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THE BIOPSYCHOSOCIAL MECHANISMS UNDERLYING THE RELATIONSHIP BETWEEN DEPRESSION, ANXIETY, AND CARDIOVASCULAR DISEASE: A LONGITUDINAL STUDY ON THE IMPACT OF CHRONIC STRESS AND INFLAMMATORY PATHWAYS IN MIDDLE-AGED ADULTS

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ABSTRACT

Background: Depression and anxiety are well-established independent risk factors for cardiovascular disease (CVD), yet the precise biopsychosocial mechanisms mediating this relationship remain incompletely understood. This paper synthesizes current longitudinal evidence to dissect the pathways through which chronic psychological distress translates into cardiovascular pathology, with a specific focus on hypothalamic-pituitary-adrenal (HPA) axis dysregulation, autonomic nervous system imbalance, and systemic low-grade inflammation.

Methods: We conducted an integrative review of population-based longitudinal studies, systematic reviews, and meta-analyses published between 2000 and 2025, with emphasis on prospective cohort studies measuring inflammatory biomarkers (C-reactive protein, interleukin-6, tumor necrosis factor-α), cortisol, endothelial function, and arterial stiffness in middle-aged adults (40–65 years).

Results: Convergent evidence demonstrates that depression and anxiety independently predict the development of cardiovascular risk factors, including hypertension, hyperlipidemia, and diabetes mellitus, and accelerate the transition from subclinical atherosclerosis to overt CVD events. HPA axis hyperactivity drives cortisol excess and catecholamine surges, which directly remodel the vascular endothelium and promote oxidative stress. Sympathetic overdrive and parasympathetic withdrawal—manifesting as reduced heart rate variability—are consistently linked to elevated inflammatory marker levels in large-scale longitudinal investigations. Inflammation emerges as a central mediator, with elevated C-reactive protein and interleukin-6 levels both predicting incident depression and anxiety and mediating the risk of myocardial infarction and stroke. Three linking pathways—sedentariness, inflammation, and metabolic syndrome—statistically account for a substantial proportion of the psychological distress–CVD association. Structural equation modeling from the Whitehall II study supports a stress-inflammation-depression-CVD cascade. Moreover, age and sex effects reveal that younger women exhibit the greatest acceleration of cardiovascular risk factor development following anxiety/depression onset.

Conclusions: The evidence reviewed robustly supports a biopsychosocial model wherein chronic stress triggers a cascade of neuroendocrine, autonomic, inflammatory, endothelial, behavioral, and socioeconomic processes that collectively promote cardiovascular morbidity. These findings underscore the clinical imperative for integrating mental health screening into cardiovascular risk assessment and for developing targeted interventions that interrupt the identified linking pathways.

KEYWORDS: depression, anxiety, cardiovascular disease, chronic stress, inflammation, HPA axis, endothelial dysfunction, biopsychosocial model, longitudinal

1. INTRODUCTION

Cardiovascular Disease (CVD) is the world's biggest killer, with an estimated 17.9 million deaths every year from cardiovascular disease (World Health Organization, 2021). Although traditional risk factors like hypertension, diabetes mellitus, dyslipidemia and smoking have long been the leading determinants in clinical algorithms for stratification of cardiovascular disease (CVD) risk, there is now an extensive and rapidly expanding body of evidence from epidemiologic and mechanistic studies that provides evidence that psychological factors, especially depression and anxiety, are independent and equally powerful risk factors for cardiovascular morbidity and mortality. Meta-analyses of prospective cohort studies have shown that major depressive disorder (MDD) is

associated with a relative risk of 1.6 to 1.9 for incident coronary heart disease (CHD) and that this risk is graded; that is, even subsyndromal depressive symptoms are associated with an increase in cardiovascular risk proportional to the level of depression (Nicholson et al., 2006). Likewise, anxiety disorders, estimated to affect 7.3% of the worldwide population, have been demonstrated to double the risk of cardiovascular events by around 50% after conventional risk factors have been taken into account (Batelaan et al., 2016).

This link between the affective disorders and CVD does not work in one direction only. The bi-directionality and synergy of the comorbidity is evident; people with pre-existing CVD run 2-3 times higher risk of developing depression, and post-MI depression alone is a powerful predictor of mortality (adjusted HR 2.4; Lichtman et al., 2014). This two-way interaction suggests that there are some common pathophysiological substrates—underlying biological mechanisms that are caused by and lead to the continuation of chronic psychological distress. Knowledge about these substrates is not just academic but has direct translative implications for risk stratification, pharmacological/behavioral intervention and public health policy.

George Engel first presented the biopsychosocial (BPS) model in 1977, which is the best theoretical framework to explain these relationships. Engel challenged the biomedical model of disease which assumed that disease could all be reduced to a single biological cause, and instead advocated that disease and health are the result of complex interactions between biological, psychological and social factors (Engel, 1977). When applied to the depression-anxiety-CVD nexus, the BPS model requires that we consider the biological (hypothalamic-pituitary-adrenal (HPA) axis and sympathetic nervous system and immune-inflammatory networks), psychological (cognitive styles, emotional regulation, and health-related behaviors), and social (socioeconomic status, occupational strain, social isolation, and access to healthcare) aspects. Importantly, these domains are not isolated, but are in constant interaction with each other, and feed forward and feedback processes amplify pathological processes.

This paper aims to bring together the existing evidence to consider the possibility of a common mechanism that underlies the link between depression, anxiety, and chronic stress and the onset of cardiovascular disease, focusing on the middle aged population (40–65 years) where the clinical burden of both affective disorders and subclinical atherosclerosis is greatest. Our hypothesis is that chronic psychological distress triggers a chain of interrelated biological processes, starting with HPA axis dysregulation and dysautonomia, followed by a state of low-grade systemic inflammation and ending with endothelial dysfunction and arterial stiffening, which all contribute to the process of atherogenesis and lead to acute cardiovascular events. We also suggest that behavioral and social factors can be important moderators and either increase or decrease the biological signaling pathways. The last synthesis will be based on a broad biopsychosocial framework of cardiovascular vulnerability to stress.

2. The Biopsychosocial Model: Historical Foundations and Contemporary Relevance

A theoretical model that requires multiple levels of analysis is needed to understand the complex interrelationships of depression, anxiety, and CVD. The biopsychosocial model was proposed in 1977 by George Engel, in the journal Science, and was a critique of the biomedical model of disease, which "assumes disease to be fully accounted for by deviations from the norm of measurable biological (somatic) variables" (Engel, 1977, p. 130). Engel, who was himself an internist with psychoanalytic training, was deeply affected by his own observations of patients, including his mother who suffered from a variety of somatic complaints for which a purely biological explanation was inadequate, and by the general systems theory, which postulates the organization of a complex system in hierarchies with the possibility that a change at one level may be transmitted across the system (Engel, 1980).

