Review

Pathophysiological Links Between Myocardial Infarction and Anxiety Disorder, Major Depressive Disorder, Bipolar Disorder and Schizophrenia

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Pathophysiological Links Between Myocardial Infarction and Anxiety Disorder, Major Depressive Disorder, Bipolar Disorder and Schizophrenia

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Simple Summary: This review explores the association between myocardial infarction (MI) and major psychiatric conditions such as depression, bipolar disorder, and schizophrenia. Research shows that people with psychiatric illnesses are at a higher risk of developing heart disease, and vice versa. This relationship is influenced by factors such as chronic inflammation, stress hormone imbalances, genetic predisposition, and oxidative stress, which can damage both the heart and brain. For example, stress and inflammation in MI can lead to changes in brain chemicals to depression, while oxidative damage in psychiatric conditions can contribute to heart disease. Additionally, genetic factors may play a role in both conditions, further strengthening their association. Understanding these shared mechanisms is essential for improving the treatment of individuals with both MI and psychiatric disorders. This review highlights the need for further research and better medical strategies to reduce the impact of these conditions and improve the quality of life for affected individuals.

Abstract: There is increasing evidence demonstrating that psychiatric conditions elevate the risk of developing accelerated atherosclerosis and early-onset cardiovascular disease (CVD) including myocardial infarction (MI). Several mechanisms contribute to this observation. Dysfunction of the autonomic nervous system and hyperactivity of the hypothalamic-pituitary-adrenal axis in these patients contribute to the development of (MI). Additionally, patients with underlying psychiatric disorders often have abnormal levels of anti-inflammatory and pro-inflammatory cytokines, which can lead to early vascular damage and subsequent atherosclerosis. Elevated PAI-1 levels, reduced tPA activity, and decreased brain-derived neurotrophic factor (BDNF), influenced by coagulation and inflammation, may contribute to depression and its link to MI. Oxidative stress, marked by increased reactive species and impaired antioxidant defenses, is associated with cellular damage and has been consistently implicated in schizophrenia and bipolar disorder, potentially contributing to myocardial infarction. Finally, molecular genetic studies have indicated that psychiatric disorders and myocardial infarction may share potential pleiotropic genes. The interplay between psychiatric conditions and myocardial infarction underscores the importance of integrated care approaches to manage both mental and physical health.

Keywords: myocardial infarction; psychiatric disorders; anxiety disorder; major depressive disorder; bipolar disorder; schizophrenia; cardiovascular disease

1. Introduction

Myocardial infarction (MI) and psychiatric conditions are two major causes of disability and death worldwide [1]. Many studies have demonstrated that survivors of MI are at an elevated risk of developing psychiatric disorders and vice versa [1]. However, the exact neurobiological pathways that link MI to psychiatric illness remain poorly understood [2]. Individuals with major psychiatric

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conditions have a life expectancy that is approximately 15 to 25 years shorter than that of the general population, with cardiovascular disease accounting for the majority of these premature deaths [3,4]. Cardiovascular disease is the leading cause of death among individuals with major psychiatric conditions with mortality rates being more than twice compared to the general population, and this continues to rise over recent decades [5].

The relationship between myocardial infarction and cardiovascular disease appears to be bidirectional, with acute coronary events and chronic cardiovascular conditions potentially triggering the development of psychiatric conditions [6]. In addition, evidence indicates that even among patients with low coronary artery calcium scores, mortality rates in those with major psychiatric conditions remain three to four times higher than in the general population [7]. Emerging research highlights shared pathophysiological mechanisms between myocardial infarction and psychiatric conditions, encompassing biological, neurohormonal and genetic factors [8]. This review aims to explore the molecular mechanisms between myocardial infarction and major psychiatric conditions.

2. Anxiety Disorder and Major Depressive Disorder

Figure 1 demonstrated the pathophysiology of myocardial infarction and depression. Studies have demonstrated that patients with MI had a higher risk of developing newly diagnosed anxiety and major depressive disorders [9]. MI serves as a significant risk factor for newly diagnosed clinical anxiety and depressive disorders within the first two years following the event [9]. The biopsychosocial model suggests that the interplay of biological, psychological, and social factors may contribute to the development of anxiety and depressive disorder post-myocardial infarction [10].

