



## Loneliness, Social Isolation, and Cardiovascular Health

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### Abstract

**Significance:** Social and demographic changes have led to an increased prevalence of loneliness and social isolation in modern society.

**Recent Advances:** Population-based studies have demonstrated that both objective social isolation and the perception of social isolation (loneliness) are correlated with a higher risk of mortality and that both are clearly risk factors for cardiovascular disease (CVD). Lonely individuals have increased peripheral vascular resistance and elevated blood pressure. Socially isolated animals develop more atherosclerosis than those housed in groups.

**Critical Issues:** Molecular mechanisms responsible for the increased cardiovascular risk are poorly understood. In recent reports, loneliness and social stress were associated with activation of the hypothalamic–pituitary–adrenocortical axis and the sympathetic nervous system. Repeated and chronic social stress leads to glucocorticoid resistance, enhanced myelopoiesis, upregulated proinflammatory gene expression, and oxidative stress. However, the causal role of these mechanisms in the development of loneliness-associated CVD remains unclear.

**Future Directions:** Elucidation of the molecular mechanisms of how CVD is induced by loneliness and social isolation requires additional studies. Understanding of the pathomechanisms is essential for the development of therapeutic strategies to prevent the detrimental effects of social stress on health. *Antioxid. Redox Signal.* 28, 837–851.

**Keywords:** loneliness, social isolation, cardiovascular disease, oxidative stress

### Introduction

LONELINESS, DEFINED AS THE discrepancy between a person's desired and actual social relationships, is an emotional response to social isolation, while social isolation is an objective measure of the lack of social connections or interactions. Consequently, loneliness is thought to be more related to relationship quality than quantity (57, 78).

In addition to physical presence, humans need relationships that provide mutual value and trust, and promote communication and collaboration toward common goals (15, 57, 78). Although it is commonly thought that social isolation leads to loneliness, loneliness can be experienced within a marriage, family, friendship, or larger social group. In contrast, one can feel socially contented while being alone (11, 12, 57, 78).

The perception of social isolation is not restricted to humans; behaviors related to social isolation have been also documented in animals (12, 14). Perceived social isolation (PSI) has damaging effects on the physical health of humans and animals manifested by activation of the hypothalamic–pituitary–adrenal (HPA) axis and increased depressive behavior (14). Experiments with animals housed individually are important for investigating the molecular mechanisms and the causal effects of social deprivation in disease development (11, 119).

Social isolation and loneliness are common sources of chronic stress in adults (82, 124). Moreover, a growing number of individuals are at risk for loneliness in modern society because of social and demographic changes (78). People are living longer and the number of people aged 60 years and older has tripled since 1950. Older age is associated

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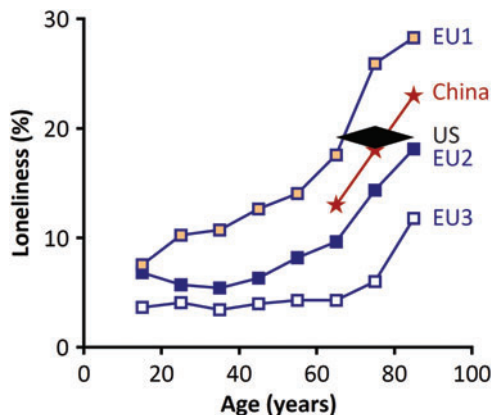
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with reduced social interactions, longer periods of time living alone, and higher prevalence of loneliness (49, 104). However, loneliness is more than simply the result of age-related losses but can be experienced at all stages of life (7, 74).