The BPS model assumes that illness and health are the result of an ongoing interplay between three major systems: biological (genetic, neurobiological and physiological); psychological (cognition, emotion, motivation and behavior); and social (interpersonal relationships, socioeconomic environment and cultural context). Key, these domains are thought to be reciprocally determining and not additive. A social factor, such as chronic social stress, can lead to negative cognitive biases (psychological factor) as well as up-regulation of pro-inflammatory cytokines (biological factor), which in turn can lead to changes in neural circuits (psychological factor) which maintain depressive symptoms, creating a self-perpetuating cycle (Slavich & Irwin, 2014).

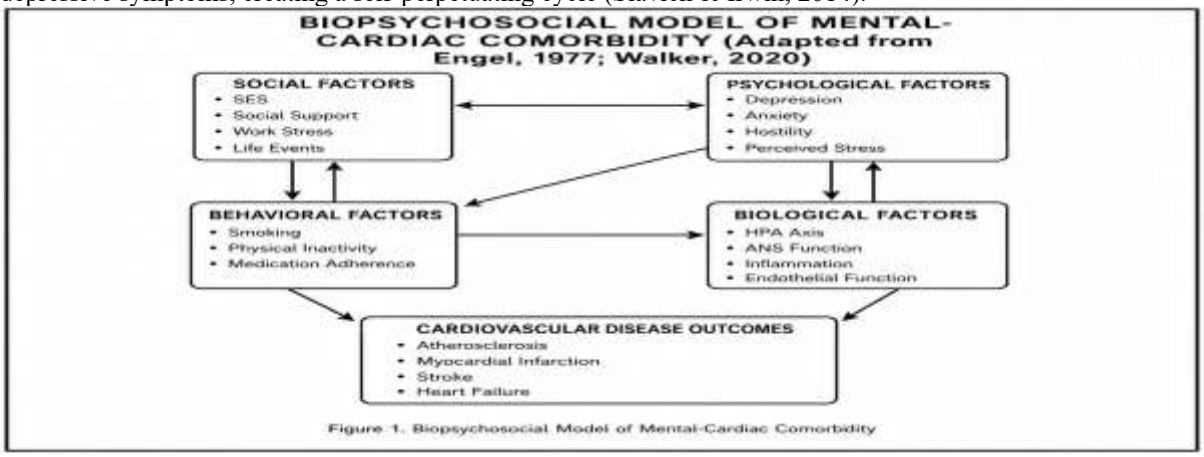

Figure 1: The Biopsychosocial Model Applied to Depression, Anxiety, and Cardiovascular Disease

Figure 1 illustrates the application of the BPS model to the depression-anxiety-CVD relationship. Notice the two-way arrows, representing the two-way interaction. Social factors (low SES and work strain) impact on psychological factors (depression and anxiety) which in turn affect behavior (physical inactivity and smoking). Psychological states, in turn, influence biological systems (HPA axis, ANS, immune-inflammatory networks), which in turn contribute to greater psychological distress. A significant link in the pathway between psychological distress and biological risk is behavioral factors.

3. Epidemiological Evidence: Depression, Anxiety, and Incident Cardiovascular Disease

3.1 Depression and CVD Risk

The association of depression and CVD is one of the strongest in the field of psychosomatic medicine. In more than 20 prospective cohort studies with more than 200,000 subjects, depression, either categorically (measured as major depressive disorder) or dimensionally (measured as higher scores on depressive symptom scales), has been found to independently predict cardiovascular morbidity and mortality. Even after taking into account traditional risk factors, a landmark meta-analysis of 25 studies concluded that depression is associated with a 1.64 (95% CI 1.29–2.08, $p < .001$) increase in the odds of developing CHD (Rugulies, 2002). This extra risk is especially high in middle-aged groups--in the NHANES I Epidemiologic Follow-up Study, 12,866 middle-aged men and women who were depressed had a 1.71-fold higher risk of CHD over 12.5 years of follow-up (Ferketich et al., 1998).

Importantly, depression is not only a risk factor for the development of CVD, but also a negative prognostic factor in patients who have developed CVD. In a systematic review and meta-analysis of 53 studies involving 21,300 CHD patients, comorbid depression was found to be a risk factor for cardiac mortality following myocardial infarction (MI) by 2.4-fold (Meijer et al., 2011). Treatment resistant depression (TRD) – defined as not responding to at least two adequate antidepressant treatments – seems to be even more cardiotoxic than responsive depression, and this has led to the hypothesis that it is not depression per se, but a persisting biological dysregulation that incites cardiovascular pathology (Carney & Freedland, 2017).

The relationship between anxiety and CVD risk is examined.

Although the evidence for anxiety as an independent cardiovascular risk factor has been lacking, in the last ten years this has increased enormously. There was a 52% higher risk of CVD (RR 1.52, 95% CI 1.02–2.27) and a 48% higher risk of cardiac death (RR 1.48, 95% CI 1.14–1.92) among participants whose anxiety status was positive, particularly for GAD and PD, in a meta-analysis of 20 prospective studies with 249,846 participants (Celano et al., 2016). The association remained even after the researchers accounted for the children's levels of depressive symptoms, suggesting that the cardiovascular toxicity of anxiety is mediated in part by pathways that are independent of depressive symptoms.

In the Normative Aging Study phobic anxiety (as measured by the Crown-Crisp Experiential Index) has been associated with three-fold higher risk for sudden cardiac death (Kawachi et al., 1994); it was posited that this effect may be due to an autonomic mediated ventricular arrhythmogenic response to anxiety. Likewise, the Women's Health Initiative Observational Study found that women who had panic attacks had 4.2 times greater hazard of CHD after menopause. The evolving picture indicates that anxiety disorders, which are often accompanied by repeated surges of catecholamines and/or increased sympathetic activity, can directly affect the myocardium and coronary vasculature.

3.3 Joint Effects of Depression and Anxiety and Mediating Pathways

Numerous methodological difficulties exist in determining the independent effects of depression and anxiety, as these disorders are highly comorbid, with up to 60% of individuals with MDD also meeting criteria for an anxiety disorder. The ATTICA study, however, is a population-based prospective study of 853 middle-aged Greek adults with 10 years of follow-up, that did address this issue by performing factor analyses to create a latent variable of "psychological distress" that combines depression and anxiety (Panagiotakos et al., 2017). The study reported that each 10-unit increase in psychological distress (on a 0–100 scale) was associated with a 1.4-fold increased risk of 10-year CVD incidence (adjusted OR 1.4, 95% CI 1.1–1.7). Path analysis showed that psychological distress had three pathways to affect it, namely through physical sedentariness, the metabolic syndrome, and systemic inflammation (both C-reactive protein and interleukin-6). The identification of these mediating pathways is in line with the BPS model proposed in this paper, with the behavioral pathway (sedentariness) mediated by psychological-behavioral pathways, the biological pathway (inflammation) mediated by neuroimmune interactions, and the metabolic pathway mediated by both behavioral and biological pathways.

