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Literature Review

The Link between Loneliness, Social Isolation, and Cardiovascular Disease

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Abstracts

Introduction: Cardiovascular disease (CVD) is a major cause of morbidity and mortality worldwide. Loneliness, a subjective feeling of social isolation, and social isolation, an objective lack of social connections, contribute to social vulnerability and physical frailty. Psychological factors and social support play important roles in CVD, affecting health behaviors and physiological mechanisms. This review aims to provide an understanding of how loneliness and social isolation impact CVD. **Methods:** A literature review was conducted to identify relevant studies investigating the association between loneliness, social isolation, and cardiovascular disease. **Results:** The findings indicate that social isolation and loneliness are significant risk factors for CVD, independent of other risk factors. The prevalence of loneliness has increased in modern society, affecting individuals of all ages. Loneliness and social isolation influence physiological processes such as activating the HPA axis, causing inflammation and alterations in immune function, and activating the sympathetic nervous system. These effects contribute to an increased risk of CVD, including elevated blood pressure, hypertension, atherosclerosis, and potential cardiac autonomic dysregulation. **Conclusion:** Loneliness and social isolation pose significant risks for cardiovascular disease (CVD), influencing physiological processes such as inflammation, immune function, and sympathetic nervous system activation. Understanding these relationships is crucial for developing effective strategies to prevent and manage CVD, emphasizing the importance of interventions targeting both psychological and physiological aspects of social well-being.

Keywords: Loneliness, Social Isolation, Cardiovascular Disease

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INTRODUCTION

Cardiovascular disease (CVD) is one of the leading causes of morbidity and mortality worldwide. The impact of CVD is significant in terms of economic burden. Understanding and identifying risk factors can enhance preventive strategies. In 2016, a systematic review indicated that participants with poor social conditions had a 30% higher risk of heart attack and stroke [1].

As social beings, humans rely on a safe and secure social environment for survival and development. The perception of social isolation, or loneliness, increases vigilance to threats and amplifies feelings of vulnerability while also intensifying the desire for social connection [2].

Loneliness is defined as the discrepancy between desired and actual social relationships of an individual [3]. Loneliness occurs when one feels alone or lacks desired relationships with others [4].

Social isolation is defined as the infrequency of direct contact with people for social relationships, such as family, friends, or members of the same community or religious group [4]. It can be an objective measure of the lack of social connection or interaction [3].

Loneliness can be an emotional response to social isolation [3]. Social isolation and feelings of loneliness are related but not identical [4]. Although it is generally believed that social isolation causes loneliness, loneliness can be experienced within marriage, family, friendships, or larger social groups. Conversely, an individual can feel socially satisfied while being alone, and loneliness is considered more related to the quality of relationships rather than quantity [2, 3]. Thus, loneliness is a subjective negative concept concerning feelings of isolation [1, 2].

Loneliness and isolation place individuals at risk of social vulnerability or weakness. This dynamic vulnerability concept is closely associated with sustainability, development, social exclusion, poverty, and lack of social support. Additionally, social vulnerability is closely linked to physical frailty and mortality [5].

Psychological conditions are linked to heart diseases in various ways, decreased cardiac output from various causes, such as congestive heart failure, arrhythmia, pulmonary embolus, and myocardial infarction; acute myocardial infarction presents with confusion as the major symptom in 13% of elderly patients; aged patients do not complain of typical pain; often they complain of indigestion; vital signs may be abnormal, and patient may look ill (ashen coloring, weak, nauseated, sweaty) and be confused [6].

Social support may influence CVD events and death by affecting health-related behaviors such as smoking, diet, physical activity, help-seeking during or after a cardiac event, and adherence to cardiac medication, or through its effects on physiologic mechanisms, such as alterations in cardiovascular, neuroendocrine, and immune function, that have been linked to increased CVD risk [7].

REVIEWS

Epidemiology

Recently, there has been an increasing number of individuals at risk of loneliness in modern society due to social factors and demographic changes [3]. About 80% of individuals under the age of 18 experience loneliness, while 40% of adults experience loneliness [2].

The increase in life expectancy has tripled the number of people aged 60 and above since 1950. Older age is associated with reduced social interaction, longer periods of living alone, and a higher prevalence of loneliness. However, loneliness is more than just a result of age-related losses; it can be experienced at all stages of life [3]. Approximately 15-30% of the general population experience chronic loneliness [2].

