

ASSOCIATION BETWEEN DEPRESSION AND ANXIETY AND THE DEVELOPMENT OF CARDIOVASCULAR DISEASES: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Objective: The aim of this study is to investigate the association between Depression, Anxiety, and the development of Cardiovascular Diseases (CVD).

Methods: A Systematic Review with Meta-Analysis was conducted, including observational studies without restrictions on date or language, in the databases PubMed, Embase, Scopus, Web of Science, PsycINFO, and grey literature, excluding letters, editorials, protocols, and conference abstracts. Descriptors from DeCS, MeSH, Emtree, and relevant keywords were applied. Three independent reviewers performed qualitative and quantitative analyses (Odds Ratio – OR and frequency) using EndnoteWeb and Comprehensive Meta-Analysis software (random-effects model, I^2 and Cochran's Q tests). Joanna Briggs Institute tools supported the assessment of risk of bias, and the GRADE approach was used to evaluate the strength of evidence.

Results: Fourteen studies published between 2008 and 2024 were included, comprising a total of 471,104 participants of both sexes, with ages ranging from 41.2 to 66.6 years, and presenting moderate to high methodological quality. Findings revealed an 85% increased likelihood of individuals with Depression developing CVD (OR = 1.85, 95% CI: 1.47–2.33, $p < 0.001$; $I^2 = 27\%$) and an 18% increased likelihood for those with Anxiety (OR = 1.18, 95% CI: 0.84–1.67, $p > 0.05$; $I^2 = 86\%$).

Conclusions: Depression and Anxiety are important psychosocial factors that significantly contribute to the risk of developing or worsening cardiovascular diseases, and the comorbidity of these conditions warrants further investigation in future research.

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Keywords: Depression. Anxiety. Cardiovascular Diseases. Systematic Review and Meta-Analysis.

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INTRODUCTION

Despite significant advances in the diagnosis and management of cardiovascular diseases (CVD), the traditional approach remains largely centered on the identification of classical risk factors such as hypertension, diabetes, dyslipidemia, obesity, smoking, and physical inactivity (Visseren, 2021). However, there is an increasing need to broaden this understanding by incorporating psychosocial and emotional variables that directly impact cardiovascular health but are still underappreciated in clinical practice.

Emotional distress – particularly in the form of depression, anxiety, and their related symptoms – has been shown to have a significant association with cardiovascular pathophysiology. Prolonged exposure to negative emotional states can trigger neuroendocrine, inflammatory, and autonomic alterations that promote the onset and progression of heart disease (Carney, Freedland, 2003, Grippo, Johnson, 2009, Smith, Blumenthal, 2011, Van Mook *et al.*, 2014). Nevertheless, in clinical practice, emotional aspects often remain overlooked in the screening, prevention, and treatment of cardiovascular patients.

The association between mental health and cardiovascular risk has garnered increasing attention over recent decades. Epidemiological evidence indicates that depression and anxiety can significantly influence both the incidence and progression of CVD (Manolis, Manolis, Manolis, 2025; Sara *et al.*, 2022).

Recent high-impact reviews, such as that of Vaccarino *et al.* (2025), reinforce that mental disorders contribute substantially to the global burden of CVD, underscoring the need to integrate mental health into preventive strategies. Similarly, multinational analyses by Krittanawong *et al.* (2023) demonstrated that the association between psychiatric disorders and CVD persists even after controlling for familial and environmental factors.

A recently published meta-analysis, comprising 39 studies and more than 800,000 participants, estimated that approximately 20% of cardiovascular patients present with clinically relevant depression, while Mendelian randomization analyses suggest potential causal relationships with specific CVD subtypes (Zeng *et al.*, 2025). This body of evidence points to a biologically plausible link between negative emotions and cardiovascular risk, while also highlighting important methodological gaps, such as heterogeneity in diagnostic instruments and the scarcity of clinical trials.

This systematic review seeks to fill a critical gap in the medical literature by qualifying and quantifying the impact of depression and anxiety on the cardiovascular system, while reinforcing the evidence base that supports the integration of emotional health as an essential

component of cardiovascular risk assessment. By acknowledging the clinical relevance of emotional factors, this study aims to provide a broader perspective for healthcare professionals, proposing a more comprehensive approach that considers the patient in their entirety – body, mind, and life history.

By presenting consistent data on this relationship, this study aims to contribute to a paradigm shift in cardiovascular care, fostering not only the prevention of clinical events but also the promotion of a more humanized, integrative, and patient-centered model of care that, when aligned with public health policies, may improve population well-being.

The objective of this research is to investigate the association between Depression, Anxiety, and the development of Cardiovascular Diseases.

METHODS

This study is a systematic review registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the number CRD420251115684. It was structured according to the guidelines of the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) checklist (Page *et al.*, 2021) and the *Meta-analyses Of Observational Studies in Epidemiology* (MOOSE) recommendations (Stroupe *et al.*, 2000).

Eligibility criteria. Participants included individuals with cardiovascular diseases of any age, sex, educational level, and geographical region, exposed to depression and/or anxiety. No comparison group was required, and the main outcome was the development of cardiovascular diseases. Initially, all study designs were considered, but only observational studies were retained for this review.

Information sources. Searches were performed in PubMed, Embase, Scopus, Web of Science, and PsycINFO, in June 2025. Grey literature was explored through the Brazilian Digital Library of Theses and Dissertations (BDTD). Authors were not contacted for missing data, and no restrictions were applied regarding publication date or language. Letters, editorials, protocols, and conference abstracts were excluded.