In a similar vein, a retrospective cohort study of 71,214 participants (median age 49.6 years, 55.3% female) from the Mass General Brigham Biobank assessed whether anxiety/depression was linked to the development of cardiovascular diseases (CVD) which could be explained by the presence of cardiovascular risk factors (CVDRFs) such as hypertension, hyperlipidaemia and diabetes mellitus (Zureigat et al., 2024). Pre-existing anxiety/depression was found to be associated with a 71% increased risk for developing incident CVDRFs (OR 1.71, 95% CI 1.59-1.83, $p< .001$), and that time to development of these risk factors was significantly shorter in those with anxiety/depression ($\beta = -0.486$, 95% CI −0.62 to −0.35, $p< .001$). Formal mediation analysis also revealed that the development of CVDRFs was a significant mediator between anxiety/depression and CVD events (log-odds 0.044, 95% CI 0.034–0.055, $p < .05$). Importantly, the authors of this study also showed that "neuro-immune pathways (high amygdala-to-cortical activity ratio (neural activity related to stress), high-sensitivity C-reactive protein (chronic inflammation), and reduced heart rate variability (autonomic dysfunction))"

were associated with accelerated cardiovascular risk factors. Of particular note, the most dramatic acceleration was seen in younger women, which may be due to estrogen-modulated stress reactivity and may have implications for sex-specific prevention strategies and early screening.

Table 1: Summary of Longitudinal Studies Examining Depression, Anxiety, and Incident CVD in Middle-Aged Adults

Study	N	Mean Age (y)	Follow-up (y)	Key Predictor(s)	Primary Outcome	Key Finding
ATTICA Study	853	45 ± 13 (men), 44 ± 18 (women)	10	Latent "psychological distress" (combined depression + anxiety)	10-year CVD incidence	OR = 1.4 per 10-unit increase (95% CI 1.1–1.7); mediated by sedentariness, inflammation, and metabolic syndrome
Whitehall II	8,348	56 (wave 7)	~10 (wave 5 to wave 9)	Workplace stress, depression symptoms, IL-6, CRP, fibrinogen	First-time CHD event	Depression symptoms mediated stress–CHD link; increases in depression and fibrinogen predicted future CHD
Mass General Brigham Biobank	71,214	49.6	10	Anxiety/Depression diagnosis (ICD)	Incident CVDRFs and CVD events	Anxiety/depression accelerated CVDRF development (OR 1.71); mediated by neuro-immune pathways; strongest in younger women
NESDA (Netherlands)	3,113	51.0 ± 8.8	5.5	Anxiety disorders (semi-structured interview)	Inflammatory markers (hsCRP, IL-6, TNF-α)	Current anxiety and agoraphobia predicted steeper increase in hsCRP; no evidence for inflammation predicting incident anxiety
PsyCoLaus	3,118	51.0 ± 8.8	5.5	Mood disorders (MDD subtypes)	hsCRP, IL-6, TNF-α	Atypical MDD subtype predicted increased hsCRP; inflammation appeared to be a consequence, not a predictor, of depression

Note: ATTICA = ATTICA Epidemiological Study; Whitehall II = Whitehall II Occupational Cohort Study; NESDA = Netherlands Study of Depression and Anxiety; PsyCoLaus = Psychiatric arm of the CoLaus study. (Adapted from Panagiotakos et al., 2017; Piantella et al., 2021; Zureigat et al., 2024; Glaus et al., 2018; Glaus et al., 2023.)

4. Chronic Stress as the Central Driver: From Allostasis to Allostatic Load

4.1 The Concept of Allostatic Load

The importance of chronic stress in the process linking psychological distress with cardiovascular disease can be illustrated by considering the notions of allostasis and allostatic load, as formulated by McEwen and Stellar (1993). Allostasis is the adaptive process of achieving stability through change, or, the body's ability to respond physiologically (hormone release, sympathetic activation, etc.) in proportion to the stressor and then turn it off when the stressor is over. The wear and tear that occurs to multiple organ systems when the stress response is chronically turned on (whether from repeated exposure to discrete stressors, failure to habituate to recurring stressors or failure to turn off after the stressor has passed) is known as allostatic load (McEwen, 1998).

The allostatic load is measured as a composite of biomarkers from several regulatory systems: the neuroendocrine system (cortisol, DHEA-S, epinephrine, nor-epinephrine), the immune-inflammatory system (CRP, Interleukin 6, fibrinogen), cardiovascular system (SBP, HRV), and metabolic system (BMI, WHR, total cholesterol, HDL, glycosylated hemoglobin) (Seeman et al., 1997). An allostatic load index, reflecting overall burden of wear and

tear on multiple physiological systems, has been linked to cardiovascular events, decreased physical and cognitive function and all-cause mortality even after adjusting for sociodemographic factors and baseline morbidity (Seeman et al., 2010).

4.2 Dysregulation of the HPA Axis in Chronic Stress, Depression and Anxiety

Hypothalamic-Pituitary-Adrenal (HPA) axis is the major neuroendocrine mediator of the stress response. In response to acute stress, parvocellular neurons of the hypothalamic paraventricular nucleus (PVN) send CRH and AVP to the hypophyseal portal circulation to stimulate the anterior pituitary to release ACTH. ACTH, in turn, stimulates the production and release of the glucocorticoids (cortisol in humans) of the zona fasciculata of the adrenal cortex. Physiologically cortisol mobilizes energy substrates, inhibits some non-essential functions (reproduction, growth and digestion), and through glucocorticoid receptors in the hippocampus, hypothalamus and pituitary gland, negatively regulates the secretion of CRH and ACTH and hence limits the duration and intensity of the stress response.

This finely tuned regulatory feedback loop is affected during chronic stress and the psychological stress found in depression and anxiety is one such factor that causes this, called "glucocorticoid resistance" (Pariante & Miller, 2001). Two main mechanisms have been proposed: (1) decreased expression and/or function of glucocorticoid receptors (GRs) in specific feedback regions (hippocampus, PVN) leading to a blunted negative feedback and maintenance of hypercortisolemia; and (2) inability of cortisol to inhibit inflammatory signaling pathways (glucocorticoid resistance in the immune cell) leading to unchecked system inflammation despite high levels of circulating cortisol. There is a considerable amount of evidence for HPA axis hyperactivity in depression, with a recent meta-analysis that analyzed 361 studies of 18,454 participants finding that depression is associated with significantly higher levels of cortisol (Stetler & Miller, 2011), especially in the afternoon/evening ($d = 0.23$) and in serial samples ($d = 0.25$). Most interesting is the presence of the greatest hypercortisolemia in treatment-resistant depression that normalizes only following successful treatment.