The prevalence of loneliness has also increased with delayed marriage, more households where both parents work, and an increase in single-family dwellings. Additionally, the internet has completely trans-

formed the way people live and interact. Despite increased digital connectivity, more people are experiencing social isolation. Recent research suggests that social media, instead of enhancing well-being, can actually harm it. The prevalence of loneliness in modern society is high enough to justify the need for interventions [3].

Social isolation and loneliness are chronic sources of stress that often occur in adults [3]. During the COVID-19 crisis, minimizing loneliness is crucial, as well as reducing stress, anxiety, and fear, to lower the risk of suicidal ideation. Social isolation, anxiety, fear of COVID-19 transmission, uncertainty, chronic stress, and economic difficulties can lead to the development or exacerbation of depression, anxiety, substance use, and other mental disorders in vulnerable populations, including individuals with pre-existing mental disorders and those living in areas with high COVID-19 prevalence [8].

Chronic social isolation has been shown to increase the risk of morbidity and mortality [2, 3], similar to other risk factors such as high blood pressure [2, 3], smoking, and obesity [3]. A meta-analysis involving 148 studies and 308,849 individuals followed for an average of 7.5 years showed that this effect of social isolation is independent of other risk factors. Strong social relationships can increase the likelihood of survival by 50% [9]. Loneliness has serious consequences for cognition, emotions, behavior, and health [2]. Loneliness and social isolation correlate to increased mortality rates. The overall likelihood of death due to loneliness and social isolation is 1.50, comparable to light smoking and greater than the risks associated with obesity and hypertension. A recent meta-analysis showed that social isolation, loneliness, and living alone increase the likelihood of death by 29%, 26%, and 32%, respectively [10].

Individuals with poor social health (socially isolated, lacking support, and lonely) are 42% more likely to develop CVD and twice as likely to die from CVD within a five-year period among adults living in the community, older adults without CVD and without dementia. Poor social health is a strong predictor of CVD events in individuals who are current smokers, live in urban areas, or are aged 70 to 75. Social isolation and low social support predict the occurrence of CVD, while loneliness predicts death from CVD. Poor social health consistently predicts ischemic stroke. Furthermore, isolation increases the need for hospitalization in heart failure patients, while low surrounding support and loneliness facilitate the occurrence of major adverse cardiovascular events (MACE). The risk of CVD events increases by 66% for socially isolated individuals and doubles for those with low social support, but no association was observed with loneliness [11].

Vallee A's research on the relationship between social isolation, loneliness, and the estimated risk of atherosclerotic cardiovascular disease (ASCVD) over a 10-year period among 302,553 volunteers from the UK Biobank population found that social isolation was associated with a higher estimated 10-year risk of ASCVD in both genders, but only loneliness was associated with a higher estimated 10-year risk of ASCVD in men. A significant trend was found between loneliness and CV risk in women [1].

A systematic review followed by a meta-analysis of various studies showed that loneliness and social isolation were correlated with an increased risk of CHD (29%) and stroke (32%) [12]. This association is comparable to anxiety and work-related stress, which are also known as risk factors for CHD. These findings reinforce existing evidence that poor social relationships clearly predict morbidity and mortality [3] and that loneliness and social isolation are additional risk factors for cardiovascular disease (CVD) [1, 3].

The Impact of Loneliness and Social Isolation

Loneliness and social isolation have various impacts. Perceived social isolation has notable effects beyond those predicted by objective isolation, including increased vascular

resistance, elevated blood pressure, elevated morning cortisol, less healthy sleep, and sedentary lifestyles [13]. Additionally, self-regulation abilities are diminished. These abilities are essential for managing thoughts, emotions, and behaviors, enabling individuals to pursue personal goals and adhere to social norms. However, feeling socially isolated undermines this ability and operates at an automatic, unconscious level. Automatic attention processes may remain intact, but the capacity for self-regulation is affected. This has implications for health, particularly in the realm of lifestyle behaviors. Emotional regulation also plays a role in enhancing self-control in other areas [2].