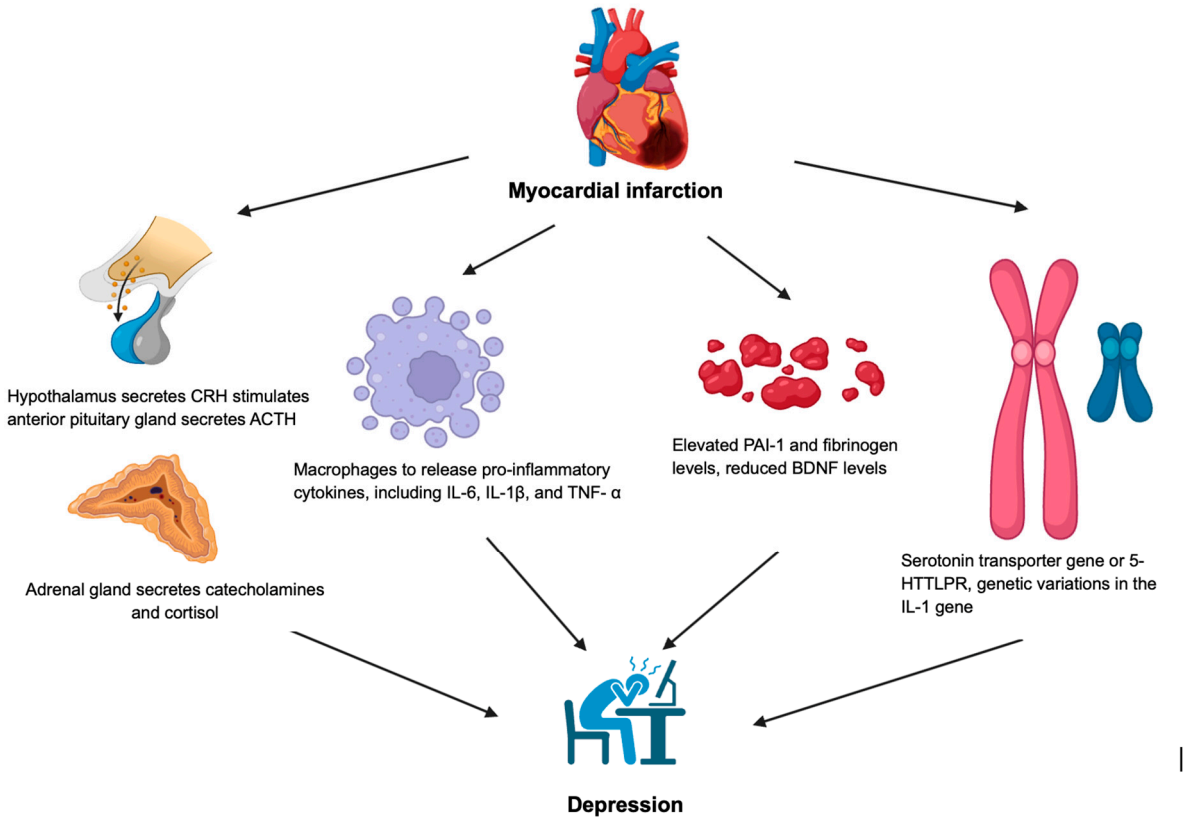

Figure 1. Pathophysiology of myocardial infarction and depression. ACTH: adrenocorticotropic hormone, BDNF: brain-derived neurotrophic factor, CRH: corticotropin-releasing hormone, IL: interleukin; PAI-1: Plasminogen activator inhibitor 1, TNF- α: tumor necrosis factor- α; 5-HTTLPR: serotonin transporter gene variant.