Feng et al. (2024) recently analyzed the special significance of hyperactivity of the HPA axis in the field of comorbid anxiety and depression in coronary atherosclerotic heart disease. In addition to some direct effects on the cardiovascular system (such as cortisol-induced increases in blood pressure and heart rate, and catecholamine-induced increases in blood pressure and heart rate), they noted, the HPA axis dysregulation has downstream effects on downstream mediators including inflammation, oxidative stress and platelet activation that also contribute to cardiovascular pathology. Moreover, they suggested that the functionality of the HPA axis could be considered as a therapeutic biomarker: normalisation of diurnal cortisol slope could be used as a marker of successful pharmacological or behavioural intervention in patients with associated affective and cardiovascular disease.

As reviewed by Shkvarok-Lisovenko and Bushman (2025), the interaction between HPA axis dysfunction and cardiovascular responses to stress is a systematic one and involves an increase in cardiac output, peripheral vasoconstriction and blood pressure, which over time will lead to left ventricular hypertrophy, vascular remodeling and increase the risk of acute coronary events. Furthermore, Chronic Hypercortisolemia increases visceral fat, insulin resistance and dyslipidemia, all factors of the metabolic syndrome, which further contributes to cardiovascular risk.

Ashraf et al. (2026) take this one step further, giving a comprehensive translational overview of the neurocardiac axis in the context of anxiety disorders. They provide evidence that chronic anxiety causes a chronic activation of the sympathetic nervous system and HPA axis resulting in an increase in catecholamines and cortisol, which in turn lead to endothelial dysfunction, oxidative stress, and systemic inflammation that correlate mechanistically to hypertension, arrhythmias, myocardial ischemia and even stress-induced cardiomyopathy (Takotsubo syndrome).

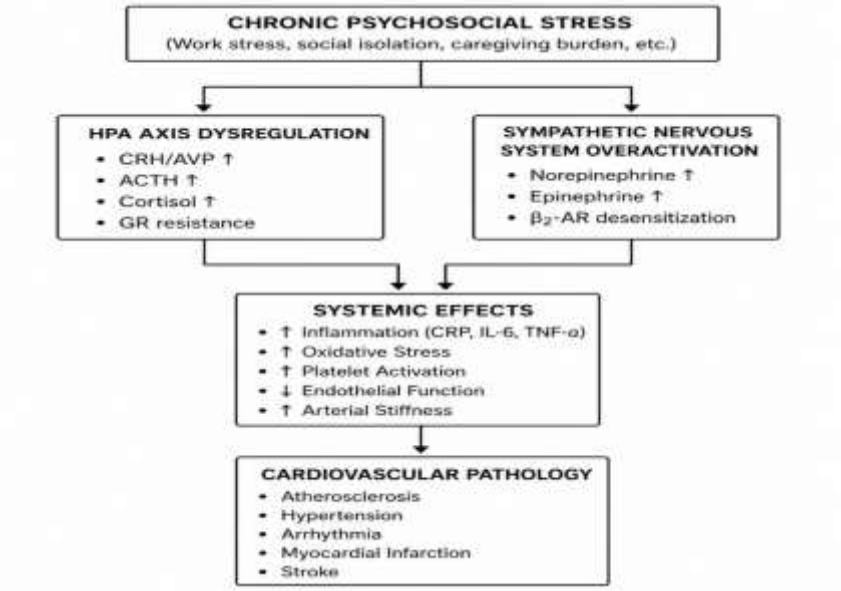

Figure 2: The Chronic Stress → Cardiovascular Disease Pathway

Figure 2 depicts the process leading from chronic stress exposure to cardiovascular pathology, focusing on the two main effector systems HPA axis dysregulation and sympathetic nervous system overactivity and their common downstream impacts on systemic low grade inflammation, endothelial dysfunction and arterial stiffness.

4.3 Dysfunction of the Autonomic Nervous System.

As well as the HPA axis dysregulation, chronic stress produces significant changes in the balance of the ANS: increased sympathetic activity and decreased parasympathetic (vagal) activity. Beat to beat oscillation in the R-R interval known as heart rate variability (HRV) is a non-invasive indicator of cardiac autonomic modulation in which high-frequency (HF) HRV indicates mostly vagal tone and low-frequency (LF) HRV indicates both sympathetic and parasympathetic modulation. Post-MI patients and the general population have reduced HRV, especially reduced indices of vagally mediated HRV (HF power, root mean square of successive differences [RMSSD]), which is a strong predictor of cardiac mortality.

HRV has been consistently linked with depression and anxiety. In one meta-analysis, 18 studies were included, showing that in patients with MDD, HRV was significantly lower than in healthy controls with an effect size (Hedges' g) of −0.30 for HF HRV (Kemp et al., 2010). The autonomic dysfunction is related to the severity of depression, and is present even after the depressive symptoms are resolved, indicating a trait, and not a state phenomenon. In addition, there is decreased vagal tone and increased sympathetic response to experimental stressors in anxiety disorders, especially panic disorder and PTSD.

The bidirectional prospective associations between cardiac autonomic function (heart rate and respiratory sinus arrhythmia [RSA] as an indicator of vagal tone) and inflammatory markers (CRP, IL-6) were examined in a sample of 2891 participants from the Netherlands Study of Depression and Anxiety (NESDA) who were evaluated at baseline and 2-year follow-up. The study revealed that both an increase in heart rate and a decrease in RSA were crosssectionally significantly associated with increased inflammatory levels. Autonomic dysfunction cross-sectionally was associated with inflammation and IL-6 at baseline predicted increased heart rate at follow-up, while CRP at baseline predicted increased IL-6 at follow-up, indicating a bidirectional relationship between autonomic dysfunction and inflammation (Hu et al., 2018). This discovery is significant because it proves that the stress-inflammation-ANS connection is a vicious cycle: autonomic imbalance contributes to inflammation, which in turn causes more autonomic imbalance, and so on—with each step contributing to further damage to the cardiovascular system.

5. Disease Particulars: Complexity and the Evolution of Diseases

5.1 The role of inflammation as a mediator of disease.

Systemic low-grade inflammation is thought to be the in vivo mediator and chronic stress the overarching trigger of the depression-anxiety-CVD connection. The “common soil” hypothesis that posits that depression and CVD share common inflammatory, metabolic, and neuroendocrine pathophysiologies has been well supported empirically and offers a parsimonious explanation for the comorbidity (Carney & Freedland, 2017).

