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Review article

Depression and cardiovascular disease: Epidemiological evidence on their linking mechanisms

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ABSTRACT

Depression's burden of disease goes beyond functioning and quality of life and extends to somatic health. Results from longitudinal cohort studies converge in illustrating that major depressive disorder (MDD) subsequently increases the risk of cardiovascular morbidity and mortality with about 80%. The impact of MDD on cardiovascular health may be partly explained by mediating mechanisms such as unhealthy lifestyle (smoking, excessive alcohol use, physical inactivity, unhealthy diet, therapy non-compliance) and unfavorable pathophysiological disturbances (autonomic, HPA-axis, metabolic and immuno-inflammatory dysregulations). A summary of the literature findings as well as relevant results from the large-scale Netherlands Study of Depression and Anxiety (N = 2981) are presented. Persons with MDD have significantly worse lifestyles as well as more pathophysiological disturbances as compared to healthy controls. Some of these differences seem to be specific for (typical versus 'atypical', or antidepressant treated versus drug-naive) subgroups of MDD patients. Alternative explanations are also present, namely undetected confounding, iatrogenic effects or 'third factors' such as genetics.

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1. Epidemiological evidence for cardiovascular consequences of depression

The impact of depression on health extends beyond mental health. Over the last 20 years, many studies illustrated the adverse impact of depression on somatic health. Evidence is convincing that depression increases the risk of subsequent cardiovascular

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disease onset. Cardiovascular disease refers to those conditions that affect the heart and blood vessels, including amongst others coronary heart disease, cerebrovascular disease, and peripheral artery disease. Meta-analyses integrating longitudinal evidence from 21 studies involving over 120,000 subjects concluded that depression results in a 80–90% increased risk of cardiovascular disease onset (Nicholson et al., 2006). In line with a dose-response gradient, the cardiovascular morbidity risk is higher for a clinical diagnosis of major depressive disorder than for self-reported depressive symptoms, but the risk is also significantly increased for the latter. Epidemiological evidence also extends to subclinical cardiovascular processes: depressed persons are at increased risk for peripheral atherosclerosis as indicated through e.g. coronary or aortic calcification, impaired endothelial function and increased arterial stiffness (Hamer et al., 2010; Seldenrijk et al., 2010, 2011). In addition, beyond increasing the risk of cardiovascular disease onset, depression also increases the risk of cardiovascular mortality when cardiovascular disease has already emerged (Doyle et al., 2015). So, there is extensive evidence that depression contributes not only to the onset but also to the progression and prognosis of cardiovascular disease. Finally, it is clear that a mutual, bidirectional link exists. Cardiovascular disease itself can – either through direct physical consequences or through indirect biological, bodily or psychosocial changes – also increase the risk of developing depressive symptoms and disorders. In fact, the association between depression and cardiovascular disease can be best considered a downward spiral in which depression and cardiovascular disease mutually reinforce each other.

In this paper, in line with this Special Issue theme 'Stress, Behavior and the Heart', the focus will be mainly on contributing mechanisms that may explain how depression contributes to cardiovascular disease onset in initially healthy subjects. It is important to realize that the impact of depression on somatic health is not restricted to cardiovascular disease alone. Various meta-analyses summarizing longitudinal studies among initially somatic-disease free subjects, converge in their findings that depression increases the risk of subsequent overall mortality (Relative Risk (RR) = 1.81, Cuijpers et al., 2014), diabetes (RR = 1.60, Mezuk et al., 2008), hypertension (RR = 1.42, Meng et al., 2012), stroke (RR = 1.34, Dong et al., 2012), obesity (RR = 1.58, Luppino et al., 2010), dementia (RR = 1.96, Cherbuin et al., 2015) and to a lesser extent potentially even cancer (RR = 1.29, Chida et al., 2008). Not only in the general population but also in specific somatic disease groups, depression increases the mortality risk with 60–80%, confirming that depression increases both onset as well as prognosis of disease (Cuijpers et al., 2014; Walker et al., 2015).

When further extending the picture, it is clear that an increased cardiovascular risk is also not specific for depression either. For various other psychiatric conditions similar observations have been described. In a large scale population-based study incorporating data from over 50,000 subjects, also panic disorder, specific phobia, post-traumatic stress disorder and alcohol use disorders were found to predict subsequent heart disease onset (Scott et al., 2013). For non-specific anxiety disorder a recent meta-analysis, summarizing a total of 37 papers including 1,565,699 persons, indicated a 50% increased risk of cardiovascular disease onset (Batelaan et al., 2016). The fact that depression is associated to other somatic conditions beyond cardiovascular disease, and that somatic risks extend to other psychiatric conditions as well, already illustrates that it is not likely that underlying mechanisms linking depression to cardiovascular disease are purely organ- or disease-specific, but are rather general. An overview of the discussed mechanisms in subsequent sections of this paper are listed in Table 1, and contain both potential causal mediating mechanisms as well alternative mechanisms.

Table 1
Summary of potential mechanisms linking depression to increased cardiovascular risk.

Causal mediating mechanisms	
Unhealthy lifestyle	Smoking Excessive alcohol use Physical inactivity Unhealthy diet Lower treatment compliance and worse medical care
Pathophysiology	Metabolic dysregulations Immuno-inflammatory dysregulations Autonomic dysregulations HPA-axis dysregulations
Alternative mechanisms	
Residual cConfounding	Depression picks up or is a prodrome of not yet discovered or not measured (sub)clinical conditions
Iatrogenic effects	Pharmacological impact of antidepressants increase cardiovascular risk
'Third underlying factors'[a]	Childhood stressors Personality Genetic pleiotropy

[a] Factors that influence in parallel both cardiovascular risk as well as depression risk, but potentially independently from each other.

2. The 'residual confounding hypothesis' as mechanism linking depression to cardiovascular health

Subjects with depression are usually older, more often female, have a lower socioeconomic status and their general health is worse than that of their non-depressed peers. Consequently, sociodemographics and baseline health conditions rather than depression per se might be in part responsible for the poorer subsequent cardiovascular health in depressed subjects. Generally, most longitudinal population studies that examined the risk of cardiovascular events in depressed persons, have found that the risk associated with depression declined only with 20% or less after considering standard sociodemographic (age, gender, education level) and baseline health conditions (Nicholson et al., 2006; Van der Kooy et al., 2007). Importantly, after adjusting for these potential confounding variables, the cardiovascular risk in depressed persons remains significantly increased compared to that of non-depressed persons. This illustrates that the link does not seem to be completely driven by simply confounding. However, it should be mentioned that some remaining confounding is hard to completely rule out, as several indicators may only partly cover the entire underlying concept. For instance, socioeconomic status may not be completely covered through an adjustment for educational level and simple dichotomous disease presence indicators do not take disease severity into account. Therefore, it can be that in some cases depression may be a prodrome of not yet discovered and diagnosed (and therefore not measurable) sociodemographic, subclinical or medical conditions that affect subsequent cardiovascular disease onset. Consequently, even in rather extensively adjusted epidemiological models, residual confounding may still exist. This 'residual confounding hypothesis' may therefore still contribute to finding worse cardiovascular outcomes among the depressed. However, it is unlikely that this completely explains the increased cardiovascular risk as results are rather consistent across studies, not restricted to older samples only (in which other health conditions are most present), and have also been confirmed in depressed subjects with an early age of onset.