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MI triggers responses like hypothalamic-pituitary-adrenal (HPA) axis activation and autonomic nervous system (ANS) dysregulation, potentially leading to prefrontal cortex and anterior cingulate gyrus dysfunction, which contributes to depression and anxiety disorder [11]. In addition, MI activates the secretion of corticotropin-releasing hormone (CRH) from the hypothalamus, stimulating the anterior pituitary gland to release adrenocorticotropic hormone (ACTH) [2]. ACTH stimulates adrenal glands to produce cortisol and catecholamines and abnormal cortisol level leading to HPA axis dysfunction due to impaired feedback control. Study demonstrated that cortisol levels in post-MI patients spike immediately after the event due to HPA axis activation but return to normal within 72 hours [12]. While post-MI patients with depression lasting over three months showed a flattened daily cortisol rhythm, those without depression had significantly lower afternoon cortisol levels compared to the morning [12]. Abnormal cortisol rhythms have been associated with cognitive impairment and diminished stress-coping abilities, potentially heightening the risk of major depressive disorder and anxiety disorders [12,13].

Inflammation is one of the main pathophysiological mechanisms of development of depression in patients post-MI [14]. During MI, damage-associated molecular patterns (DAMPs) like heat shock proteins (HSPs) and high-mobility group box 1 (HMGB1) are released from the heart muscles due to oxygen deprivation [14]. These molecules activate immune cells, such as macrophages to release pro-inflammatory cytokines, including interleukin (IL)-6, IL-1β, and tumor necrosis factor (TNF)- α which is essential for phagocytosis of damage cardiac muscle and cardiac repair [14,15]. Inflammatory cytokines are implicated in the development of depression, as demonstrated in both animal and human studies [11]. Research in rodent models reveals that inflammatory cytokines such as IL-1β and TNF-α can induce depressive-like behavior which is also observed in humans where elevated inflammatory markers may lead to depressed mood [16,17]. Inflammatory cytokines can disrupt neurotransmitter systems, such as reducing serotonin levels via increased indoleamine 2,3-dioxygenase activity and altering dopamine and norepinephrine metabolism and production leading to dysregulation of mood [18–20]. In addition, inflammatory cytokines activate the kynurenine pathway, which increases quinolinic acid production which actives the N-methyl-D-aspartate (NMDA) receptor activation leading to the development of depressive symptoms [21].

Plasminogen activator inhibitor 1 (PAI-1), encoded by the SERPINE1 gene, serves as a key inhibitor of tissue plasminogen activator (tPA) in the extracellular space and has been associated with increased the risk to depression and the response of selective serotonin reuptake inhibitors [22,23]. PAI-1 levels increase during periods of psychological stress and depression, while serotonergic antidepressant treatment has been associated with reduced PAI-1 levels [22,24]. Additionally, patients with depression often exhibit lower baseline tPA levels, which significantly increase following antidepressant therapy, highlighting a potential relationship between depression and MI [25]. Elevated PAI-1 and fibrinogen levels may inhibit fibrinolysis leading to evaluated risk of MI [11]. The coagulation system may lead to the development of depression through the tPA-plasmin pathway, which converts pro-Brain-derived neurotrophic factor (BDNF) into BDNF, a neurotrophin essential for synaptic plasticity and neuronal connectivity [26]. In addition, increased inflammatory cytokines also shown to decreased levels of BDNF [27,28]. Reduced BDNF levels, particularly in brain regions involved in mood regulation like the amygdala, prefrontal cortex, hippocampus, and amygdala, have been consistently linked to emotional stress and depression [29].

Mendelian randomization studies have demonstrated a significant link between genetic predisposition to depression and a higher risk of developing MI [11]. Otte et al identified an association between the serotonin transporter gene variant (5-HTTLPR) and an increased risk of depression in patients with myocardial infarction (MI), with carriers of this variant exhibiting a poorer response to treatment with antidepressants [30]. In addition, patients with both depression and MI have increased sensitivity or upregulation of serotonin receptors and reduced expression of serotonin-transporter receptor leading to increased thromboembolic risk [31]. Furthermore, the S allele of the 5-HTT gene polymorphic region has been linked with both depressive symptoms and adverse cardiac outcomes [32]. Genetic differences in the IL-1 gene demonstrated to have a higher

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likelihood of developing depression following a MI, potentially due to increase in the inflammatory response during MI [33].