A number of independent studies have found increased circulating levels of inflammatory markers, most consistently C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α) and fibrinogen in patients with depression compared to healthy controls. A large-scale meta-analysis of 58 studies (Howren et al., 2009) reported that depression was significantly associated with elevated CRP (d = 0.15, 95% CI 0.10–0.21), IL-6 (d = 0.25, 95% CI 0.18–0.31), and IL-1 (d = 0.35, 95% CI 0.03–0.67). The nature of the association has been a focus of considerable research: does increased inflammation lead to depression or does depression cause increased inflammation? The answer seems to be both – depending on the population examined and the biomarker analyzed.

5.2 Longitudinal Evidence using Population-based Cohorts

The most methodologically sound and largest studies to tackle this issue are the longitudinal studies of the CoLaus/PsyCoLaus cohort in Switzerland. Glaus et al. (2018) analyzed the bidirectional relationships between anxiety disorders and levels of circulating inflammatory markers (hsCRP, IL-6, and TNF-α) in 3,113 participants (53.7% women) with a mean age of 51.0 ± 8.8 years and a mean follow-up of 5.5 years. The main finding was that baseline current anxiety disorders (β = 0.09, 95% CI 0.00–0.17) and in particular agoraphobia (β = 0.25, 95% CI 0.07–0.43) were significantly associated with a greater increase in hsCRP levels during the follow-up period after thorough adjustment for sociodemographic, lifestyle, and physical health factors. Interestingly, the opposite effect was not found; baseline inflammatory markers were not associated with incident anxiety disorders at follow-up. The pattern indicates that systemic inflammation is a consequence of chronic anxiety (at least within the 5 years assessed here) and that hsCRP may be a more sensitive measure of the inflammatory burden associated with anxiety than is IL-6 or TNF-α.

The complementary PsyCoLaus study investigated the bidirectional question in the case of mood disorders (Glaus et al., 2023). In the 3,118 subjects (53.7% women; mean age at baseline 51.0 ± 8.8 years; follow-up 5.5 years), a higher level of hsCRP at follow-up was linked to current MDD at baseline (only atypical MDD, characterized by hyperphagia, hypersomnia and leaden paralysis; β = 0.32, 95% CI 0.10–0.55). Prospective increase of inflammatory markers was not related to melancholic depression. This subtype specific finding is important as it mirrors the known metabolic profile of atypical depression (hypercortisolemia, increased visceral adiposity,

insulin resistance), and highlights that the relationship between inflammation and depression may be largely mediated by metabolic comorbidities that tend to cluster with atypical depression and less by depression itself. Once again, little evidence was seen of baseline inflammation predicting follow-up mood disorders, thus supporting the directionality found in the anxiety study.

These results dovetail with the Whitehall II study which underwent the first empirical test of the complete stress-inflammation-depression-CVD pathway via structural equation modeling (Piantella et al., 2021). A sample of 8,348 British civil servants (with mean age of 56 years) was followed at three waves of data collection (phases 5, 7 and 9) covering around 10 years. The hypothesized pathway, from workplace stress to increased depressive symptoms to increased levels of IL-6, CRP, and fibrinogen to increased risk for incident first-time CHD events, was supported by the structural equation model which showed excellent fit ($\chi^2(72) = 3582.96$, *p* < .001, CFI = 0.896, RMSEA = 0.076). The mediation of the relationship between workplace stress and CHD incidence by depression symptoms was found to be B = 0.003, CI_{90} 0.001–0.004. On survival analysis, higher mean scores of depression symptoms or fibrinogen levels were significantly associated with first CHD event during the follow-up period. This study is the most direct empirical evidence of the cascade model in this paper.

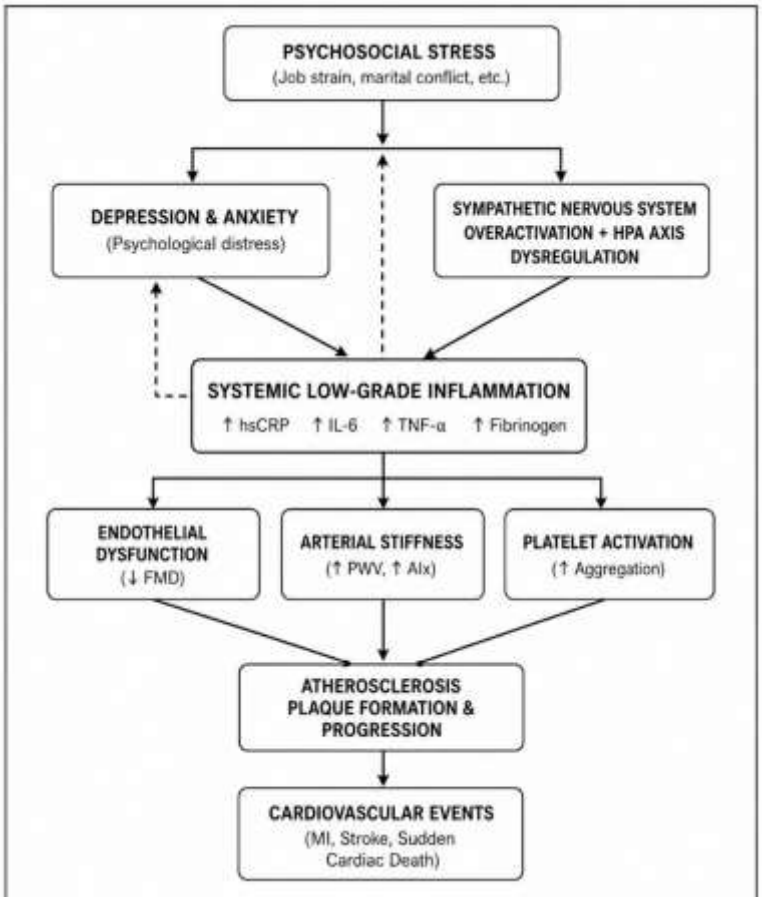

Figure 3: Inflammation as the Hub: Bidirectional Relationships with Stress, Depression, Anxiety, and CVD

Inflammation becomes the "hub" in the biopsychosocial network between stress, affective disorders, and cardiovascular outcomes (Figure 3). Solid arrows indicate known longitudinal relationships, dashed arrows indicate bidirectional/feedback relationships. Abbreviations are: FMD, flow-mediated dilation; PWV, pulse wave velocity; hsCRP, high-sensitivity C-reactive protein; IL-6, interleukin-6; and TNF-α, tumor necrosis factor-alpha.

The Vascular End-Organ: Endothelial Dysfunction and Arterial Stiffness

The Endothelial Function in Mental Stress.

The vascular endothelium, a single layer of cells lining the entire circulatory system, is much more than a passive barrier. It controls vascular tone, thrombosis, inflammation and vascular remodeling by synthesizing and releasing the vasoactive substances, particularly nitric oxide (NO), a potent vasodilator and anti-atherogenic molecule. Endothelial dysfunction, defined as a decrease in NO bioavailability and a pro-inflammatory and pro-thrombotic endothelial phenotype, is thought to be the "sentinel" event in atherogenesis and to independently predict cardiovascular events.