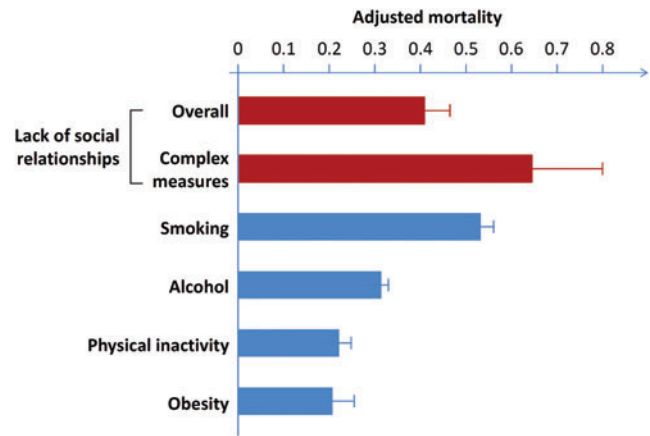
The prevalence of loneliness has increased commensurate with deferred marriage, increased two-income households, and increased residence in single-family homes (78). In addition, the Internet has completely changed the way people live and interact (15). Despite increased digital connectivity, more people are experiencing social isolation (15). Rather than enhancing well-being, recent studies suggest that social media may undermine it (68). The prevalence in modern society (Fig. 1) is high enough to justify intervention (92).

### Loneliness as a Mortality Risk Factor

Chronic social isolation has been shown to increase the risks of morbidity and mortality similar to known factors, including high blood pressure, smoking, and obesity (60). 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 was independent of other risk factors (Fig. 2). The quantity and quality of relationships have been inversely correlated with health risks (58, 59). Strong social relationships can increase the likelihood of survival by as much as 50% relative to individuals whose relationships are weaker (59). An increase in mortality has been correlated with both loneliness and social isolation (58, 125). The overall odds of mortality due to loneliness and social isolation are 1.50, which was comparable to light smoking and greater than the risks due to obesity and hypertension (59). A recent meta-analysis indicated that social isolation, loneliness, and living alone increased the possibility of death by ~29%, 26%, and 32%, respectively (58).



**FIG. 1. Prevalence of loneliness.** The reported prevalence of loneliness in Europe (148) and China (149), respectively. The overall prevalence of loneliness among adults older than 65 in the United States (135) is shown for comparison. There are significant differences in the prevalence among European countries with a higher prevalence in group EU1 (Bulgaria, Hungary, Latvia, Poland, Romania, Russia, Slovakia, and Ukraine) than group EU2 (Austria, Cyprus, Estonia, France, Portugal, Slovenia, and Spain), and group EU3 (Belgium, Denmark, Finland, Germany, Ireland, the Netherlands, Norway, Sweden, Switzerland, and the United Kingdom) (148). To see this illustration in color, the reader is referred to the web version of this article at [www.liebertpub.com/ars](http://www.liebertpub.com/ars)



**FIG. 2. Impact of social support on mortality.** The odds of mortality due to social isolation and loneliness are similar to light smoking (15 cigarettes/day) and alcohol consumption (6 drinks/day), and exceed the risks conferred by physical inactivity and obesity. Note: Effect size of zero indicates no effect. Complex measures of social integration are single measures that assess multiple components of social integration such as marital status, network size, and participation (59). Reproduced and modified from Holt-Lunstad *et al.* (59), which is an open-access article distributed under the terms of the Creative Commons Attribution License. To see this illustration in color, the reader is referred to the web version of this article at [www.liebertpub.com/ars](http://www.liebertpub.com/ars)

### Loneliness as a Cardiovascular Risk Factor

An early study published in 1992 showed that coronary heart disease (CHD) patients who were not married and did not have a confidant had a significantly higher 5-year incidence of mortality (50%) than that (18%) observed in patients with a spouse or partner (146). Two reviews about social relationships and CHD associated the degree of loneliness with the incidence and prognosis of CHD, although the evidence was relatively weak (3, 124)

A recent systematic review followed by a meta-analysis of 16 prospective longitudinal studies showed that loneliness and social isolation were correlated with increased risks of CHD (29%) and stroke (32%) (138). The association was comparable to anxiety and job stress, which are recognized risk factors for CHD (138). This finding reinforces existing evidence demonstrating that poor social connections robustly predict morbidity and mortality, and that loneliness and social isolation are additional risk factors of cardiovascular disease (CVD) (57).