3. Bipolar Disorder

Figure 2 showed the pathophysiology of myocardial infarction and bipolar disorder. Patients with bipolar disorders experienced prolonged stress due the acute mania or depression leading to disrupted parasympathetic response [34]. The heart-brain axis allows communication between the cardiovascular and nervous systems, with sympathetic and parasympathetic activity mediated by acetylcholine, epinephrine, and norepinephrine to regulating cardiac contractility and heart rate variability [35,36]. Limited research has reported that patients with bipolar disorders have decreased heart rate variability, a key indicator of autonomic nervous system activity [37,38]. Reduced heart rate variability is associated with a 32–45% higher risk of development cardiovascular disease [39]. During the acute phase of mania or depression in bipolar disorders, the HPA is activated, leading to the paraventricular nuclei to secret CRH [34]. This stimulates the anterior pituitary gland to produce ACH, leading to elevated cortisol levels [34]. Hypercortisolemia contributes to insulin resistance and hyperglycemia, leading to increase the release of pro-inflammatory cytokines [34]. The inflammatory cytokines damage endothelial cells, accelerate the formation of atherosclerotic plaque due to oxidization of low-density lipoprotein (LDL) leading to cholesterol crystal build-up and MI [40].

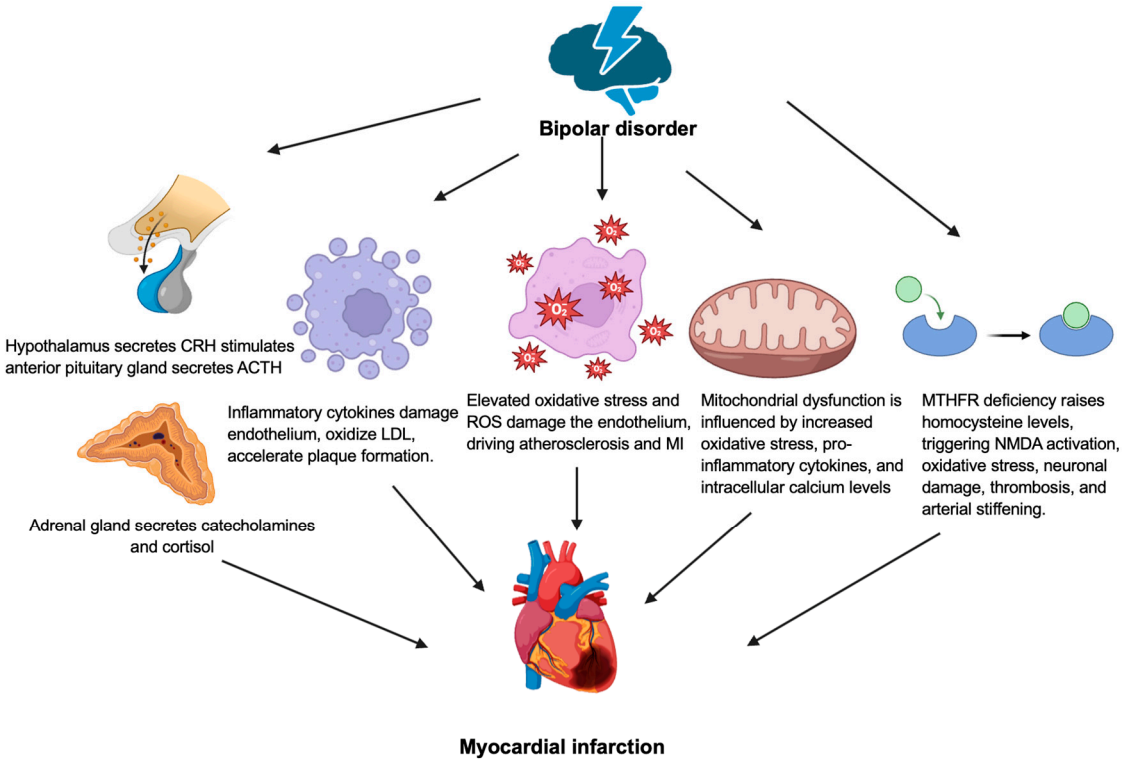

Figure 2. Pathophysiology of myocardial infarction and bipolar disorder. ACTH: adrenocorticotropic hormone, CRH: corticotropin-releasing hormone, LDL: low-density lipoprotein, MI: myocardial infarction, MTHFR: methylenetetrahydrofolate reductase, NMDA: N-methyl-D-aspartate, ROS: reactive oxygen species,.