Mental stress (acute or chronic) has been consistently demonstrated to induce decreased endothelial function. The mechanisms are multifactorial: acute mental stress increases levels of the hormone-catecholamines, (norepinephrine, epinephrine) and cortisol directly increase heart rate and blood pressure, trigger vasoconstriction and produce oxidative stress that inactivates NO. Ghiadoni et al. (2000) did a landmark study showing that a

standardized mental arithmetic task caused a significant, transient decrease in brachial artery flow-mediated dilation (FMD) (a measure of endothelium-dependent vasodilation) in healthy young adults with recovery to baseline within 45 minutes. But, if mental stress is chronic, repeated endothelial insults cannot be adequately repaired, especially repopulation of damaged endothelium by endothelial progenitor cells (EPCs) from the bone marrow, resulting in chronic endothelial dysfunction. However, clinical studies have suggested that people suffering from depressive symptoms have lower circulating EPCs and less FMD even without a clear history of CVD (Chen et al., 2009).

6.2 Arterial Stiffness as an Intermediate Phenotype

Arterial stiffness is a non-invasive measure of pulse wave velocity (PWV) and augmentation index (AIx), which is a global indicator of the degenerative changes that take place in the arterial wall as a result of aging and cardiovascular risk factors. Rigidification of the large elastic arteries (especially the aorta and carotid arteries) leads to an increased cardiac afterload, decreased diastole coronary flow, and uprifting of pulsatile energy into the microcirculation of the brain and kidneys responsible for left ventricular hypertrophy, myocardial ischemia, and target-organ damage. PWV is a powerful independent predictor of cardiovascular events and all-cause mortality in the middle aged and elderly (Mitchell et al., 2010).

Two recent studies have found direct evidence for the association between depression and anxiety with increased arterial stiffness in clinical populations. Yanartas et al (2021) studied 30 depressed patients receiving antidepressant treatment and 25 age- and gender-matched healthy controls, in which they focused on comparing arterial stiffness parameters (PWV and AIx). They found that PWV was significantly higher in depressed patients (6.40 ± 1.31 m/s) compared to controls (5.51 ± 0.41 m/s, *p* = 0.001), and AIx was similarly elevated (26.9 ± 12.1% vs. 17.4 ± 11.3%, *p* = 0.004). There was a positive and significant correlation between both stiffness parameters and depression scores (Beck Depression Inventory) and anxiety scores (Beck Anxiety Inventory). These observations are significant as elevations remained despite the antidepressant treatment, indicating that vascular stiffening is a relatively stable effect of depressive illness, or that standard pharmacotherapy is not sufficient to completely reverse the vascular pathology.

Original research by Jud et al. (2025) further supported these findings with an examination of the interaction between anxiety, depression, vascular function and inflammatory markers in post-myocardial infarction patients. In a cohort of 105 post-MI patients, clinically relevant anxiety (29.5% of the sample) was significantly related to increased arterial stiffness and younger age, and depression (21.9% prevalence) was related to elevated levels of the pro-thrombotic acute-phase protein fibrinogen. Interestingly, no significant relationship was found between endothelial function (FMD) and Hospital Anxiety and Depression Scale (HADS) scores, suggesting macrovascular stiffening may precede the FMD observed changes as a correlate of psychological distress in this population or the FMD methodology may not be sensitive enough to detect the distress-related changes in this clinical sample. Anxiety was associated with decreased concentration of endocan (an index of endothelial activation) and BDNF (brain-derived neurotrophic factor), which may indicate endothelial repair dysfunction and diminished neuroplasticity. The findings highlight the significance of early psychological assessment in the post-MI setting and the need for psychological screening to be incorporated into cardiac rehab protocols.

7. Social and Behavioral Interface: Pathways to Cardiovascular Risk

7.1 Health Risk Behaviors as Mediators

A purely biological model would be simplistic and inadequate. Perhaps most importantly, the BPS framework has highlighted that psychological distress does not simply act through neuroendocrine and immune pathways but is also linked to a cluster of behavioral risk factors which have independent and synergistic effects on cardiovascular risk, including physical inactivity, poor diet, smoking and medication non-adherence.

The symptoms of depression, including anergia, anhedonia and motivational deficits, predictably lead to a decrease in physical activity. One meta-analysis of 12 prospective studies found that baseline depression was associated with a 1.3 fold increase in the risk of being physically inactive at follow-up and that this association was reciprocal (Roshanaei-Moghaddam et al., 2009). Physical inactivity, in turn, leads to obesity, insulin resistance, dyslipidaemia and alone to a 1.5–2.0 fold risk increase of CHD. Sedentariness was one of the three core mediators of the association between psychological distress and 10-year incidence of CVD identified by the ATTICA study, the others being inflammation and metabolic syndrome, adding to the behavioral pathway being a modifiable target for intervention.

People with depression and anxiety are significantly more likely to start smoking, and are less likely to quit than people who don't have depression. In a survey of a representative sample of the U.S. adult population, adults with depression were 1.5 times more likely to be smokers and quit with significantly lower frequency than those without depression (Lasser et al., 2000). Likewise, depression and anxiety are strong predictors of poor adherence to prescribed cardiovascular medications (antiplatelets, statins, antihypertensives) which results in poor blood pressure control, poor lipid profile and an increased risk of acute events. A 50 percent drop in the likelihood of taking medications at 1 month after discharge was linked to depressive symptoms after an MI, and such non-adherence accounted statistically for the association between depression and the adverse cardiovascular outcomes, the Mechanisms and Outcomes of Myocardial Infarction (MOMI) study said. (Gehi et al., 2005).