### Hypertension

Results from longitudinal (54) and cross-sectional (13) studies have shown the association between increased blood pressure and loneliness in older and middle-aged individuals; this association strengthens with increasing age of individuals (52). Moreover, individuals who were lonelier by one standard deviation had systolic blood pressure (SBP) that was 3.7 mmHg greater at study initiation and was predicted to increase by 2.3 mmHg over the next 4 years (52). Thus, these findings would predict that over 4 years, the most lonely individuals would exhibit an increase in SBP that was 14.4 mmHg (3.6 mmHg/year) higher than the least lonely individuals (54).

Increase in total peripheral resistance (TPR) is the main cause of elevated SBP in individuals up to 40 years of age, when arterial stiffness assumes a growing role (43). TPR levels are chronically increased in young adults who are lonely relative to nonlonely individuals of the same age (13, 50). The more rapid increase in TPR leads to premature arterial stiffening and increase of SBP (43). Consequently, lonely individuals may develop earlier or more severe structural abnormalities in resistance arteries that promote deposition of collagen and decrease elastic fiber content (54).

### Atherosclerosis

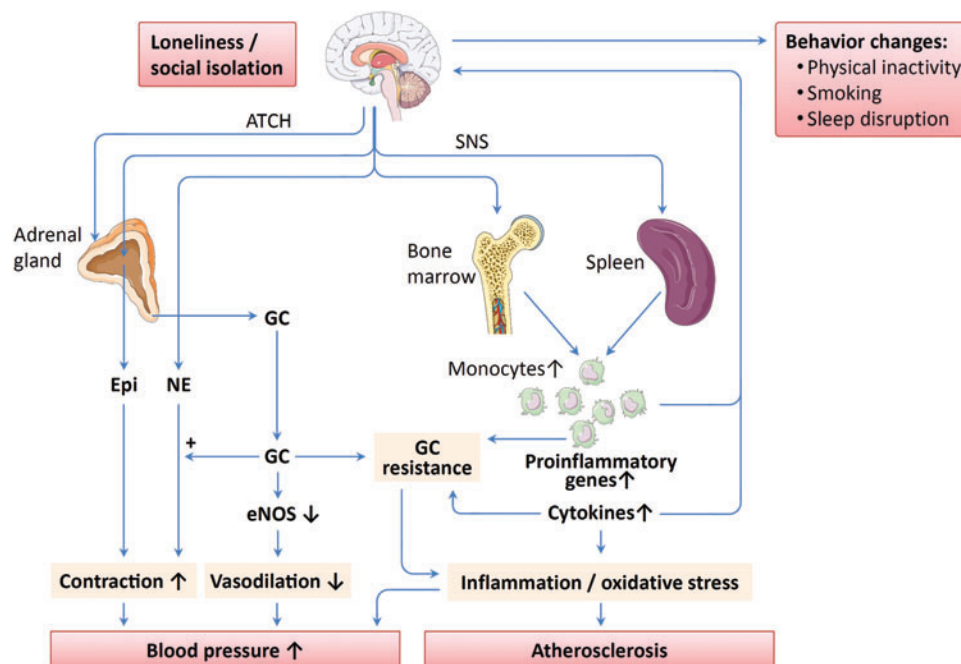
There is a large body of evidence from animal studies showing that social isolation and social stress accelerate atherogenesis. Male cynomolgus monkeys exposed to social stress (*e.g.*, via periodic reorganizing of groups with different conspecifics) and fed a diet low in fat and cholesterol developed more severe atherosclerosis of the coronary artery compared with control monkeys under nonstress conditions (maintained in stable groups) (63). The lack of significant effects of social stress on blood pressure, serum lipid, and glucose levels, or ponderosity indicated that atherogenesis

in these stressed monkeys was independent of serum lipid levels (63). In female cynomolgus monkeys that consumed a moderately atherogenic diet, social deprivation by individual housing significantly increased coronary artery atherosclerosis without a change in plasma lipid concentrations (115). Similarly, Watanabe heritable hyperlipidemic rabbits (79, 96) and apolipoprotein E-knockout mice (6) housed in social isolation showed greater atherosclerotic lesion areas than those in an affiliative social environment.