The neurobiological basis of bipolar disorders may involve dysfunctions in neurotrophic pathways and energy metabolism, with increased oxidative stress causing lipid and protein peroxidation, impairing signal transduction, structural plasticity, and cellular resilience [41]. In vivo magnetic resonance spectroscopy studies demonstrated altered levels of phosphocreatine, phosphomonoesters, and intracellular pH, highlighting disruptions in oxidative phosphorylation, energy production, and phospholipid metabolism in bipolar disorders [41]. The acute phase of

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bipolar disorder leads to increased oxidative stress, characterized by elevated levels of oxidants including peroxides and malondialdehyde, and reduced antioxidants such as vitamin E, coenzyme Q10, catalase that results in generating reactive oxygen species (ROS) through pathways involving redox factor 1, activator protein 1, and hypoxia-inducible factor 1 [42,43]. This oxidative damage contributes to endothelial wall injury, promoting atherosclerosis and cardiovascular diseases [44]. In addition, lipid peroxidation, driven by excess ROS damages polyunsaturated fatty acids in cell membranes, leading to the formation of lipid hydroperoxides and cellular dysfunction [45]. This oxidative damage can compromise mitochondrial integrity, disrupt energy metabolism, and trigger inflammatory responses, contributing to the development and progression of MI [45].

Mitochondrial dysfunction in bipolar disorder is influenced by increased oxidative stress, pro-inflammatory cytokines, and intracellular calcium levels, which are more pronounced during manic episodes [46]. Increased calcium ions and oxidative stress enhance oxidative phosphorylation through pathways involving adenosine triphosphate (ATP) synthase, AMP-activated protein kinase (AMPK), SIRT-1, SIRT-3, and NAD+ [47]. Mitochondrial dysfunction in bipolar disorders leading to excessive calcium and oxidative stress may exacerbate myocardial injury in individuals with underlying ischaemic heart disease. Excessive calcium entry into mitochondria via the mitochondrial calcium uniporter (MCU) and impaired extrusion by the Na^{+}/Ca^{2+} exchanger (NCX) results in mitochondrial calcium overload, leading to the opening of the mitochondrial permeability transition pore (MPTP) [48]. This, combined with oxidative stress-induced damage to mitochondrial membranes and proteins, results in ATP depletion, mitochondrial swelling, and cardiomyocyte death [49]. These processes exacerbate myocardial injury and infarct.

Bipolar disorder is associated with deficiency of methylenetetrahydrofolate reductase (MTHFR) enzyme which essential for homocysteine metabolism leading to increased central and peripheral homocysteine levels during the manic and euthymic phases [50]. Increased homocysteine level leads to NMDA receptor activation, causing increased intracellular calcium, ROS production, and subsequent causing neuronal autophagy or necrosis [51]. Hyperhomocysteinemia depletes nitric oxide and antioxidants, leading to an increase in platelet-derived growth factors and the activation of clotting factors which leads to platelet adhesion, aggregation, thrombus formation [52]. In addition, hyperhomocysteinemia also disrupts the structural integrity of collagen, proteoglycans and elastin leading to arterial stiffening [53]. All these factors contribute to vessels occlusion and increased risk of MI in patients with bipolar disorders [34].

4. Schizophrenia

Inflammation and immune system dysfunction have been observed in individuals with schizophrenia [54]. Cytokines play an essential role in mediating the effects of inflammation in schizophrenia, potentially associating prenatal insults to the schizophrenia [54]. Prenatal infections and maternal immune system alterations have been identified as significant factors, increasing the likelihood of schizophrenia and related neurocognitive and neuroanatomical abnormalities in offspring [55]. Patients with psychosis may demonstrate a higher level of pro-inflammatory cytokines [56]. The activation of the inflammatory response system may lead to microglial activation, as evidenced by post-mortem studies showing an increase in microglial density in the brains of patients with schizophrenia [57]. This process is believed to disrupt neuronal circuit development and function in the brain [58]. Cytokines may also induce neuronal apoptosis, potentially contributing to the functional brain deficits associated with schizophrenia [58]. Elevated levels of cytokines, such as IL-1β, IL-6, and transforming growth factor-β, have been reported during acute relapses and the first episodes of schizophrenia but often normalize following antipsychotic treatment [59]. However other cytokines, including IL-12, IL-γ, TNF-α, and soluble IL-2 receptor, remain elevated during acute relapses, first episodes, and even with antipsychotic therapy [37]. Increased levels of cytokines including IL-1α, IL-6, IL-8, IL-12, IL-33 and IL-35 have a positive correlation with atherosclerosis and increased risk of developing myocardial infarction [60].