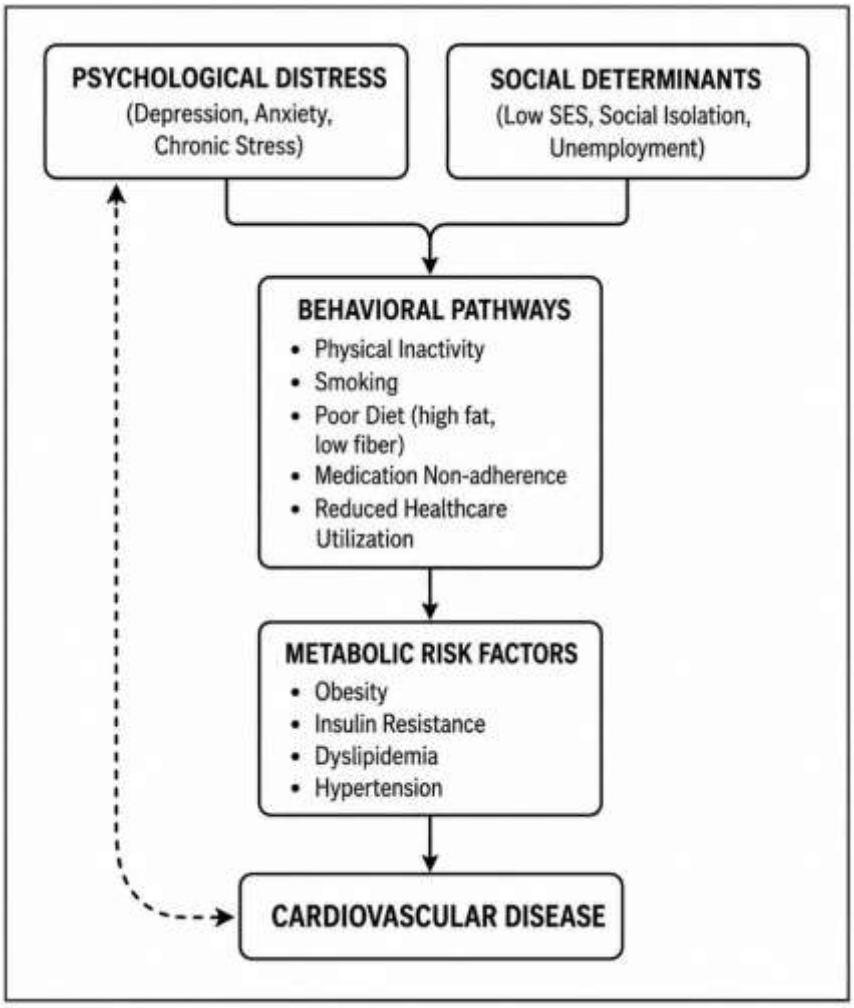

Figure 4: The Behavioural Interface between Psychological Distress and CVD

Figure 4 illustrates the psychological distress/cardiovascular disease behavioral interface. Notice the two way arrows: CVD and its symptoms (e.g., chest pain and dyspnea) can lead to anxiety and depression, which in turn can lead to other symptoms of CVD.

7.2 The Socioeconomic Context

It is important to note that socioeconomic factors are crucial in any description of the depression-CVD link. Low socioeconomic status (SES) (based on education, income or occupational grade) has a disproportionately high prevalence of both depression and CVD, and the link between psychological distress and CVD is much stronger among low-SES groups. In the ATTICA study, a direct link between the association of SES and psychological distress with CVD was found: a low SES was associated with significantly higher scores on the psychological distress measure, and psychological distress was an independent predictor of CVD incidence over a 10-year period. This discovery joins the broader literature showing that social adversity (be it monetary stress, job insecurity, or neighborhood deprivation) has the same impact as any other stressor in triggering the stress-responsive biological systems discussed throughout this paper, making it a sociobiological pathway to cardiovascular disease.

Social support and social integration are protective factors which buffer against the pathogenic effects of stress. In fact, a meta-analysis of 148 studies determined that people who had greater social relationships were 50% more likely to survive from all causes of death, and the magnitude of this effect was similar to that of quitting smoking and greater that of quitting smoking and reducing obesity (Holt-Lunstad et al., 2010). In the cardiovascular arena, the Enhancing Recovery in Coronary Heart Disease Patients (ENRICHD) trial failed to show the expected reduction in recurrent MI and mortality in the intervention group that had a cognitive-behavioral intervention to reduce depression and increase social support, perhaps because enhanced usual care was also delivered in the control group, and perhaps because, despite the group's psychosocial improvement, it was not enough to reduce recurrent MI and death (Berkman et al., 2003).

8. Synthesis: An integrated Biopsychosocial Model

The evidence examined in this paper comes to a conclusion of an integrated model where chronic psychological stress (defined as depression, anxiety or high allostatic load) is the most general cause of cardiovascular pathology

in middle-aged persons. The links between stress and the development of CVD are not as simple as one pathway; there are multiple, redundant, and reciprocally reinforcing pathways. They may be divided into three main axes:

1. **Chronic stress**: causes chronic overactivity of HPA axis and sympathetic nervous system and down regulation of parasympathetic system leading to chronic overproduction of cortisol, excess of catecholamines, decrease in HRV, and immune cell glucocorticoid resistance. These changes directly affect the endothelium, raise systemic vascular resistance and cause cardiac arrhythmia.
2. **Immune-inflammatory axis**: Hyperactivity of the immune-inflammatory axis with high levels of CRP, IL-6, TNF-α and fibrinogen due to stress-induced dopamine and cortisol dysregulations. These inflammatory mediators mediate endothelial activation, recruitment of leukocytes, foam cell formation and smooth muscle cell proliferation, the cellular components of atherogenesis. Inflammation and affective symptoms are bidirectional, forming a feed-forward loop, with inflammation exacerbating depression/anxiety and increased psychological distress causing an increase in inflammation.
3. **Behavioral-socioeconomic axis**: Depression and anxiety lead to health risk behaviors (physical inactivity, smoking, medication non-adherence, poor diet) that have independent effects on the risk of CVD. These behaviours are not only disproportionately common in low-SES populations, but also that social adversity directly switches on stress biology, without any need for behaviour.

Allostatic overload through all of the described mechanisms culminates as endothelial dysfunction and arterial stiffening as the final common pathway, a mechanism by which subclinical atherosclerosis progresses to an acute event mediated by rupture of atherosclerotic plaques.