Molecular mechanisms underlying the enhanced atherosclerosis in socially isolated animals may involve sympathetic nervous system (SNS) overactivation and physical inactivity, as well as enhanced vascular inflammation and oxidative stress (79, 86, 87).

### Pathways Affected by Loneliness—The Molecular Link

In a review article published in this Forum, Meyer and Wirtz addressed the molecular mechanisms linking cytokine function and HPA axis components to mitochondrial redox signaling under psychosocial stress (83). In the present article, we discuss how loneliness and social isolation affect health by activating behavioral and psychological mechanisms as well as pathophysiological pathways (Fig. 3).



**FIG. 3. Proposed mechanisms of loneliness-associated cardiovascular disease (CVD).** Loneliness and social isolation lead to activation of the hypothalamic–pituitary–adrenal (HPA) axis and the sympathetic nervous system (SNS), and to behavioral alteration, including physical inactivity, smoking, and sleep disruption. SNS activation enhances monocytopoiesis in the bone marrow resulting in expansion of immature proinflammatory monocytes. In addition, SNS also stimulates monocyte egress from the spleen. Chronic social stress leads to glucocorticoid (GC) resistance, upregulation of proinflammatory gene expression, as well as enhanced cytokine production by immune cells. Cytokines, in turn, can potentiate GC resistance. The resulting enhanced inflammation and oxidative stress may be involved in atherosclerosis development and blood pressure elevation. Both proinflammatory monocytes and cytokines can traffic to the brain and amplify loneliness by inducing “sickness behaviors.” Epinephrine (Epi) and norepinephrine (NE) induce vasoconstriction, an effect that is enhanced by GC. Moreover, GC reduces endothelial nitric oxide synthase (eNOS) gene expression and serine 1177 phosphorylation in endothelial cells resulting in decreased nitric oxide (NO) production and impaired vasodilation. However, the causal role of these mechanisms in the development of loneliness-associated CVDs has not been demonstrated so far, although their involvement is likely. ACTH denotes adrenocorticotropic hormone. The images of brain, bone, spleen, and monocytes used in this figure are from Servier Medical Art licensed under the Creative Commons Attribution 3.0 Unported License (111). To see this illustration in color, the reader is referred to the web version of this article at [www.liebertpub.com/ars](http://www.liebertpub.com/ars)

### *Behavioral and psychological changes*

Social species create organizations (ranging from dyads and families to societies) beyond the individual, which have benefits such as mutual protection and assistance (12). Therefore, social isolation represents a dangerous situation, through which a socially isolated individual may react with implicit vigilance for social threats, fragmented sleep to evade predation, and increased cardiovascular activity to deal with potential assaults (12). Although these responses may be protective for short-term survival, when isolation becomes chronic, they have long-term detrimental effects on mental and physical health (12).

Social isolation and loneliness are associated with health risk behaviors such as reduced physical activity, reduced sleep quality, and smoking (7, 53, 57, 113, 138). Loneliness also has been associated with depression, anxiety, dysphoria, and social withdrawal (12). Similar observations have been made in animal studies. Male adult rodents subjected to social isolation exhibit a significant decrease in physical activity and sleep quality (11, 13). Mice subjected to social isolation exhibited disrupted sleep and reduced slow-wave sleep (65).

### *The HPA axis*

The major neuroendocrine systems involved in the stress response are the HPA axis and sympathetic adrenomedullary axis (11). Activation of the HPA axis is a consistent finding in lonely individuals (51), whereas the association between loneliness and increased circulating levels of catecholamines is less consistent (11).

The HPA axis plays an important role in regulating the response to stress (12). The HPA axis is the main producer of glucocorticoids, including cortisol (humans) and corticosterone (rodents). Glucocorticoid release follows the circadian rhythm, where highest levels occur in the morning and lowest levels occur in the evening. Loneliness in humans is associated with larger morning cortisol rises (1), higher circulating cortisol levels (23, 33), and decreased glucocorticoid receptor (GR) sensitivity (21, 25), indicating higher levels of HPA activation in lonely individuals (12).

