



# Depression, anxiety and incident cardiometabolic diseases

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## Purpose of review

It is well established that depression is associated with increased risk of incident coronary heart disease (CHD). The strong research focus on this particular comorbidity may obscure an appreciation of the breadth of mental disorder–medical comorbidities. Some of the most prevalent of these are highlighted in this review, which features recent research on epidemiological associations of depression and anxiety disorders with a range of cardiometabolic diseases. The clinical implications of this broader set of mental–physical connections are discussed.

## Recent findings

New findings support the existence of an association between depression and a range of subtypes of heart disease, stroke and diabetes. The associations between anxiety and coronary heart disease are robust and there is emerging evidence of associations of anxiety with stroke and diabetes.

## Summary

The predictive associations of mental disorders with incident medical diseases extend well beyond the established association between depression and CHD. The breadth of mental–physical associations suggests a need for greater clinical attention to the physical health and health-related behavior of young people with persistent mental disorders of all types, at the time of life when the seeds of mental–physical comorbidity are sown.

## Keywords

anxiety, cardiovascular disease, depression, diabetes, stroke

## INTRODUCTION

Over the past two decades, many prospective studies have demonstrated that depression measured among initially healthy populations is associated with increased risk of incident coronary heart disease (CHD) [1–5]. Depression also has a well-established association with earlier mortality in people with existing heart disease, but the focus in this review is on incident disease, rather than prognosis. Although there is debate as to the causal significance of the depression–incident CHD association (compare, for example, recent contrasting opinions [6,7]), its reliability is now well proven. Research on this association and its many hypothesized underlying mechanisms has, in the words of one reviewer [8<sup>\*</sup>], ‘exploded’ in recent years.

What is perhaps less well appreciated, but is becoming increasingly clear, is that the depression–CHD association is but one of a broader set of links between temporally prior mental disorders and subsequent increased risk of chronic physical conditions. The purpose of this review is to

highlight recent research on some of these other mental–physical associations. Appreciating that depression and CHD occur within the context of a wider pattern of mental–physical associations has conceptual and practical implications, particularly for prevention. This review highlights epidemiological research published in 2013 relating to associations of depression and anxiety with the onset of a wider set of cardiovascular diseases, and with diabetes. Relevant studies were identified through searches undertaken in Medline and Google Scholar limited to 2013, using various combinations of the following keywords: depression, anxiety, incident,

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## KEY POINTS

- The prospective association between depression and coronary heart disease is well established, but it is only one of a broader set of mental–physical links.
- Recent evidence on the associations of depression and anxiety disorders with incidence of a range of cardiometabolic diseases is highlighted.
- The pathogenesis of most chronic physical diseases begins in young adulthood when mental disorders are most prevalent.
- The prevention of the development of depression/anxiety–cardiometabolic comorbidities will require greater clinical attention to the physical health and health-related behavior of young people with persistent mental disorders of all types.

heart, coronary, diabetes, stroke, cardiovascular, cardiometabolic, cerebrovascular.

It should be noted that prospective associations between mental disorders and subsequent physical conditions extend beyond the associations highlighted in this review, additionally involving psychotic disorders, eating disorders, substance use disorders and a broader range of physical health outcomes. But, because of the breadth of the topic, some restriction in scope was necessary, and the focus on depression, anxiety and subsequent cardiometabolic diseases was chosen because it highlights some of the most prevalent associations of greatest clinical and public health significance.

### DEPRESSION AND INCIDENT CARDIOVASCULAR DISEASES

Whooley and Wong [8<sup>■</sup>] review research in this area indicating that depression has prospective (and prognostic) associations with a variety of subtypes of cardiovascular disease, although the links with coronary artery disease have been the main focus of past research. Whooley and Wong suggest that links between depression and coronary artery disease, peripheral heart disease and congestive heart failure probably share similar mechanisms. Their review provides a detailed discussion of each of these mechanisms including lifestyle factors, medication non-adherence, social factors and a range of biological pathways.

Many studies have found a relationship between depression and incident stroke, with a 2011 meta-analysis of 28 prospective studies finding an approximately 50% increased risk among people with baseline depression symptoms or depression diagnosis [9]. Two studies in the past year add to this

topic. Jackson *et al.* [10<sup>■</sup>] examined the association between depression and stroke incidence in 10 547 women aged 47–52 years, over a period of 3 years with 177 incident strokes. They found an approximate two-fold increased risk of first ever stroke associated with prior depression, after adjustment for confounders. Although this study is not large, two aspects of the findings are noteworthy. One is that the magnitude of the elevated risk associated with depression was somewhat greater than the overall estimate in the most recent meta-analysis by Pan *et al.*, but it is consistent with a subgroup analysis conducted by Pan *et al.* that found stronger associations between depression and stroke among people younger than 65 years. The other finding of note is that the association between depression and stroke was only slightly reduced (and remained significant) after excluding all those who had taken antidepressant medication. This is of interest because there has been some suggestion that antidepressant medications increase risk of cardiovascular disease, including stroke [11,12].