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Oxidative stress, characterized by elevated reactive species and diminished antioxidant defences, is implicated in cellular damage and has been consistently observed in schizophrenia [61]. Research assessing oxidative stress in schizophrenia has utilising several peripheral biomarkers like reduced plasma antioxidant and glutathione levels and diminished antioxidant enzymes activities including superoxide dismutase (SOD) and glutathione peroxidase [61]. Studies indicate that patients with acute coronary syndrome exhibit significantly lower SOD levels compared to healthy controls, with NSTEMI patients showing even lower levels than STEMI patients, suggesting more severe oxidative stress [62]. The reduced SOD and catalase levels may result from increased utilization to neutralize free radicals generated during myocardial ischemia, reflecting a depletion of antioxidant defenses [62]. In addition, approximately one-third of schizophrenia patients exhibit pronounced redox dysregulation, with acute-phase polyunsaturated fatty acid (PUFA) deficits and detrimental responses to eicosapentanoate (EPA) or vitamin E and C, although these effects stabilize during remission, marked by persistent redox imbalance in low-PUFA subgroups [63,64]. A reduced serum PUFA level has been shown to an increased risk of cardiovascular events including myocardial infarction [65].

Genome-wide association studies demonstrated shared genetic variants associated with schizophrenia and cardiovascular diseases due to the similar pathophysiology of inflammation and metabolism [66]. Four distinct genetic loci (rs35044849, rs3118357, rs9257136, and rs9257248) have demonstrated significant colocalization between schizophrenia and cardiovascular disease, suggesting that these variants may influence both cardiovascular and neurological systems [67]. The shared genetic loci highlights a potential role for this locus in the heart-brain axis through the regulation of CX3CL1 expression which is a chemokine that implicated in immune responses and neuroinflammation, potentially linking cardiovascular disease and schizophrenia [67]. CX3CL1 is overexpressed in atherosclerotic plaques, contributing to their formation and progression by recruiting inflammatory cells like monocytes to vascular walls leading to an increased risks of myocardial infarction [68]. In addition, elevated CX3CL1 levels have been observed in heart failure patients, correlating with increased risk of cardiac dysfunction through mechanisms involving inflammation and tissue remodeling [69]. Furthermore, the association rs35044849 with various schizophrenia phenotypes and proHB-EGF reduces cardiac contractility, causes interstitial fibrosis and exacerbate cardiac remodeling after myocardial infarction leading to worsening cardiac function [67].