Adequate sleep is crucial for countering the physiological effects of emotional, cognitive, and behavioral challenges and promoting recovery. Sleep deprivation, as observed in experiments, negatively impacts cardiovascular function, inflammation levels, and metabolic risk factors. Loneliness severity aligns with the exacerbation of insomnia [14]. Loneliness intensifies feelings of vulnerability and subconscious vigilance towards social threats, which can conflict with relaxation and restful sleep. In fact, loneliness and poor-quality social relationships have been associated with lower sleep quality and increased daytime dysfunction, such as low energy and fatigue [2].

The connection between loneliness, cardiovascular disease (CVD), and mortality can be attributed to physiological changes that start at a young age. Persistent social isolation, rejection, or feelings of loneliness during childhood, adolescence, and early adulthood have a cumulative effect and can predict risk factors for cardiovascular health in young adults, such as elevated blood pressure [2].

Neuroendocrine Effects and HPA Axis

Loneliness can affect physiological processes such as the autonomic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis, which in turn influence changes in total peripheral resistance (TPR). The sympathetic branch of the autonomic nervous system, responsible for maintaining vascular tone, is particularly involved in hypertension development. Loneliness has been linked to higher levels of epinephrine in overnight urine samples of middle-aged and older adults. Elevated epinephrine concentrations can bind to α-1 receptors on smooth muscle cells, causing vasoconstriction and potentially increasing systolic blood pressure (SBP) in lonely individuals [2].

Loneliness and social isolation activate the hypothalamic-pituitary-adrenal (HPA) axis, which is responsible for producing glucocorticoids like cortisol in humans and corticosterone in rodents. The production of cortisol follows a daily rhythm, being higher in the morning and lower in the evening. Individuals experiencing loneliness exhibit greater increases in morning cortisol levels, elevated concentrations of circulating cortisol, and impaired sensitivity of the glucocorticoid receptors (GR). This suggests that loneliness leads to excessive HPA axis activity [15].

Glucocorticoids can contribute to the development of hypertension and atherosclerosis within the vascular system by increasing vasoconstriction, reducing the production of endothelial nitric oxide (NO), and promoting oxidative stress. They enhance the effects of vasoconstrictors, including catecholamines, on smooth muscle cells in blood vessels. Within endothelial cells, glucocorticoids decrease the production of NO by suppressing the expression of endothelial NO synthase (eNOS). Furthermore, glucocorticoids reduce the enzymatic activity of eNOS by decreasing its phosphorylation at serine 1177. Conversely, when the glucocorticoid receptor is suppressed through siRNA-mediated knockdown, eNOS expression and NO production increase in endothelial cells. Studies on socially isolated prairie voles have shown that social isolation leads to decreased endothelium-dependent vasodilation, indicating reduced endothelial NO production. However, the specific role of glucocorticoids in this effect is still not fully understood. Besides

its involvement in regulating blood pressure, endothelial NO also plays a crucial role in protecting against atherosclerosis. The decreased production of endothelial NO caused by glucocorticoids likely contributes to the atherogenic effects of social isolation [15].

The Function of The Immune System

The immune system plays a crucial role in the potential link between loneliness and cardiovascular disease (CVD) through the mechanism of increased inflammation. Cytokines, which are inflammatory proteins in the immune system, not only coordinate the body's response to inflammation but also trigger "sickness behavior," including fatigue and social withdrawal, as part of the individual's response to illness. This inflammatory response allows sick individuals to prepare for potential infections or threats. Therefore, the pro-inflammatory response observed in loneliness can be viewed as a short-term defense against safety threats, as individuals who are socially disconnected are more susceptible to diseases. However, if this inflammation persists, it can also raise the risk of developing CVD [16].

Loneliness and social isolation, along with socioeconomic stress, have been associated with a specific immune response called the conserved transcriptional response to adversity (CTRA) in leukocytes. This response is characterized by an increase in the expression of pro-inflammatory genes and a decrease in the expression of genes related to antibodies and antiviral immune functions. In lonely individuals, activation of the sympathetic nervous system (SNS) leads to increased circulation of cortisol, which in turn induces changes in pro-inflammatory and anti-inflammatory signaling. Loneliness is also associated with higher levels of norepinephrine metabolites. SNS activation promotes the production of myeloid cells and regulates gene expression related to CTRA [3].