Search strategy. The strategy was developed using DeCS, MeSH, and Emtree descriptors, in addition to keywords, following PRESS (Peer Review of Electronic Search Strategies) recommendations. Terms included: "cardiovascular disease" OR "cardiac disease" AND "negative emotion" OR "negative affect" OR "negative feeling" OR "Fear" OR "Anger" OR "Sadness" OR "Disgust" OR "Shame" OR "Contempt" OR "Guilt" OR "Envy" OR "Jealousy" OR "Anxiety" OR "Hopelessness" OR "Helplessness" OR "Loneliness" OR "Frustration" OR "Disappointment" OR

"Resentment" OR "Grief" OR "Despair" OR "Rejection" OR "Mistrust" OR "fear of death" OR "Anguish" OR "Hurt".

Study selection. EndNoteWeb software was used for reference management and screening, performed independently by three reviewers. Reviewers participated in all stages: (1) *Identification* – retrieval of studies from databases; (2) *Screening* – removal of duplicates, application of inclusion and exclusion criteria through title/abstract and full-text reading; and (3) *Inclusion* – data extraction and analysis of eligible studies. These steps are illustrated in a PRISMA flow diagram provided in the Results section. Relevance tests were applied to guide article inclusion or exclusion. Inclusion criteria considered the association between depression and/or anxiety and the development of cardiovascular diseases, with effect measures such as Frequency, Odds Ratio (OR), Hazard Ratio (HR), and Relative Risk (RR). Exclusion criteria included studies restricted to specific populations (e.g., metabolic syndromes and others).

Data synthesis and analysis. A descriptive synthesis was elaborated, including type of study, country, objectives, sample, and conclusions, followed by quantitative analysis (meta-analysis) by subgroups (anxiety and depression), according to reported outcomes. Meta-analyses were performed using *Comprehensive Meta-Analysis* software, Version 4.0.000. A random-effects model was applied due to high heterogeneity. Heterogeneity was assessed using I^2 based on Cochran's Q test. Subgroup analyses by sex, follow-up time, geographic region, or CVD subtype could not be performed due to inconsistent reporting formats. Results were displayed in forest plots. Publication bias was not assessed given the small number of included studies.

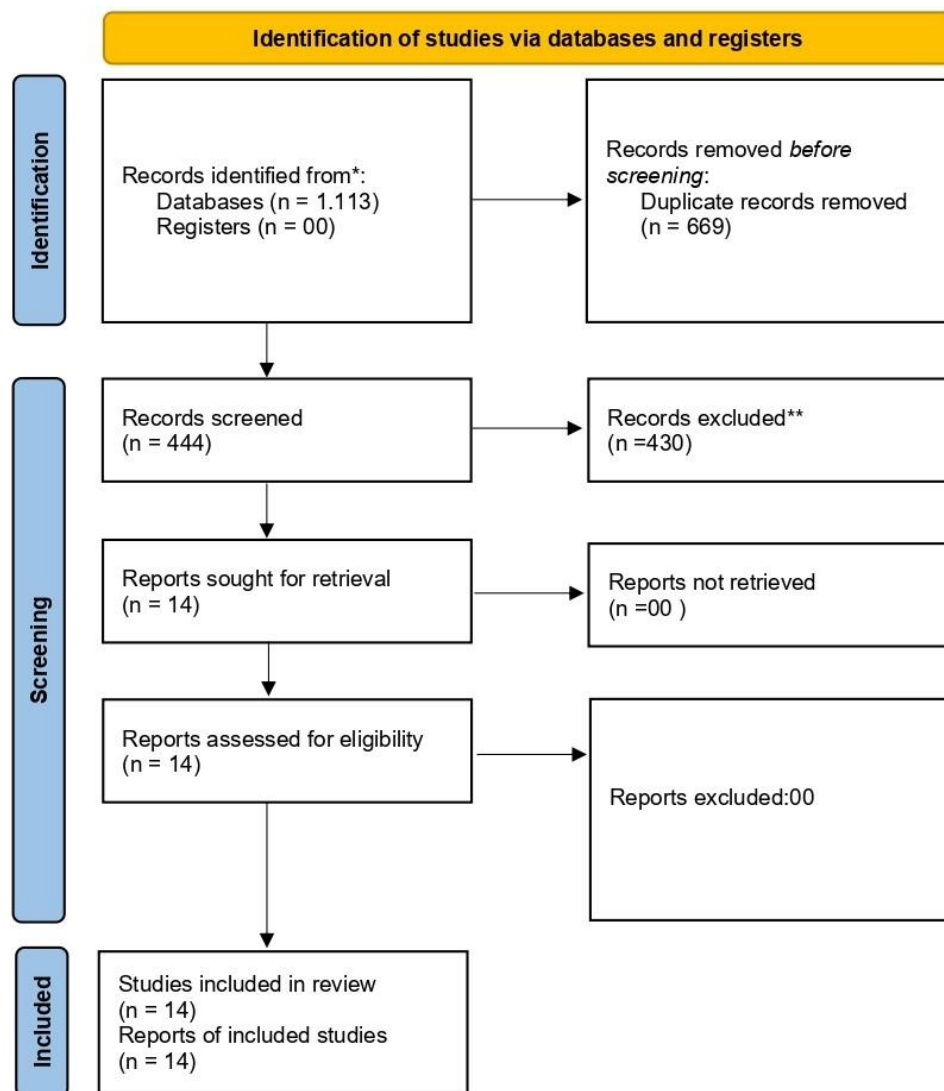
Risk of bias assessment. The Joanna Briggs Institute (JBI) tools for observational studies were used. Studies meeting $\geq 80\%$ of items were considered *high quality* (low risk of bias); those meeting 60–79% were considered *moderate quality* (moderate risk of bias); and those meeting $< 59\%$ were classified as *low quality* (high risk of bias).

Certainty of evidence. The strength of evidence was evaluated using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) framework. Factors considered included study design, methodological limitations, inconsistency, indirectness, imprecision, publication bias, effect magnitude, dose–response gradient, and residual confounding.