Similar HPA axis activation has been observed in animal models of PSI. Chronic separation of pair-bonded prairie voles was associated with increased levels of corticosterone (10, 81, 126), whereas chronic separation from a low-preference partner (*e.g.*, same-sex sibling) resulted in no increase in levels of corticosterone (10).

Glucocorticoids govern physiological functions, including immunity, metabolism, cardiovascular activity, reproductive processes, neurodegeneration, and apoptosis (11). Glucocorticoids mediate these physiological functions *via* rapid-acting, nongenomic effects and slow-acting genomic effects. For example, stimulation of GRs in leukocytes by cortisol results in suppression of proinflammatory gene networks. However, chronic social stress induces glucocorticoid resistance (Fig. 4) in which the GR becomes less efficient in transducing glucocorticoid signals (27). Glucocorticoid resistance, in turn, leads to excessive inflammation as well as hyperactivity of corticotropin-releasing hormone and SNS pathways (94), which may contribute to development of diseases, including atherosclerosis, diabetes, neurodegeneration and tumor metastasis (11). Interestingly, CHD patients show a blunted cortisol stress response (less cortisol

release in response to acute stress) (140), and depressed individuals with CHD have increased inflammatory marker expression and decreased GR expression and GR sensitivity compared with nondepressed CHD patients (89).

A variety of molecular mechanisms have been implicated in glucocorticoid resistance (Fig. 4), including GR degradation, disruption of GR translocation, and/or GR-DNA binding, as well as changes in GR phosphorylation status (94, 105, 117). Importantly, inflammatory cytokines potentiate glucocorticoid resistance (94). As glucocorticoid resistance exacerbates inflammation and production of proinflammatory cytokines, there may exist a positive feedback mechanism in the development of glucocorticoid resistance. In addition, glucocorticoid resistance can be attenuated by  $\beta$ -adrenoceptor blockade in socially isolated mice, which indicates a contribution of the SNS to glucocorticoid resistance (48, 101).

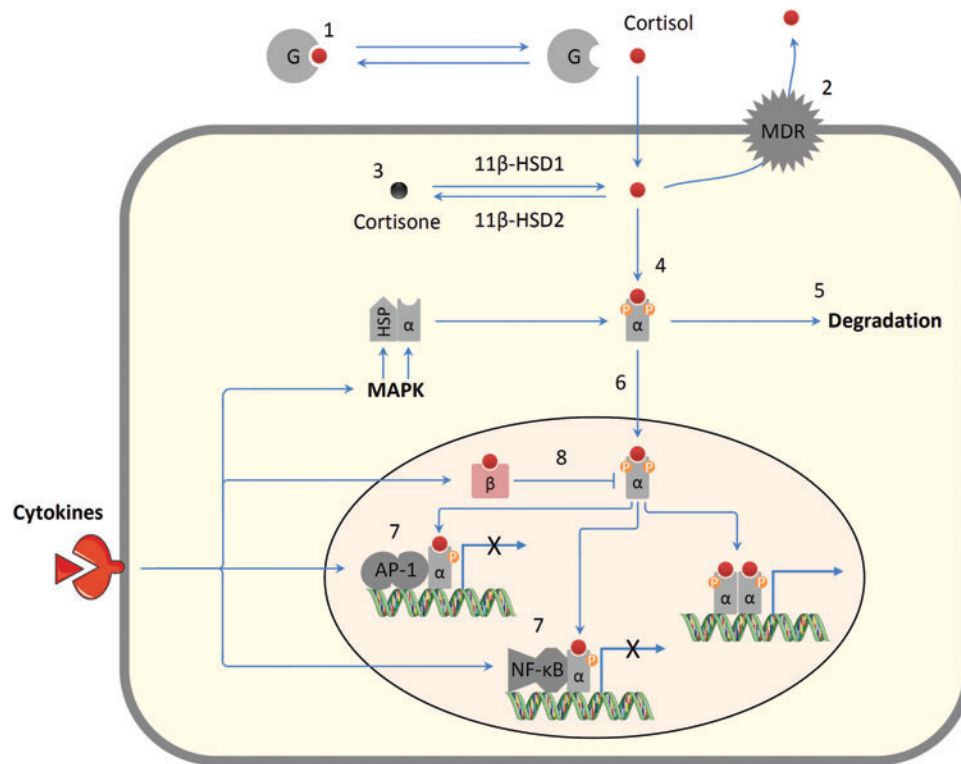
In endothelial cells, glucocorticoids reduce nitric oxide (NO) production *via* endothelial NO synthase (eNOS). NO derived from eNOS is a crucial antihypertensive and anti-atherosclerotic factor (42, 70). Both the expression level (142) and serine 1177 phosphorylation (136) of eNOS are decreased by glucocorticoid treatment. Reduced endothelial NO production represents a crucial mechanism in the development of glucocorticoid therapy-induced hypertension (107, 141, 142). Moreover, glucocorticoids also potentiate the vasoconstricting effect of catecholamines (150). However, the contribution of these mechanisms to blood pressure elevation and atherosclerosis in lonely and socially isolated individuals remains to be determined. It is not clear whether the loneliness-associated glucocorticoid resistance also occurs in endothelial cells or is restricted to immune cells. Nevertheless, acetylcholine-induced, endothelium-dependent vasodilation is impaired in the aorta of socially isolated prairie voles (97), which suggests reduced endothelial NO production from eNOS.

