

# **Meta-Analysis of Anxiety as a Risk Factor for Cardiovascular Disease**

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**Abstract**

Whether anxiety is a risk factor for a range of cardiovascular diseases is unclear. We aimed to determine the association between anxiety and a range of cardiovascular diseases. MEDLINE and EMBASE were searched for cohort studies that included participants with and without anxiety, including individuals with anxiety, worry, post-traumatic stress disorder, phobic anxiety and panic disorder. We examined the association of anxiety with cardiovascular mortality, major cardiovascular events (defined as the composite of cardiovascular death, stroke, coronary heart disease and heart failure), stroke, coronary heart disease, heart failure and atrial fibrillation. We identified 46 cohort studies containing 2017276 participants and 222253 individuals with anxiety. Anxiety was associated with a significantly elevated risk of cardiovascular mortality (RR 1.41 CI 1.13, 1.76), coronary heart disease (RR 1.41 CI 1.23, 1.61), stroke (RR 1.71 CI 1.18, 2.50) and heart failure (RR 1.35 CI 1.11, 1.64). Anxiety was not significantly associated with major cardiovascular events or atrial fibrillation, although confidence intervals were wide. Phobic anxiety was associated with a higher risk of coronary heart disease than other anxiety disorders and PTSD was associated with a higher risk of stroke. Results were broadly consistent in sensitivity analyses. Anxiety disorders are associated with an elevated risk of a range of different cardiovascular events, including stroke, coronary heart disease, heart failure and cardiovascular death. Whether these associations are causal is unclear.

**Key Words:** Psychosocial factors, Anxiety, Cardiovascular disease, Coronary heart disease

## **Introduction**

Despite the substantial evidence that depression and general psychological distress are associated with incident cardiovascular disease, the association between anxiety and cardiovascular disease is less clear. Previous results in studies conducted in cardiovascular disease populations, such as heart failure, have shown that anxiety is associated with a higher risk of adverse outcomes.<sup>1</sup> However, these results may be due to reverse causality, that is, more severe cardiovascular disease causing greater anxiety rather than anxiety causing adverse outcomes. In a previous meta-analysis of 20 cohort studies, anxiety disorders were associated with a 26% higher risk of coronary heart disease.<sup>2</sup> However, prior studies have provided conflicting results on whether anxiety disorders are associated with risk of stroke<sup>3</sup>, heart failure<sup>4</sup> or cardiovascular mortality.<sup>5,6</sup> Contribution of anxiety disorders to the development of cardiovascular disease would have substantial implications for the estimation of the global and regional burden of anxiety disorders, for prevention and treatment of anxiety disorders and for future research into the relationship between anxiety disorders and cardiovascular disease. We therefore aimed to conduct a comprehensive meta-analysis on the association between anxiety and incident cardiovascular disease and death.

## **Methods**

Cohort studies or case-control studies nested within cohort studies were eligible for inclusion. Studies were required to contain adults with and without anxiety and were required to have a minimum of three months follow-up. Anxiety was defined as anxiety symptoms, generalized anxiety disorder (GAD), panic, phobia, post-traumatic stress disorder (PTSD), and worry, consistent with prior studies.<sup>2</sup> Only studies that were conducted in a general population were eligible for inclusion; studies conducted on specific populations (e.g. type 2 diabetes, myocardial infarction) were

excluded. We restricted our analysis to studies conducted in a general population to minimize the risk of reverse causality, that is, cardiovascular disease causing anxiety symptoms, and to ensure that our results were broadly applicable. Eligible studies also reported a measure of relative risk for at least one of the following outcomes: cardiovascular mortality, major cardiovascular events (defined as a composite of cardiovascular death, stroke, coronary heart disease and incident heart failure), stroke, coronary heart disease (coronary heart disease death, including sudden cardiac death, and non-fatal myocardial infarction), heart failure, atrial fibrillation and chronic kidney disease. No language restrictions were applied.

MEDLINE and EMBASE were searched from inception (1966) to July 2015 by an experienced research librarian. The following search terms were used for anxiety: “anxiety or post traumatic stress disorder or tension or anxiety symptoms or anxiety disorder or panic or panic attacks or phobic anxiety or phobia or worry”.<sup>2</sup> Bibliographic review of included studies was also conducted to identify potentially eligible studies. Two researchers screened all abstracts identified in the search in duplicate, excluding those that did not meet eligibility criteria. Following this screen, full texts of eligible studies were again assessed in duplicate by two separate researchers.