RESULTS

A total of 1,113 records were initially identified across the databases, as shown in Table 1 (Supplementary Files). Fourteen studies were selected for qualitative data synthesis, as illustrated in Figure 1.

Figure 1 – PRISMA 2020 flow diagram of study selection



The studies were published between 2008 and 2024 in the following countries: Canada, the Netherlands, the United Kingdom, the United States, Germany, Greece, Jordan, and China. The total sample comprised 471,104 participants, with study designs including cross-sectional and cohort studies. The mean age ranged from 41.2 to 66.6 years. To assess Depression, Anxiety, and Cardiovascular Disease, the studies employed a variety of instruments, as detailed in Table 2 (Supplementary Files).

Table 3 provides a comprehensive synthesis of the 14 studies included in this systematic review, encompassing diverse study designs, populations, and geographic regions. The findings consistently demonstrate that both depression and anxiety are associated with an increased risk of cardiovascular disease (CVD), although the strength and specificity of these associations

vary. While depression emerged as a robust and independent risk factor across multiple cohorts, anxiety showed more heterogeneous results, with stronger associations observed in specific conditions such as coronary heart disease or panic disorder. Furthermore, studies highlight the influence of sociodemographic and lifestyle factors in mediating these relationships, as well as the potential additive effects of comorbid depression and anxiety. Collectively, the evidence underscores the clinical relevance of incorporating mental health assessments into cardiovascular risk evaluation and management.

Table 3 – Synthesis of the 14 selected studies

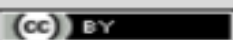
Authors / Year	Study Design / Country	Study Objective	Sample Profile (n, age, sex)	Main Results	Study Conclusions
Wang <i>et al.</i> (2024)	Cross-sectional / China	To estimate the association of depressive and anxiety symptoms with the risk of CVD in middle-aged and older Chinese women, and to evaluate the influence of sociodemographic factors.	n = 9,544; age: 40-70 years; sex: women.	Depressive symptoms increased the risk of CVD by 89% (OR = 1.89; 95% CI: 1.52–2.36; p < 0.001), while anxiety symptoms increased the risk of CVD by 55% (OR = 1.55; 95% CI: 1.21–1.98; p < 0.001).	Findings highlight the importance of recognizing and managing depressive and anxiety symptoms to reduce CVD risk in middle-aged and older women, particularly those of lower socioeconomic status.
Kyrou <i>et al.</i> (2017)	Prospective Cohort / Greece	To explore associations between depressive symptoms, anxiety levels, and the 10-year incidence of CVD in healthy Greek adults.	n = 853; mean age: men 45 ± 13 women 44 ± 18 years; sex: 453 men, 400 women.	Depression was associated with nearly a fourfold increased risk (adjusted OR = 3.6; 95% CI: 1.3–11; p = 0.01) of CVD within 10 years. Higher baseline anxiety levels were also associated with increased CVD incidence over 10 years (OR = 1.03; 95% CI: 1.0–1.1; p = 0.08).	Depression is a strong and independent risk factor for the development of CVD in healthy Greek adults. Elevated anxiety levels were also linked to increased CVD incidence.
Riahi <i>et al.</i> (2023) ¹³	Cohort / USA	To determine the association of chronic stress, depressive symptoms, anxiety, and emotional social support with the incidence of hard CVD (HCVD).	n = 6,779; age: 45-84 years (mean 62.2 ± 10.2); sex: 47.2% men, 52.8% women	Each additional point on the depressive symptoms scale was associated with a 2% higher risk of CVD (HR = 1.02; 95% CI: 1.01–1.03).	The study demonstrated a longitudinal association of depressive symptoms, chronic stress, and emotional social support with the incidence of HCVD; higher levels of chronic stress and depressive symptoms were linked to increased risk, while greater emotional social support was associated with reduced risk.
Vogelzangs <i>et al.</i> (2010)	Cohort / Netherlands	To examine the association between psychiatric diagnoses of depressive and/or anxiety disorders and CVD, as well as the specificity of these	n = 2,807; mean age: 41.8 years; sex: 66.4% women	Current anxiety disorders were more strongly associated with Coronary Heart Disease (CHD). OR = 2.70 (95% CI: 1.31–5.56; p < 0.05) for anxiety alone; OR = 3.54 (95% CI:	Anxiety disorders are more strongly associated with CHD than depressive disorders and may partly explain the association between depression and heart disease. The highest prevalence

		associations.		1.79–6.98; $p < 0.05$) for comorbidity with depression.	of CHD was observed among individuals with more severe psychiatric symptoms.
Kinley <i>et al.</i> (2015)	Cross-sectional / Germany	To explore the relationship between anxiety and depressive disorders with heart conditions and metabolic risk factors using DSM-IV medical and psychiatric diagnoses.	n = 4,181; age: 18-65 years; sex: 50.3% men, 49.7% women	Anxiety disorders were associated with increased odds of angina (AOR = 3.49; 95% CI: 2.13–5.72; $p < 0.001$), myocardial infarction (AOR = 3.05; 95% CI: 1.33–6.99; $p < 0.01$), dyslipidemia (AOR = 1.42; 95% CI: 1.11–1.82; $p < 0.01$), obesity (AOR = 1.26; 95% CI: 1.00–1.58; $p < 0.05$), and diabetes (AOR = 1.66; 95% CI: 1.02–2.71; $p < 0.05$).	Having an anxiety disorder was significantly associated with higher odds of angina, myocardial infarction, dyslipidemia, obesity, and diabetes. In contrast, depression was not significantly associated with any of these conditions.
Seldenrijk <i>et al.</i> (2015)	Cohort / Netherlands	To examine the 6-year associations between depressive and anxiety disorders, clinical characteristics, and newly developed CVD.	n = 2,510; mean age: 41.2 years; sex: 67.7% women	Recurrent Major Depressive Disorder was associated with a two-to threefold increased risk of CVD over six years. No overall association was found for anxiety disorders, except for Panic Disorder (HR = 2.12; 95% CI: 1.27–3.55; $p < 0.001$).	Depression, more than anxiety, entails an increased risk of subsequent CVD, with a dose-response association observed for symptom severity.
Frasure-Smith e Lespérance (2008)	Prospective Observational / Canada	To examine the relationship between DSM-IV-based diagnoses and self-reported measures of anxiety and depression assessed approximately 2 months after hospital discharge for acute coronary syndrome (ACS), and the occurrence of major adverse cardiac events (MACEs) during the subsequent 2 years; and to determine whether the combination of anxiety and depression confers greater risk	n = 804; mean age: 60.0 years; sex: 19.3% women	All DSM-IV diagnoses and self-reported measures of anxiety and depression significantly predicted MACEs. Major Depressive Disorder (OR = 2.34) and Generalized Anxiety Disorder (OR = 2.46) remained significant predictors after adjustment.	Both MDD and GAD, as well as self-reported symptoms, predict MACEs within 2 years in patients with stable CAD. However, comorbidity does not confer additional risk compared with the presence of either disorder alone.