### *The SNS*

The SNS projects from the central nervous system through the splanchnic nerve directly to the adrenal medulla. This direct innervation enables a rapid response to acute stress *via* secretion of epinephrine (and smaller amounts of norepinephrine and dopamine) into the circulation (11). In addition, the SNS innervates the entire body, including the lymphoid system (48), and SNS nerve fibers release norepinephrine directly into the thymus, spleen, and lymph nodes (11).

Evidence for the association between loneliness and elevated catecholamine levels (44) has not been as consistently shown as the effect of loneliness on the HPA axis (11, 52). In humans and macaques, chronic PSI has been associated with elevated urinary levels of norepinephrine metabolites but not epinephrine (23).

Interestingly, social stress appears to be much more strongly related to local catecholamine levels in SNS-innervated tissues (*e.g.*, thymus, spleen, lymph nodes, and tumors) than systemic catecholamine levels. For instance, poor social support and high prevalence of depression in ovarian cancer patients were associated with significantly higher norepinephrine levels in tumor tissues compared with patients with strong social networks and lower prevalence of depression. In contrast, no effect of social support on plasma norepinephrine was found in the same patient population (75, 76). Moreover, the high tumor norepinephrine levels were



**FIG. 4. Mechanisms of glucocorticoid resistance.** Reduction in glucocorticoid sensitivity can be ascribed to alteration of factors that regulate glucocorticoid bioavailability and activity such as [1] increased corticosteroid-binding globulin (G); [2] increased expression of the multidrug resistance transporter (MDR pump); [3] increased expression of cortisol-inactivating enzyme 11 $\beta$ -HSD-2; [4] reduced glucocorticoid binding to the glucocorticoid receptor (GR $\alpha$ ); [5] inflammasome-mediated degradation of GR $\alpha$ ; [6] reduced GR nuclear translocation due to phosphorylation by p38 and JNK classes of mitogen-activated protein kinase (MAPK); [7] increased GR interaction with inflammatory-related transcription factors, such as NF- $\kappa$ B or AP-1; and [8] increased expression of the inhibitory glucocorticoid receptor GR $\beta$ . HSP, heat shock protein. X indicates inhibition of gene expression. Partly adapted from Refs. 94, 105, 117, 139. To see this illustration in color, the reader is referred to the web version of this article at [www.liebertpub.com/ars](http://www.liebertpub.com/ars)

paralleled by stronger norepinephrine effects mediated by  $\beta$ -receptors, for example, transcription pathways that mediate inflammation, metastatic capacity, and cell proliferation (19, 28, 75, 76).