The second recent study of interest is a 4-year follow-up of a large cohort of 36 654 elderly Swedish twins [13<sup>■</sup>] with 833 incident strokes. Depression was associated with an approximately 70% increase in risk of stroke occurrence, whether or not antidepressants were taken. Of additional interest was the finding that there was no elevated risk of stroke in the subgroup who took antidepressant medications in the absence of a diagnosis of depression. It is worth noting, however, that this study only examined ischemic stroke, and a recent meta-analysis concluded that selective serotonin reuptake inhibitors (SSRIs) are associated with increased risk of brain hemorrhage [14]. In summary, both of these recent studies contribute to the body of evidence linking depression with stroke risk, independently of antidepressant use.

### DEPRESSION AND INCIDENT DIABETES

Meta-analyses published in the past decade have concluded that there is increased risk of incident diabetes among people with prior depression [15,16], but there have been several large studies finding no association, including some subsequent to those meta-analyses (see [17<sup>■</sup>] for review). For this reason, the most recent meta-analysis by Rotella and Mannucci [17<sup>■</sup>] published in 2013 is a useful contribution to this topic. This analysis included 23 longitudinal studies with 424 557 subjects and 19 977 cases of incident diabetes. Depressive symptoms were associated with increased risk of diabetes in both unadjusted [hazard ratio (HR): 1.56, 1.37–1.77] and adjusted models (HR: 1.38, 1.23–1.55).

The authors note some major methodological drawbacks of many of the contributing studies, however, including the use of screening scales to measure depression, or the use of antidepressant drugs as a proxy for depression. This latter is particularly problematic because of the possibility that antidepressant medications have an independent association with diabetes risk, and, indeed, the meta-analysis found a stronger association between antidepressant medications and diabetes than between depression and diabetes.

In a cross-sectional study including 52 095 individuals in 19 countries as part of the World Mental Health surveys initiative, de Jonge *et al.* [18<sup>■</sup>] examined the association of a wide range of Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) mental disorders with subsequent diagnosis of diabetes. This study is limited by retrospective self-report of mental disorders and diabetes, but it is a novel contribution in its ability to take comorbidity among mental disorders into account. In adjusted models, depression was independently associated with a small elevated risk of subsequent diabetes diagnosis. Stronger associations were found between bulimia nervosa, binge eating disorder and intermittent explosive disorder and subsequent diabetes diagnosis.

These recent studies add to the evidence that there is an association between depression and incident diabetes, although there remains some uncertainty around the extent to which the association is confounded by antidepressant medication use.

## ANXIETY DISORDERS AND INCIDENT CARDIOVASCULAR DISEASES

Although depression has been most intensively studied, there are now many studies testifying to the significant elevated risk of incident CHD associated with anxiety symptoms or disorders [19,20]. Thurston *et al.* [21<sup>■</sup>] provide an excellent new review of the relationship between anxiety and onset of cardiovascular diseases, with a particular focus on the clinical implications. They conclude that there is a robust association between anxiety and incident CHD.

With regard to specific anxiety disorders, there is burgeoning research on the connection between posttraumatic stress disorder (PTSD) and onset of CHD, and two recent studies make important contributions to this body of research. In a prospective study of 562 male twins from the Vietnam Era Twin registry with follow-up over 13 years [22<sup>■</sup>], the incidence of CHD was doubled in those with a lifetime history of PTSD relative to those without, after adjustment for lifestyle factors, other risk factors for

CHD and depression. This study also found that coronary flow reserve (measured with positron emission tomography imaging) was significantly lower in twins with PTSD than in those without, denoting worse myocardial perfusion. An interesting finding in this study was that the association with risk of CHD was only slightly reduced when comparing twins discordant for PTSD, suggesting that it could not be explained by differences between people with versus without PTSD in background factors such as genetics and early environment.

The first meta-analysis of the prospective association of PTSD with incident CHD in initially healthy populations was published last year [23]. This analysis included six studies, including the twin study just discussed, with a total of 402 274 individuals. The pooled HR for the association of baseline PTSD with risk of incident CHD was 1.55 (1.34–1.79) before adjustment for depression and 1.27 (1.08–1.49) after adjustment for depression. The authors also noted that one of the outstanding issues for the future is that most studies on this topic only include depression as a covariate and, because PTSD is often comorbid with many other mental disorders, the unique contribution of PTSD remains to be determined.