		compared to either factor alone.			
Kollia <i>et al.</i> (2017).	Prospective Cohort / Greece	To explore the combined effects of depression and anxiety on the 10-year incidence of CVD in relation to other lifestyle determinants.	n = 853; mean age: men 45 ± 13, women 44 ± 18 years; sex: 453 men, 400 women.	“Psychological Distress” (a combined measure of depression and anxiety) was positively and significantly associated with 10-year CVD incidence (OR = 1.4 per 10 units).	“Psychological Distress” (a combined measure of depression and anxiety) was positively and significantly associated with 10-year CVD incidence (OR = 1.4 per 10 units).
Peter <i>et al.</i> (2020) ¹⁴	Cohort / Germany	To identify trajectory classes of anxiety and depression in patients with stable Coronary Artery Disease (CAD) and their association with the risk of subsequent cardiovascular events.	n = 1,109; mean age: 59.4 years; sex: 15.4% women	Chronically high depression trajectory classes were associated with an HR of 2.47 for subsequent cardiovascular events in CAD patients.	Trajectory classes of anxiety and depression were identified among patients with stable CAD. Persistently high depression and high-decreasing anxiety trajectories were associated with an increased risk of subsequent cardiovascular events.
Whang <i>et al.</i> (2014)	Cross-sectional / USA	To provide insights into the mechanisms by which depression and anxiety are differentially related to cardiac mortality.	n = 5,906; mean age: 62 years	Elevated depressive symptoms were associated with increased odds of T-wave inversions on electrocardiogram (ECG) (OR = 2.02; 95% CI: 1.33–3.06; p = 0.001), while elevated trait anxiety was associated with reduced odds of T-wave inversions (OR = 0.47; 95% CI: 0.29–0.77; p = 0.003).	Depressive and anxiety symptoms were independently—but oppositely—associated with cardiac repolarization. Elevated depressive symptoms increased the likelihood of T-wave inversions on ECG (other than leads V1–V3), whereas elevated trait anxiety symptoms were associated with reduced likelihood of T-wave inversions.
Pelletier <i>et al.</i> (2015)	Prospective Observational / Canada	To evaluate whether depression and anxiety increase the risk of mortality and major adverse cardiac events (MACE) in patients with and without Coronary Artery Disease (CAD).	n = 2,390; mean age: 57 years (range 18–75); sex: 33% women	Depression was an independent risk factor for all-cause mortality (RR = 2.84; 95% CI: 1.25–6.49), with the risk being even more pronounced in patients without CAD (RR = 4.39; 95% CI: 1.12–17.21).	Depression, but not anxiety, was an independent risk factor for all-cause mortality in patients without CAD.
Breik e Elbedour (2021)	Cross-sectional / Jordan	To determine whether Type D personality, depression, and anxiety have predictive value	n = 309; age: 19-82 years (mean 45 years);	Anxiety was a significant predictor of heart problems (OR = 1.04; p = 0.020).	Type D personality, depression, and anxiety have predictive value for CVD, confirming the cross-cultural

		for CVD.	sex: 54% men		validity of these factors in predisposing individuals to cardiovascular disease.
Holt <i>et al.</i> (2013)	Cohort United Kingdom	To determine the relationship between depressive and anxiety symptoms and CVD in a population-based cohort.	n = 2,995; age: men 65.7 years, women 66.6 years; sex: 1,578 men, 1,417 women	Depressive symptoms were independent predictors of incident CVD and cardiovascular mortality in men. High HAD-D scores were associated with ORs for CVD of 1.162 in men and 1.107 in women. High HAD-A scores were associated with an OR of 1.101 for CVD in men, but not in women. The association between HAD-D and CVD was not fully explained by traditional risk factors.	There is a relationship between depressive symptoms and CVD (both cross-sectional and longitudinal). Depressive and anxiety symptoms are more common in individuals with CVD, and depressive symptoms are independent predictors of CVD in men.
Nakada <i>et al.</i> (2023)	Cohort United Kingdom	To examine the individual and joint associations of anxiety disorder and depression with incident CVD and its subtypes.	n = 431,973; mean age: 56.1 years; sex: 55.0% women	Depression alone was associated with HR = 2.07 (95% CI: 1.79–2.40) for overall CVD, and anxiety alone was associated with HR = 1.72 (95% CI: 1.32–2.24) for overall CVD.	Anxiety disorder and depression are independently associated with incident CVD, and their coexistence increases risk more than either condition alone. The combined effect is additive.

