in individuals with depression. Education of health care professionals, including those working in primary care, is required to improve detection and treatment of depression, and also to enhance surveillance and management of concurrent cardiovascular risk factors in depressed individuals. Few data are currently available on strategies for tobacco cessation and for increasing physical activity in people with depression.<sup>31</sup> Development in this area is necessary in order to offset the influence of these factors on cardiovascular risk in this group. Health system managers, as suggested by the WHO, should

also create health policies to reduce vulnerability in this population.<sup>28</sup>

## Conclusion

Cardiovascular risk is higher in individuals with depression. This association is at least partly explained by higher vulnerability, reduced access to health care services, lower adherence, biological alterations, use of psychiatric medication, and higher frequency of classic cardiovascular risk factors.

## Conflicts of interest

The authors declare no conflicts of interest.

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