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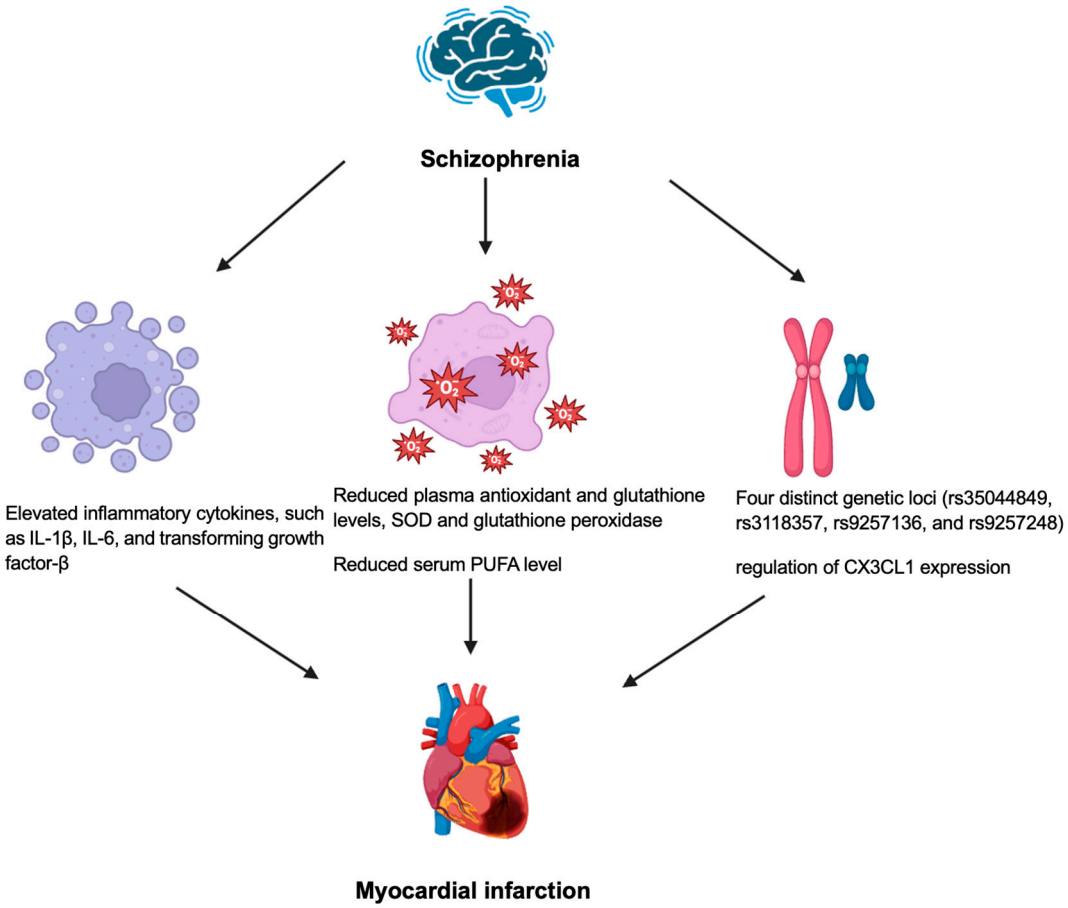

Figure 3. Pathophysiology of myocardial infarction and schizophrenia. IL: interleukin, PUFA: polyunsaturated fatty acid, SOD: superoxide dismutase.

5. Conclusions

This review highlights the bidirectional relationship between MI and major psychiatric conditions. The shared pathophysiological mechanisms, such as inflammation, oxidative stress, neurohormonal dysregulation, and genetic factors, underlie this connection between MI and psychiatric illnesses. Advancements in understanding the pathophysiological mechanisms provide critical insights regarding the complexity of managing patients with comorbid MI and psychiatric disorders. Further research is essential to identify targeted interventions addressing these shared mechanisms to improve both mental and cardiovascular diseases. A holistic approach incorporating multidisciplinary care, early diagnosis, and innovative therapeutic strategies is essential for optimizing outcomes in this vulnerable population.

Conflicts of Interest: The authors declare no conflicts of interest

Abbreviations

The following abbreviations are used in this manuscript:

ACTH	Adrenocorticotropic hormone
AMPK	AMP-activated protein kinase
ANS	Autonomic nervous system
ATP	Adenosine triphosphate
BNDF	Brain-derived neurotrophic factor
CRH	Corticotropin-releasing hormone
DAMP	Damage-associated molecular patterns
EPA	Eicosapentanoate

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HMGB1	High-mobility group box 1
HPA	Hypothalamic-pituitary-adrenal
HSP	Heat shock proteins
IL	Interleukin
LDL	Low-density lipoprotein
MI	Myocardial infarction
MTHFR	Methylenetetrahydrofolate reductase
MPTP	Mitochondrial permeability transition pore
MCU	Mitochondrial calcium uniporter
NCX	Na^+/Ca^{2+} exchanger
NMDA	N-methyl-D-aspartate
NSTEMI	Non-ST elevation MI
PAI-1	Plasminogen activator inhibitor 1
PUFA	Polyunsaturated fatty acid
ROS	Reactive oxygen species
SOD	Superoxide dismutase
STEMI	ST elevation myocardial infarction
TNF	Tumor necrosis factor
tPA	tissue plasminogen activator

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