CVD: Cardiovascular Disease; OR: Odds Ratio; CI: Confidence Interval; HCVD: Hard Cardiovascular Disease; HR: Hazard Ratio; CHD: Coronary Heart Disease; AOR: Adjusted Odds Ratio; DSM: Diagnostic and Statistical Manual of Mental Disorders; ACS: Acute Coronary Syndrome; MACEs: Major Adverse Cardiac Events; MDD: Major Depressive Disorder; GAD: Generalized Anxiety Disorder; CAD: Coronary Artery Disease; ECG: electrocardiogram; RR: Relative Risk; HAD-D: Hospital Anxiety and Depression - Depression Scores; HAD-A: Hospital Anxiety and Depression - Anxiety Scores.



Risk of Bias Assessment

As shown in Table 4 (Supplementary Files), 12 studies demonstrated high quality, while only 2 studies were classified as moderate quality. In cohort studies, the items that warrant closer attention include: reliability of outcome measurement, length of follow-up, completeness of follow-up, and the presence of strategies to address loss to follow-up. In cross-sectional studies, the critical items are: method of measuring the condition, identification of confounding factors, strategies for managing confounders, and method of measuring outcomes.

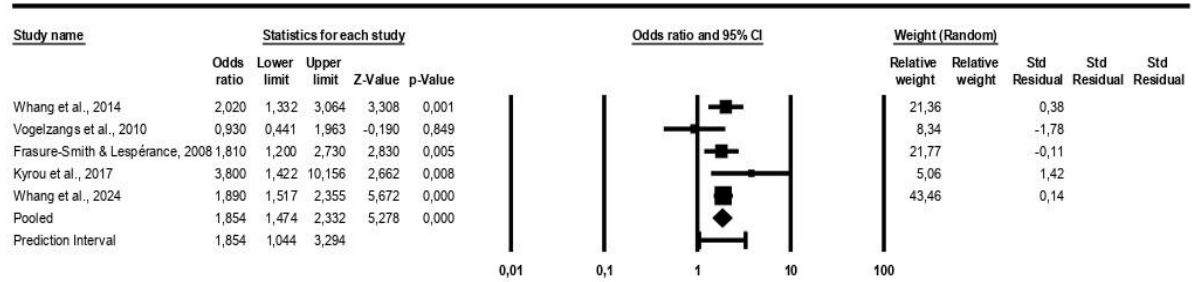
Meta-Analysis

The meta-analysis included only those studies reporting effect measures as Odds Ratios (OR). This approach allowed us to address the following research question: *What are the odds of developing Cardiovascular Disease (CVD) in individuals exposed to Depression or Anxiety compared with those unexposed?* A random-effects model was applied. Importantly, only adjusted effect measures were considered. Table 5 (Supplementary Files) summarizes the odds ratios from the included studies.

The following studies were excluded from the meta-analysis: Kinley *et al.* (2015), which assessed Depression and Anxiety in relation to specific cardiovascular conditions; Kollia *et al.* (2017), which combined Depression and Anxiety under the construct of *Psychological Distress*; Breik e Elbedour (2021), which did not provide confidence interval values; and Holt *et al.* (2013), which did not report results for the general population. For the first analysis, data from five studies were included (Wang *et al.*, 2014; Vogelzangs *et al.*, 2010, Frasure-Smith, Lespérance, 2008; Kyrou *et al.*, 2017; Wang *et al.*, 2024). All employed OR as the effect measure to evaluate the association between Depression and the development of Cardiovascular Diseases.

The results indicate an 85% increased likelihood of individuals with Depression developing CVD (OR = 1.85, 95% CI: 1.47–2.33, $p < 0.001$; $I^2 = 27\%$), as illustrated in Figure 2. For the second analysis, data from five studies were included (Wang *et al.*, 2014; Vogelzangs *et al.*, 2010, Frasure-Smith, Lespérance, 2008; Kyrou *et al.*, 2017; Wang *et al.*, 2024). All employed OR as the effect measure to evaluate the association between Anxiety and the development of CVD.

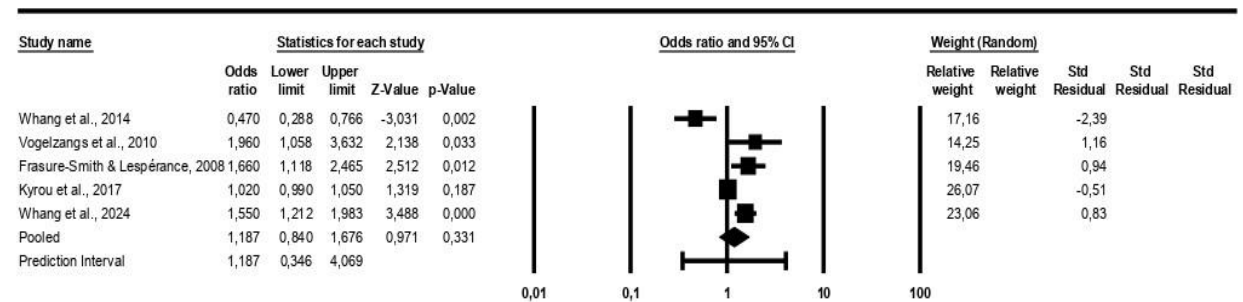
Figure 2 – Forest plot of the odds ratio (OR) for the risk of patients with Depression developing Cardiovascular Disease (CVD).



Meta Analysis

The results show an 18% increased likelihood of individuals with Anxiety developing CVD (OR = 1.18, 95% CI: 0.84–1.67, $p > 0.05$; $I^2 = 86\%$), as illustrated in Figure 3.