Monocytes, specifically the immature CD14++/CD16- subset, are the main contributors to the pro-inflammatory effects observed in CTRA. Loneliness leads to an expansion of these monocyte subsets and an increase in the regulation of genes associated with inflammation. Although the overall count of circulating leukocytes remains unaffected in lonely individuals, there is a higher percentage of circulating monocytes, accompanied by an upregulation of CTRA-related gene expression. This upregulation is likely attributed to the selective expansion of immature CD14++/CD16- monocyte subsets [3].

Lonely individuals with high perceived social isolation exhibit glucocorticoid resistance in their circulating lymphocytes, which is characterized by a downregulation of glucocorticoid receptor (GR) expression and an upregulation of NF-κB expression [3].

Another aspect of the CTRA leukocyte response involves reduced activity of type I interferons and decreased expression of genes related to antibodies. These effects are likely attributed to dendritic cells, which produce interferons, and B lymphocytes, which are involved in antibody production. Consequently, immune regulation may be disrupted. The expression of CTRA genes can also influence loneliness in a reciprocal manner. In lonely individuals, immature pro-inflammatory monocytes can enter the brain, leading to anxiety and alterations in social behavior [3].

Sympathetic Nervous System

The sympathetic nervous system (SNS) from the central nervous system directly connects to the adrenal medulla through the splanchnic nerves, enabling a quick response to acute stress by releasing epinephrine (and small amounts of norepinephrine and dopamine). The SNS extends throughout the body, including the lymphoid system, and its nerve fibers release norepinephrine directly into the thymus, spleen, and lymph nodes [3].

In a recent study, the influence of perceived social isolation on the effects of oxytocin on cardiac autonomic control in humans was examined. Administering 20 IU of oxytocin

intranasally resulted in a significant increase in both parasympathetic and sympathetic control of the heart. Specifically, oxytocin enhanced high-frequency heart rate variability, indicating improved parasympathetic control, and reduced the pre-ejection period, indicating enhanced sympathetic control. Analyzing autonomic co-activity and reciprocity revealed that oxytocin significantly enhanced overall cardiac autonomic control. Additionally, the impact of oxytocin on cardiac autonomic control was influenced by feelings of loneliness. Higher levels of loneliness were associated with reduced parasympathetic cardiac responsiveness to intranasal oxytocin. These effects on cardiac autonomic control were not dependent on changes in circulating pro-inflammatory cytokines or stress hormone levels. Therefore, individuals experiencing loneliness may exhibit decreased responsiveness to the positive effects of oxytocin on cardiovascular regulation [17].

The SNS plays a role in increasing the production of immature and pro-inflammatory monocytes in the bone marrow as a response to social stress, mediated by β-adrenergic receptors. Social stress leads to a pro-inflammatory state characterized by heightened monocyte production and selective expansion of immature monocyte subsets (Ly-6cHigh and CD16-). These immature monocytes exhibit pro-inflammatory properties, while the more mature Ly6c monocytes have immunoregulatory functions [3].

Outlined below are proposed mechanisms regarding the impact of loneliness and social isolation on health, involving behavioral, psychological, and pathophysiological pathways (Figure 1).