Data was extracted using a standardized form in duplicate. General study characteristics, including the population under study, number of participants with and without anxiety, duration of follow-up, mean age, number of men and number of participants with cardiovascular disease at baseline, were extracted. Maximally adjusted measures of relative risk and associated 95% confidence intervals for outcomes of interest (cardiovascular mortality, major cardiovascular events, stroke, coronary heart disease, heart failure, atrial fibrillation and chronic kidney disease) were extracted, as well as the published covariates that investigators included in the

regression model. Studies were then categorized as unadjusted, minimally adjusted or adequately adjusted, as previously performed. Unadjusted studies did not adjust for any potential confounders and were excluded from analysis. Minimally adjusted studies adjusted for age and were excluded in a sensitivity analysis. Adequately adjusted studies adjusted for age, sex and at least two established cardiovascular risk factors (blood pressure, cholesterol, smoking status, body mass index and diabetes). For studies that reported multiple anxiety categories (e.g. high symptoms of anxiety, moderate symptoms of anxiety, no anxiety symptoms), the relative risk for the most severe category was used. For studies that reported risk of cardiovascular disease per standard deviation of anxiety symptoms or by quantile (e.g. top fourth relative to the bottom fourth of anxiety symptoms), a normal distribution was assumed and the measure of relative risk standardized to correspond to the top 13.5% of the study population compared to the bottom 86.5% of the study population (13.5% being the mean proportion of the population with anxiety among included studies). Risk of bias in included studies was assessed using the Newcastle-Ottawa Scale.

Inverse-variance weighted random effects meta-analysis was used to derive overall summary estimates for all analyses. For studies that reported separate measures of relative risk for subgroups (for example, men and women), inverse-variance weighted fixed effects meta-analysis was used to derive a study-level relative risk prior to random effects meta-analysis. Heterogeneity was quantified using the  $I^2$  statistic and the Q-test. Publication bias was assessed using forest plots and Egger's test for coronary heart disease, cardiovascular mortality and stroke (the only outcomes reported in more than five studies).

Five sensitivity analyses were undertaken. First, studies were stratified by baseline year of assessment. Second, studies were stratified by length of follow-up. Third, studies were stratified by mean participant age. Tests for trend were performed

for these continuous outcomes using meta-regression. Fourth, studies were stratified by the type of anxiety under investigation (generalized or unspecified anxiety, PTSD, panic disorder, phobic anxiety or worry), to examine whether different anxiety types differed in their association with cardiovascular disease. Fifth, studies were stratified by level of adjustment (minimally adjusted versus adequately adjusted), to examine whether further adjustment, as well as adjustment for potential mediators such as hypertension, attenuated the observed association between anxiety and cardiovascular disease. These five sensitivity analyses were again restricted to coronary heart disease, cardiovascular mortality and stroke, as other outcomes were reported in fewer than five studies.

## **Results**

1804 studies were identified in the search and 1564 studies excluded in the abstract screen (Figure 1). After excluding an additional 194 studies in the full text screen, 46 studies were included in the meta-analysis. These 46 studies included 2017126 participants, in total, and 222253 participants with anxiety. Although we included chronic kidney disease as an outcome of interest in our protocol, no studies were identified that examined the association between anxiety and chronic kidney disease. Characteristics of included studies are provided in Table 1. Eleven studies were minimally adjusted while 35 studies were adequately adjusted (Supp. Table 1). Most studies were at low risk of bias when assessed using the Newcastle-Ottawa scale (Supp. Table 2).

Eight studies examined the association of anxiety with cardiovascular mortality. Anxiety was associated with a 41% higher risk of cardiovascular mortality (RR 1.41 CI 1.13, 1.73; Figure 2 and Supp. Figure 1), with high heterogeneity among studies ( $I^2 = 65\%$ ). Twenty-eight studies examined the association of anxiety with coronary heart disease. Anxiety was associated with a 41% higher risk of coronary heart disease (RR

1.41 CI 1.23, 1.61; Figures 2 and 3). Heterogeneity among studies was high ( $I^2 = 96\%$ ). The strongest association observed was for stroke; anxiety was associated with a 71% higher risk of stroke (RR 1.71 CI 1.18, 2.50; Figures 2 and 4), albeit with high heterogeneity ( $I^2 = 90\%$ ). Anxiety was also associated with a 35% higher risk of heart failure (RR 1.35 CI 1.11, 1.6; 4;  $I^2 = 57\%$ ; Figure 2 and Supp. Figure 2) but was not significantly associated with major cardiovascular events (RR 1.64 CI 0.84, 3.19; Figure 2 and Supp. Figure 3) or atrial fibrillation (RR 1.27 CI 0.90, 1.80; Figure 2 and Supp. Figure 4).

No evidence of publication bias was observed for coronary heart disease or stroke (Supp. Figures 5 and 6). Evidence of publication bias was, however, observed for cardiovascular mortality ( $p=0.018$ , Supp. Figure 7). A trim-and-fill estimate for cardiovascular mortality was non-significantly elevated (RR 1.15 CI 0.92, 1.44).