Figure 3 – Forest plot of the odds ratio (OR) for the risk of patients with Anxiety developing Cardiovascular Disease (CVD)



Meta Analysis

Regarding the strength of evidence, according to the GRADE framework (Table 6 – Supplementary Files), the finding of an 85% increased likelihood of individuals with Depression developing CVD (OR = 1.85, 95% CI: 1.47–2.33, $p < 0.001$; $I^2 = 27\%$) was rated as *high certainty of evidence*. In contrast, the result indicating an 18% increased likelihood of individuals with Anxiety developing CVD (OR = 1.18, 95% CI: 0.84–1.67, $p > 0.05$; $I^2 = 86\%$) was graded as *low certainty of evidence*, due to inconsistency and imprecision.

DISCUSSION

The aim of this study was to investigate the association between Depression, Anxiety, and the development of Cardiovascular Diseases (CVD). While previous meta-analyses have addressed this objective, they typically examined either depression or anxiety in isolation. For instance, Krittanawong *et al.* (2023) concluded that depression exerts a significant negative impact on cardiovascular disease development. Earlier, Emdin *et al.* (2016) identified anxiety as a risk factor for several cardiovascular events. To the best of our knowledge, this is the first meta-analysis to demonstrate, within a single study, the association of both disorders (Depression and Anxiety, separately) with CVD development, while also providing consistency in its conclusions by applying the GRADE tool to certify the strength of evidence. This conclusion is in line with the most recent *European Society of Cardiology Clinical Consensus Statement* (Bueno *et al.*, 2025), which proposed a multidirectional relationship between mental health, cardiovascular health, and their impact on cardiovascular risk and prognosis.

The present findings are consistent with other large-scale studies. Cao, Zhao e Shen (2022), in a cohort of more than 400,000 participants, confirmed depression as a robust risk factor for coronary artery disease. Likewise, large-scale evidence, such as a Japanese study involving over 4 million individuals published by Pennells and Mascie-Taylor (2024), demonstrated a persistent association between clinically diagnosed depression and incident CVD, with stronger effects observed among women. These data converge with our findings, reinforcing depression as a cardiovascular risk factor.

Complementary evidence by Shen *et al.* (2023) indicated that cardiovascular risk associated with psychiatric disorders cannot be fully explained by familial or environmental factors, suggesting an independent and multifactorial effect. This interpretation supports the view that depression – and, to a lesser extent, anxiety – functions as both a clinical and biological determinant of cardiovascular risk (Kyrou *et al.*, 2017; Wang *et al.*, 2024; Seldenrijk *et al.*, 2015; Frasure-Smith, Lespérance, 2008).

Kollia *et al.* (2017) and Kinley *et al.* (2015) found stronger associations between anxiety disorders and Coronary Heart Disease, Angina, Myocardial Infarction, Dyslipidemia, Obesity, and Diabetes.

The meta-analysis by Emdin *et al.* (2016) provides robust evidence that anxiety is significantly associated with increased risk of cardiovascular mortality, coronary heart disease (CHD), stroke, and heart failure. Similarly, Frasure-Smith and Lespérance (2008)³⁵

demonstrated that both Generalized Anxiety Disorder (GAD) and self-reported anxiety symptoms predicted major adverse cardiac events (MACEs) in patients with stable coronary artery disease (CAD).

Professional guidelines have also emphasized this relationship. Levine *et al.* (2021), from the American Heart Association, recommend systematic screening for depressive symptoms in CVD patients, while Visseren *et al.* (2021), from the European Society of Cardiology, highlight psychosocial factors as essential modulators of risk. The present review reinforces these recommendations, providing both qualitative and quantitative evidence supporting the need to integrate mental health systematically into cardiovascular prevention strategies.

Adopting a comprehensive lifestyle intervention may further reduce the CVD burden in individuals with Depression and Anxiety, as lifestyle factors strongly influence mental health (Bourke *et al.*, 2022; 2025). According to the American Heart Association (2022), cardiovascular health is determined by eight essential components: diet, physical activity, nicotine exposure, sleep health, body mass index, blood lipids, blood glucose, and blood pressure (Chen *et al.*, 2024; Lloyd-Jones *et al.*, 2022).

In summary, this Systematic Review and Meta-Analysis demonstrates that depression and anxiety are important psychosocial factors that significantly contribute to the risk of developing or worsening cardiovascular diseases. The complexity of these interaction and the influence of additional factors demand comprehensive and individualized healthcare approaches.

Despite the generally high methodological quality of the included studies, the predominance of cross-sectional designs limits causal inference. The heterogeneity of diagnostic instruments and frequent reliance on self-reported measures of depression, anxiety, and CVD may introduce information bias. Given the limited number of studies in the meta-analyses ($n < 10$), publication bias could not be formally assessed.

Depression and anxiety should be formally incorporated into cardiovascular risk stratification strategies, with systematic screening in primary care, outpatient cardiology, and secondary prevention programs. At the population level, mental health interventions must be integrated into public health policies targeting cardiovascular disease, given their direct impact on disease incidence and progression.

There is an urgent need for longitudinal and clinical trials with better confounder control and standardized diagnostic instruments. Research evaluating psychotherapeutic,

pharmacological, and spiritual interventions in the cardiovascular context is also a priority. Studies assessing the coexistence of depression and anxiety and their combined impact on cardiovascular health remain scarce. Demonstrating whether effective treatment of depression and anxiety reduces cardiovascular events represents the main remaining scientific gap.

CONCLUSION

This systematic review and meta-analysis demonstrates that depression increases the risk of cardiovascular disease by 85%, a magnitude comparable to or even greater than classical risk factors such as hypertension, smoking, and obesity. Anxiety alone, although supported by low-certainty evidence, was associated with an 18% increased risk of cardiovascular disease.