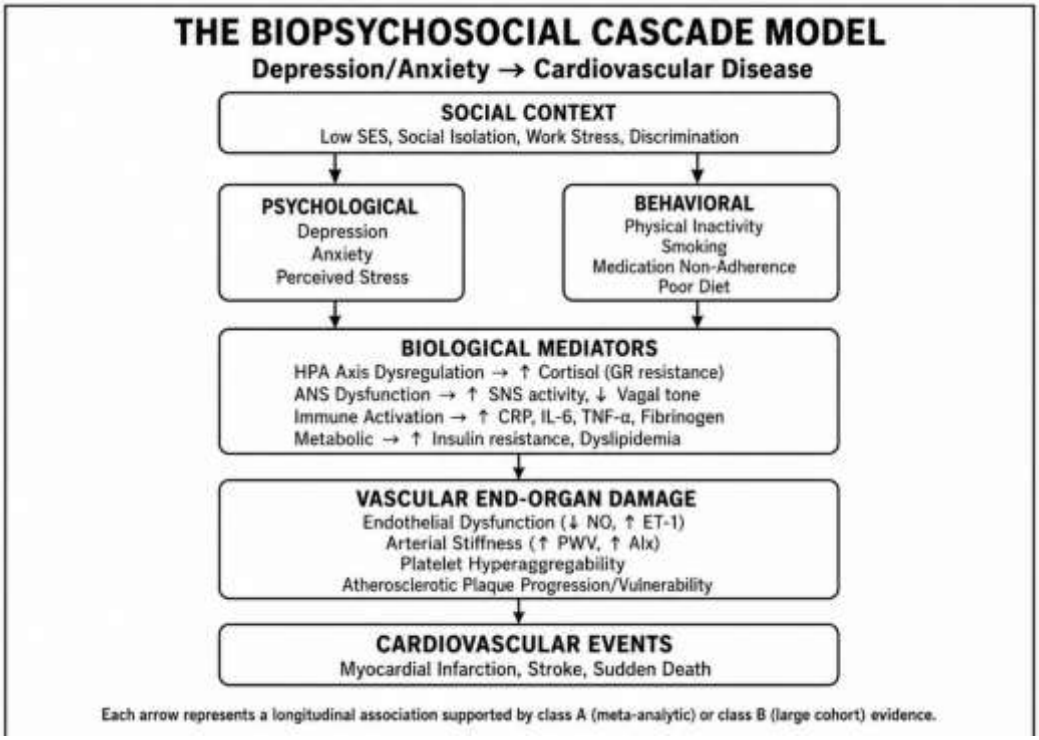

Figure 5: Integrated Biopsychosocial Model of Depression/Anxiety → CVD

The complete model is shown in figure 5. Bidirectional (not depicted, for clarity) arrows are interpreted to indicate that at each level, CVD events and associated physical impairments exacerbate depression, anxiety, and social isolation, and these, in turn, worsen CVD events and impairments.

9. Clinical Implications and Future Directions

9.1 Implications for Cardiovascular Risk Assessment and Prevention

The synthesis described in this paper is relevant to clinical practice. First, it provides further evidence of the need for systematic mental health screening in all middle-aged adults seeking cardiovascular risk assessment, using brief instruments that have been shown to have good validity such as the Patient Health Questionnaire-9 (PHQ-9) and the Generalized Anxiety Disorder-7 (GAD-7) for depression and anxiety, respectively. The evidence of both depression and anxiety predicting CVD events independently of conventional risk factors suggests that these psychological risk factors may need to be included in risk prediction algorithms. This has been recently confirmed in the 2021 European Society of Cardiology (ESC) guidelines for cardiovascular disease prevention, which have added psychosocial risk factors to the list of risk factors to be assessed and treated in comprehensive cardiovascular disease prevention.

Second, identifying specific intervening pathways (inflammation, sedentariness, metabolic syndrome and endothelial dysfunction) provides a number of potential targets for intervention. In secondary prevention,

pharmacological strategies that target inflammation (low-dose colchicine and canakinumab) have proven effective to reduce cardiovascular events and post hoc analyses have indicated that this effect is especially strong in persons with elevated hsCRP. The possibility of similar anti-inflammatory treatments being effective for reducing depressive or anxiety symptoms, or whether the cardio protective effect is, in part, through an impact on the depression-inflammation association, is worthy of study. Behavioral interventions (such as structured exercise programs and cognitive-behavioral therapy (CBT) have the benefit of modulating several pathways at once: exercise has a positive effect on endothelial function, increases HRV and decreases inflammation, and CBT decreases depressive symptoms, improves coping and increases medication adherence.

9.2 Psycho-Cardiology as a New Field of Knowledge

Given the increasing awareness of the mind-heart connection, there has been a recent new interdisciplinary subspecialty of "psycho-cardiology" which is practiced at the interface of psychiatry, cardiology, and behavioral medicine. Psycho-cardiology programs like at Beijing Anzhen Hospital bring mental health professionals into the cardiovascular care team, and offer psychological assessment and intervention to patients with cardiovascular and affective disorders both inpatients and outpatients. As stressed in the above recent editorial by Laher et al. (2026), Heart and Mind, the behavioural, nutritional, pharmacological, and social aspects of cardiovascular care must be combined, and a life course view should be considered, acknowledging the interplay of stress on the heart from early adult years through old age.

9.3 Priority Research Directions

As noted above, while significant strides have been made, there are several key areas that are still not fully understood and are the subject of ongoing research. First, the majority of the longitudinal studies that have looked at the depression-inflammation-CVD pathway have studied a predominantly white, North American/European population, and the results might not apply to other racial/ethnic groups. Sex-specific analyses were performed in the McGill study (2025), where a relationship between psychosocial stress and subclinical cardiac inflammation was found in women but not in men, highlighting the need for sex-specific analyses and indicating that the stress-cardiac axis may work differently in women, possibly involving estrogen-regulated inflammatory responses. Second, the molecular biology of "stress-induced inflammation" is not well described. New techniques in proteomics and metabolomics allow for complete profiling of the circulating proteome and metabolome, and future research should focus on finding a multi-marker panel that can completely and with high sensitivity and specificity capture the stress-inflammation-vascular injury axis. Third, randomized controlled trials are needed to evaluate the ability of interventions specifically aimed at reducing stress-inflammation-CVD pathway – such as anti-inflammatory pharmacotherapy (canakinumab, colchicine), structured aerobic exercise and mindfulness-based stress reduction – to reduce incident cardiovascular events in high-risk adults with depression or anxiety symptoms around middle age. Fourth, there is a need for the use of network analysis and other computational methods using these data to model the hundreds of biomarkers, behaviors and psychosocial factors that comprise the biopsychosocial network, and determine which of these factors are the most influential – the "hubs" – that if changed, would yield the greatest cardiovascular benefit.

10. CONCLUSION

Depression and anxiety disorders are no longer a matter of speculation or clinical anecdote, but are epidemiologic truths with a solid and expanding body of translational evidence linking the disorders to cardiovascular disease. Chronic psychological stress, the common pathogenic substrate, leads to initiation and maintenance of a cascade of neuroendocrine perturbations (HPA-axis dysregulation, sympathetic overdrive), immune-inflammatory perturbations (systemic low-grade inflammation), vascular perturbations (endothelial dysfunction, arterial stiffening), and behavioral perturbations (physical inactivity, medication non-adherence), all of which promote and accelerate atherogenesis and lead to acute cardiovascular events. The "biopsychosocial" model of health and disease, which focuses on a multi-level, interdependent relationship between the biological, psychological and social factors that influence health and disease processes, is the most appropriate conceptual framework for incorporating these diverse findings and for designing multidimensional interventions that address both the biological pathways of cardiovascular disease risk and the psychological and social determinants. The message for the clinician is clear: depression and anxiety assessment and management should be considered as core elements of cardiovascular risk stratification and prevention, especially in middle-aged adults where burden of subclinical disease is high and potential for effective prevention is still to be exploited.

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