For coronary heart disease, no evidence of an interaction was observed when studies were stratified by baseline year, period of follow up, mean age or level of adjustment in sensitivity analyses (Supp. Figure 8). However, phobic anxiety was more strongly associated with incident coronary heart disease than general/unspecified anxiety ( $p$  value for the interaction = 0.004). For cardiovascular mortality, no evidence of an interaction was observed in sensitivity analyses (Supp. Figure 9). For stroke, stronger associations of anxiety were observed among adequately adjusted studies and among studies examining PTSD (Supp. Fig 10). Stronger associations were also observed among studies with later baseline year and studies with shorter follow up, although tests for trend were of borderline significance ( $p$  trend > 0.02).

## **Discussion**

In this meta-analysis, anxiety was associated with a 41% higher risk of cardiovascular mortality, a 41% higher risk of coronary heart disease, a 71% higher risk of stroke and a 35% higher risk of heart failure. Although anxiety was not

significantly associated with atrial fibrillation and major cardiovascular events, confidence intervals were wide and point estimates similar to other outcomes. Estimates were broadly similar in sensitivity analyses, although phobic anxiety was associated with a higher risk of coronary heart disease and PTSD associated with a higher risk of stroke than other anxiety types.

A large body of evidence has demonstrated that depression is a risk factor for cardiovascular disease.<sup>5,7</sup> In a meta-analysis of 21 prospective studies, depression was associated with a 81% higher risk of coronary heart disease (RR 1.81 CI 1.53, 2.15).<sup>7</sup> Our results suggest that, like depression, anxiety should be considered a risk factor for a wide range of cardiovascular diseases.

This meta-analysis extends prior work demonstrating anxiety to be associated with coronary heart disease. In a meta-analysis of twenty studies reporting on the association of anxiety and incident CHD, anxiety was associated with a 26% higher risk of CHD (HR 1.26 CI 1.15, 1.38).<sup>2</sup> Our meta-analysis identified an additional eight studies and the pooled association of anxiety and coronary heart disease was similar (RR 1.41 CI 1.23, 1.61). However, we also observed strong associations between anxiety and cardiovascular mortality, heart failure and stroke. Indeed, the association of anxiety with stroke was stronger (RR 1.71 CI 1.18, 2.50) than that of the association of anxiety with coronary heart disease, although confidence intervals were wider. Although the association of anxiety with the composite endpoint of major cardiovascular events (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke and non-fatal heart failure) was not significant, this is likely due to a lack of power, as only three studies were identified which reported on a cardiovascular composite and anxiety was independently associated with stroke, heart failure and coronary heart disease. Similarly, the lack of an association with atrial fibrillation was also likely due to a lack of power, as only three studies were identified that reported on



the association between anxiety and atrial fibrillation, the effect estimate was similar to other outcomes and confidence intervals were wide. Larger studies examining the association between anxiety and atrial fibrillation could confirm this hypothesis.

Although there are several biological pathways by which anxiety may increase the risk of cardiovascular disease, it is unclear if the associations reported here are causal. However, even if the associations reported here are not causal, an elevated risk of cardiovascular disease among anxiety sufferers would support greater screening and more aggressive measures to prevent cardiovascular disease among individuals with anxiety.

This analysis has several strengths. We included more studies than any previous meta-analysis on anxiety and examined a wider range of outcomes. However, our analysis also has several limitations. First, we observed high levels of heterogeneity ( $I^2 > 50\%$ ) for all our outcomes, similar to prior meta-analyses of psychosocial risk factors for cardiovascular disease.<sup>2,8</sup> These may be due to differences in the populations under study, such as types of anxiety under investigation and use of cardiovascular risk reducing therapies, as well as methodological characteristics, such as study design, length of follow-up and endpoint ascertainment. Second, we lacked individual patient data for studies, which would have allowed us to undertake consistent adjustment for potential confounders. Third, studies which observed positive associations between anxiety and cardiovascular disease may have been more likely to be published. However, we did not observe evidence of publication bias for any outcomes other than cardiovascular mortality.

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**Disclosures**

No conflicts of interests exist.

**Contributors**

CE had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. CE conceived of the study, acquired, analysed and interpreted the data, and drafted and critically revised the report. AO, JT, BH, AH, CW acquired, analysed and interpreted the data, and critically revised the report.

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**Figures**

Figure 1. Identification of studies.

Figure 2. Association of anxiety with cardiovascular disease.

Figure 3. Association of anxiety with coronary heart disease.

Figure 4. Association of anxiety with stroke.