In light of these findings, we advocate that depression should be formally incorporated into cardiovascular risk stratification scores, in alignment with recent recommendations from the AHA (2021) and ESC (2021). Systematic screening using validated instruments (PHQ-2/PHQ-9), structured psychosocial follow-up, and integration between mental health and cardiovascular prevention programs should be considered essential measures in contemporary clinical practice.

The next scientific challenge is to determine, through clinical trials, whether effective treatment of depression and anxiety can reduce the incidence of cardiovascular events. Until such evidence is available, the implementation of public health policies and clinical protocols that consider mental health as an inseparable component of cardiovascular prevention is not only recommended but necessary.

DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES IN THE MANUSCRIPT PREPARATION PROCESS

During the preparation of this work the author(s) used NotebookLM in order to assist in the data extraction process. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the published article.

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ADDITIONAL INFORMATION

Registration and Protocol:

This review was registered in PROSPERO under the number CRD420251115684.

The full protocol can be accessed at:

https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD420251115684.

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The authors declare no relevant conflicts of interest for this publication.

Availability of Data, Code, and Other Materials:

Data extraction templates, the database used for the meta-analysis, and forest plots are available upon request from the corresponding author. The analytical code employed in the *Comprehensive Meta-Analysis* software follows the default settings and is documented in the review protocol.

SUPPLEMENTARY FILES

Table 1 – Results of study searches

Databases	Search Strategy	Results
Medline / Pubmed	("cardiovascular disease"[Title] OR "cardiac disease"[Title]) AND ("negative emotion"[Title] OR "negative affect"[Title] OR "negative feeling"[Title] OR "Fear"[Title] OR "Anger"[Title] OR "Sadness"[Title] OR "Disgust"[Title] OR "Shame"[Title] OR "Contempt"[Title] OR "Guilt"[Title] OR "Envy"[Title] OR "Jealousy"[Title] OR "Anxiety"[Title] OR "Hopelessness"[Title] OR "Helplessness"[Title] OR "Loneliness"[Title] OR "Frustration"[Title] OR "Disappointment"[Title] OR "Resentment"[Title] OR "Grief"[Title] OR "Despair"[Title] OR "Rejection"[Title] OR "Mistrust"[Title] OR "fear of death"[Title] OR "Anguish"[Title] OR "Hurt"[Title])	170
Scopus	(((title ("cardiovascular disease") or title ("cardiac disease"))) and ((title ("negative emotion") or title ("negative affect") or title ("negative feeling") or title ("fear") or title ("anger") or title ("sadness") or title ("disgust") or title ("shame") or title ("contempt") or title ("guilt") or title ("envy") or title ("jealousy") or title ("anxiety") or title ("hopelessness") or title ("helplessness") or title ("loneliness") or title ("frustration") or title ("disappointment") or title ("resentment") or title ("grief") or title ("despair") or title ("rejection") or title ("mistrust") or title ("fear of death") or title ("anguish") or title ("hurt"))))	259
Embase	'cardiovascular disease':ti OR 'cardiac disease':ti AND 'negative feeling':ti OR 'negative emotion':ti OR 'negative affect':ti OR fear:ti OR 'anger':ti OR 'sadness':ti OR disgust:ti OR shame:ti OR 'contempt':ti OR 'guilt':ti OR 'envy':ti OR 'jealousy':ti OR 'anxiety':ti OR 'hopelessness':ti OR 'helplessness':ti OR 'loneliness':ti OR 'frustration':ti OR 'disappointment':ti OR 'resentment':ti OR hurt:ti OR grief:ti OR despair:ti OR 'rejection':ti OR 'distrust':ti OR 'fear of death':ti OR 'anguish'	220
PsycINFO	((title: ("cardiovascular disease")) OR (title: ("cardiac disease"))) AND ((title: ("negative emotion") OR title: ("negative affect") OR title: ("negative feeling") OR title: ("Fear") OR title: ("Anger") OR title: ("Sadness" OR "Disgust") OR title: ("Shame") OR title: ("Contempt") OR title: ("Guilt") OR title: ("Envy") OR title: ("Jealousy") OR title: ("Anxiety") OR title: ("Hopelessness") OR title: ("Helplessness") OR title: ("Loneliness") OR title: ("Frustration") OR title: ("Disappointment") OR title: ("Resentment" OR "Grief" OR "Despair" OR "Rejection" OR "Mistrust" OR "fear of death") OR title: ("Anguish" OR "Hurt"))))	98
Web of Science	(TI=(cardiovascular disease OR cardiac disease)) AND TI=(negative feeling OR negative emotion OR negative affect OR fear OR anger OR sadness OR disgust OR shame OR contempt OR guilt OR envy OR jealousy OR anxiety OR hopelessness OR helplessness OR loneliness OR frustration OR disappointment OR resentment OR hurt OR grief OR despair OR rejection OR distrust OR fear of death OR anguish)	366
BDTD	"cardiovascular disease" OR "cardiac disease" AND "negative emotion" OR "negative affect" OR "negative feeling" OR "Fear" OR "Anger" OR "Sadness" OR "Disgust" OR "Shame" OR "Contempt" OR "Guilt" OR "Envy" OR "Jealousy" OR "Anxiety" OR "Hopelessness" OR "Helplessness" OR "Loneliness" OR "Frustration" OR "Disappointment" OR "Resentment" OR "Grief" OR "Despair" OR "Rejection" OR "Mistrust" OR "fear of death" OR "Anguish" OR "Hurt"	0
Total		1,113

Table 2 – Instruments for the Assessment of Depression, Anxiety, and Cardiovascular Diseases