A recent study by Scott *et al.* [24<sup>■</sup>] provides a perspective on this issue of the unique (independent) contribution of specific anxiety disorders to CHD risk. This study of 52 095 individuals (3197 with CHD) uses the same World Mental Health Surveys dataset as the diabetes study discussed above, and so has the same limitations of retrospectively collected information on timing of mental disorders and CHD, and use of self-reported physician's diagnosis of CHD. The study investigated the independent associations of 16 DSM-IV mental disorders (including seven anxiety disorders) with subsequent diagnosis of CHD. After adjustment for mental disorder comorbidity, depression, specific phobia, panic disorder, PTSD and alcohol use disorders remained independently associated with CHD, with depression as the weakest predictor.

The Thurston *et al.* review discussed above concluded that, although associations between anxiety and CHD are now quite robust, the picture for stroke is less clear, with far fewer studies and the available studies providing conflicting results. Since the Thurston review, a new prospective study on anxiety and incident stroke has been published [25<sup>■</sup>]. This study was a 16-year follow-up of 6019 of the first National Health and Nutrition Examination Survey cohort and included 419 incident strokes. It found a small but significant elevation in risk of incident stroke associated with elevated anxiety symptoms at baseline, independently of

depression. Behavioral factors (particularly smoking and physical activity) had the largest attenuating effect on the association. As the study's authors note, these findings conflict with an earlier study that found no association between diagnosis of generalized anxiety disorder and incident stroke [4]; this is an area that requires more research, preferably with diagnostic measures of anxiety disorders.

### ANXIETY AND INCIDENT DIABETES

Relatively few studies have examined prospective associations between anxiety and diabetes, although one study [26] in a military cohort found that baseline PTSD, panic disorder and the category of 'other anxiety disorders' were all significantly associated with incident diabetes, over a 3-year follow-up. Boyko *et al.* [27\*] have recently published a 6-year follow-up of the same cohort, with 47 093 participants and 871 incident self-reported diabetes cases. PTSD remained significantly associated with incident diabetes, and the association between panic disorder and diabetes was of borderline significance. It is interesting to consider these findings in light of the de Jonge *et al.* study discussed above, which found that anxiety disorders were no longer associated and subsequent diabetes diagnosis once bulimia and binge eating disorders were taken into account. PTSD and traumatic stress have been associated with binge eating [28,29], so this may be one behavioral pathway by which PTSD is linked with diabetes risk. One other recent study [30] of potential relevance to this topic found that elevated resting heart rate was associated with incident diabetes over a 5-year period, suggesting that sympathetic overactivity may be a contributing factor to the development of diabetes. Sympathetic overactivity has been strongly associated with anxiety disorders [21\*\*].

### CLINICAL IMPLICATIONS

Treatment trials of depression in patients with CHD have been disappointing in their impact on cardiac outcomes [31,32]. One reason for this may be that these interventions are occurring too late in the natural history of the depression-CHD comorbidity. Mental disorders have first onset typically in adolescence or early adulthood, some in childhood. The pathogenesis of cardiometabolic diseases also begins many years before they manifest in the kinds of 'hard endpoints' used in the prospective studies discussed above. Although there are ways in which depression and anxiety could impact on physical disease through quite short time frames [33], the

kinds of biological and behavioral mechanisms that have been most implicated in research to date are likely to play out over decades. If these mental-physical associations are causal, then lessening the impact of mental disorders on subsequent disease risk will require much greater attention from clinicians and health services to the physical health and health-related behaviors of young people with a wide range of mental disorders, especially those with persisting or recurrent disorders.

Although many clinicians and researchers have lobbied for better mental health services for young people [34], the need to simultaneously focus on the physical health and health behaviors of this young group has not usually been emphasized. There is awareness of the need to address physical health in young people with psychotic disorders [35] but much less focus on the physical health of young people with depression and anxiety disorders. The comprehensive review by McCloughen *et al.* [36] found a broad range of physical health problems and elevated cardiovascular risk factors in young people (16-24 years) with mental disorders, including those with depression and anxiety disorders. There are existing clinical interventions that could be adapted to help prevent the development of cardiometabolic disease among those with affective disorders. Examples include: extending existing primary care monitoring of physical health among middle-aged people with mental disorders [35] to the younger age groups, and extending existing programs aimed at identification and prevention of cardiometabolic disease among young people with psychotic disorders [37] to young people with persistent or recurrent depression or anxiety disorders.

### CONCLUSION

Associations of mental disorders with incident medical disease extend well beyond the most intensively researched association of depression with CHD. The behavioral and biological seeds of many chronic medical conditions are sown in early adulthood when mental disorders are most prevalent. Reduction in the development of these mental-physical comorbidities will require multidisciplinary clinical attention to the physical health and health-related behavior of all young people with persistent mental disorders, not just those with psychotic disorders.

### Acknowledgements

None.

### Conflicts of interest

There are no conflicts of interest.

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- of special interest
- of outstanding interest

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