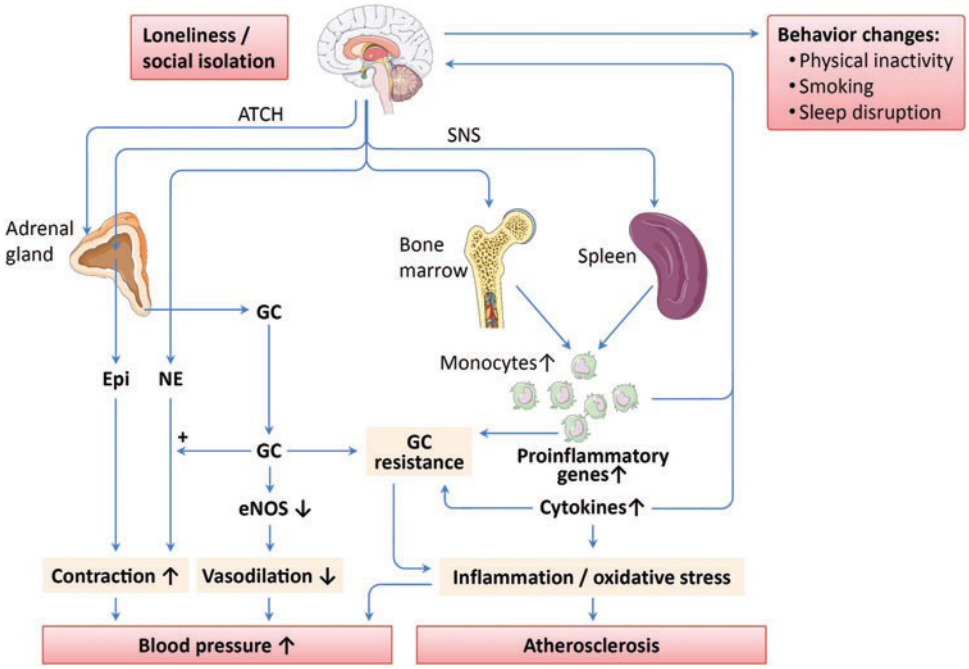

Figure 1. Proposed mechanisms of loneliness-associated cardiovascular disease [3]. ACTH: adrenocorticotropic hormone. Epi: epinephrine. eNOS: endothelial nitric oxide synthase. GC: glucocorticoid. NE: norepinephrine. SNS: sympathetic nervous system.

Loneliness and social isolation trigger activation of the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS), accompanied by behavioral changes such as alterations in physical activity, smoking habits, and sleep distur-

bances. SNS activation leads to increased monocyte production in the bone marrow, resulting in the expansion of immature pro-inflammatory monocytes. Additionally, the SNS stimulates monocyte release from the spleen. Prolonged social stress causes resistance to glucocorticoids (GC), upregulation of pro-inflammatory gene expression, and heightened cytokine production by immune cells. Cytokines, in turn, can exacerbate GC resistance. These processes contribute to heightened inflammation and oxidative stress, potentially contributing to the development of atherosclerosis and elevated blood pressure. Pro-inflammatory monocytes and cytokines can circulate to the brain, reinforcing feelings of loneliness by triggering sickness behavior. Epinephrine (Epi) and norepinephrine (NE) induce vasoconstriction, a response that is further amplified by GC. Furthermore, GC reduces the expression of endothelial nitric oxide synthase (eNOS) genes and the phosphorylation of serine 1177 in endothelial cells, resulting in reduced nitric oxide (NO) production and impaired vasodilation. However, the precise causal role of these mechanisms in the development of loneliness-related cardiovascular disease remains incompletely understood, although several research findings indicate the involvement of some of the factors mentioned [3].

Other Impacts

Loneliness and social isolation contribute to the development of cardiovascular disease through other impacts as well. Notably, individuals experiencing loneliness or isolation often engage in harmful behaviors linked to cardiovascular risks, including smoking, reduced exercise [18], alcohol consumption, and unhealthy dietary choices. Moreover, the limited social network of socially isolated individuals poses challenges in accessing both emergency and routine medical care [19]. The inadequate provision of healthcare to this group, viewed by professionals as difficult to treat or time-consuming, further exacerbates the negative impact of loneliness and social isolation on cardiovascular health [20].

CONCLUSION

Loneliness and social isolation have emerged as important risk factors for cardiovascular disease (CVD), with implications for both psychological well-being and physiological mechanisms. The prevalence of loneliness has been on the rise, affecting individuals across different age groups. The impact of loneliness and social isolation on CVD is mediated through activation of the hypothalamic-pituitary-adrenal (HPA) axis, inflammation, immune system alterations, and activation of the sympathetic nervous system. These pathways contribute to the development of elevated blood pressure, hypertension, atherosclerosis, and potential dysregulation of cardiac autonomic control. Moreover, individuals experiencing loneliness often engage in harmful behaviors, including smoking, reduced exercise, alcohol consumption, and unhealthy dietary choices, while the limited social network of socially isolated individuals poses challenges in accessing medical care, further exacerbating the negative impact on cardiovascular health. Understanding the role of loneliness, social isolation, and social support in CVD is essential for the development of effective preventive and management strategies, highlighting the need for interventions that address both psychological and physiological aspects of social well-being.

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CONFLICT OF INTEREST

No conflict of interest was reported by the author in conducting this literature review. The authors declare that they have no financial or personal relationships that could po-

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