Condition	Assessment instruments
Depression	<ul style="list-style-type: none"> - Chinese version of the Patient Health Questionnaire-9 (PHQ-9) - Zung Self-Rating Depression Scale (ZDRS) - Center for Epidemiologic Studies Depression Scale (CES-D) - Inventory of Depressive Symptomatology (IDS/IDS-SR30) - Beck Depression Inventory-II (BDI-II) - Composite International Diagnostic Interview (CIDI) - Modified version of the CIDI (DIA-X/M-CIDI) - Structured Clinical Interview for DSM-IV (SCID) - Depression subscale of the Hospital Anxiety and Depression Scale (HADS-D) - Hospital admission and mortality data using ICD-10 codes (F32–33 for depression)
Anxiety	<ul style="list-style-type: none"> - Spielberger State-Trait Anxiety Inventory (STAI) - Beck Anxiety Inventory (BAI) - Fear Questionnaire (FQ) for measuring avoidance - Penn State Worry Questionnaire (PSWQ) - Anxiety subscale of the Hospital Anxiety and Depression Scale (HADS-A) - Composite International Diagnostic Interview (CIDI) - Modified version of the CIDI (DIA-X/M-CIDI) - Structured Clinical Interview for DSM-IV (SCID) - Hospital admission and mortality data using ICD-10 codes (F40–43 for anxiety)
Cardiovascular Diseases (CVD)	<ul style="list-style-type: none"> - Self-reported medical diagnoses of stroke or cardiac events (myocardial infarction, coronary heart disease, congestive heart failure, angina) - Confirmation through the use of specific medications for heart disease, hypertension, or dyslipidemia (inspection of medication containers, ATC coding) - Medical and hospital records data - Adjudication by trained physicians and review using International Classification of Diseases (ICD-9/10) codes - Electrocardiograms (ECG) for T-wave abnormalities, QRS duration, and major Q waves - Physical examinations such as blood pressure, weight, height, and biomarkers (troponins, creatine kinase-MB fraction, fasting glucose, triglycerides, BMI) - Cardiac magnetic resonance imaging (MRI) for left ventricular mass index (LVMI) - SPECT imaging for myocardial ischemia - Database records used for all-cause mortality and major adverse cardiac events (MACE)

Table 4 – Risk of bias assessment of the included studies.

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	%
1. Seldenrijk et al., 2015 (Cohort)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100%
2. Frasure-Smith & Lespérance, 2008 (Cohort)	Y	Y	Y	Y	Y	S	N	N	Y	Y	Y	81%
3. Kollia et al., 2017 (Cohort)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100%
4. Peter et al., 2020 (Cohort)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100%
5. Pelletier, R. et al., 2015 (Cohort)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100%
6. Holt et al., 2013 (Cohort)	Y	Y	Y	Y	Y	Y	Y	Y	N	N	Y	81%
7. Riahi et al., 2023	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100%
8. Kyrou et al., 2017 (Cohort)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100%
9. Nakada et al., 2023 (Cohort)	Y	Y	Y	Y	Y	Y	Y	Y	UC	UC	Y	100%
10. Wang et al., 2024 (Cross-sectional)	Y	Y	Y	N	Y	Y	N	Y	NA	NA	NA	75%
11. Vogelzangs et al., 2010 (Cross-sectional)	Y	Y	Y	Y	Y	Y	Y	Y	NA	NA	NA	100%
12. Whang et al., 2014 (Cross-sectional)	Y	Y	Y	Y	Y	Y	Y	Y	NA	NA	NA	100%
13. Kinley et al., 2015 (Cross-sectional)	Y	Y	Y	Y	Y	Y	Y	Y	NA	NA	NA	100%
14. Breik e Elbedour, 2021 (Cross-sectional)	Y	Y	Y	S	N	N	Y	Y	NA	NA	NA	75%

Legend: Evaluation across 11 domains of methodological quality. Y = Yes; N = No; UC = Unclear; NA= Not Applicable.

Table 5 – Effect measures (Odds Ratios, ORs) of the association between depression, anxiety, and cardiovascular disease (CVD).

Authors	Measure of Association	Value (95% CI)	Mental Disorder
Whang et al., 2014	OR	2.02 (1.33–3.06)	Depression
	OR	0.47 (0.29–0.77)	Anxiety
Vogelzangs et al., 2010	OR	0.93 (0.44–1.96)	Depression
	OR	1.96 (1.06–3.64)	Anxiety
	OR	2.35 (1.33–4.20)	Depression and Anxiety
Frasure-Smith & Lespérance, 2008	OR	1.81 (1.20–2.73)	Depression
	OR	1.66 (1.12–2.47)	Anxiety
	OR	1.42 (1.14–1.75)	Depression and Anxiety
Kyrou et al., 2017	OR	3.80 (1.4–10)	Depression
	OR	1.02 (0.99–1.05)	Anxiety
Wang et al., 2024	OR	1.89 (1.52–2.36)	Depression
	OR	1.55 (1.21–1.98)	Anxiety

Legend: Summary of individual study estimates with 95% confidence intervals.

Table 6 – GRADE (The Grading of Recommendations, Assessment, Development and Evaluation)

Assessment of the Strength of the Evidence						
Participants (Studies/Follow-up)	Risk of Bias	Inconsistency	Indirect Evidence	Imprecision	Other Considerations	Certainty of the Evidence
Odds ratio for the risk of patients with Depression developing CVD						
(5 observational studies)	Not serious	Not serious	Not serious	Not serious	No publication bias detected. Low effect magnitude. Potential confounding factors may have reduced the demonstrated effect. Significant dose-response gradient.	⊕⊕⊕⊕ High
Odds ratio for the risk of patients with Anxiety developing CVD						
(5 observational studies)	Not serious	Serious ^a	Not serious	Serious ^b	No publication bias detected. Low effect magnitude. Potential confounding factors may have reduced the demonstrated effect. Significant dose-response gradient.	⊕⊕○○ Low ^{a,b}

^a High heterogeneity; serious inconsistency. ^b 95% CI crosses the line of no effect; serious imprecision.