The social regulation of tissue norepinephrine levels is not only a result of functional but also structural changes. Studies in nonhuman primates have found a substantial amount of socially regulated plasticity in the innervation of lymph nodes (120, 122). Animals housed under unstable conditions showed catecholaminergic innervation of lymph nodes that was more than twice as dense as animals socialized under stable social conditions. These animals had an impaired antiviral immune response, normally mediated by type I interferon, which resulted in increased simian immunodeficiency virus (SIV) load (122). Given lymphoid organs' fundamental immunoregulatory role, social stress-induced innervation of lymph nodes may have a range of effects on immunity and inflammation (120, 121).

The SNS is also involved in upregulated production of immature and proinflammatory monocytes by the bone marrow in response to social stress, an effect that is mediated by  $\beta$ -adrenergic receptors (101). Social stress leads to a proinflammatory state characterized by increased monocytopoiesis and selective expansion of an immature monocyte subset (Ly6c<sup>hi</sup> and CD16<sup>-</sup> in mice and humans, respectively) (55, 101).

These immature monocytes are proinflammatory, while the more mature Ly6c<sup>lo</sup> monocytes are immunoregulatory (127).

Peripheral blood mononuclear cells (PBMCs) from young adults subjected to chronic socioeconomic stress showed total monocyte transcriptome expansion and immature proinflammatory CD16<sup>-</sup> monocyte transcriptome expansion (101). Moreover, this proinflammatory gene expression profile was mediated by upregulation of myelopoiesis induced by the SNS (101). The bone marrow microenvironment, where hematopoiesis and differentiation of monocytes take place, is innervated by the SNS (35), which implies that mobilization of hematopoietic stem cells is regulated by the SNS (4, 64).

Repeated social defeat (RSD) in mice is used as a model for social disruption stress (SDR). Like SDR, RSD results in activation of the HPA axis and the SNS. RSD in mice results in increased bone marrow monocytopoiesis and Ly6c<sup>hi</sup> monocyte accumulation in blood, spleen, bone marrow, and brain (80, 101). Pretreatment of mice with propranolol ( $\beta$ -adrenergic receptor blocker) before RSD prevented peripheral Ly6c<sup>hi</sup> monocyte expansion and proinflammatory gene upregulation in monocytes from peripheral blood (101).

Interestingly, SNS activation in the spleen results in the release of primed monocytes (80). Splenomegaly and glucocorticoid resistance in CD11b<sup>+</sup> and CD11c<sup>+</sup> myeloid populations of the spleen were observed in mice subjected to



RSD (48). Pretreatment of mice with propranolol before RSD led to decreased RSD-induced plasma IL-6 and splenomegaly, and attenuated anxiety-like behavior (48).

The re-establishment of anxiety-like behavior in RSD mice in response to subthreshold stress was correlated with Ly6c<sup>hi</sup> monocyte release from the spleen and accumulation in the brain. Moreover, trafficking of monocytes to the brain and anxiety-like behavior induced by subthreshold stress were prevented by splenectomy before RSD in these mice. Thus, trafficking of monocytes to the brain was associated with the recurrence of anxiety-like behavior in these RSD mice (80, 128, 147).

### The vagal system

An important function of the vagal system is to prevent the detrimental effects of SNS overactivation (18, 67). Heart rate variability (HRV) is measured by the variation in the beat-to-beat interval (112, 133), which is partly modulated by the autonomic nervous system at the sinoatrial node of the heart (45, 69). High-frequency heart rate variability (HF-HRV) denotes heart rate variations associated with respiration. Respiratory sinus arrhythmia occurs when the heart rate accelerates and decelerates on inspiration and expiration, respectively (112). HF-HRV is determined by vagally mediated parasympathetic activity (112). The cardiovascular center inhibits vagal outflow during inhalation and restores vagal outflow during exhalation (112). Although the heart is dually innervated, the influence of the SNS on the heart occurs too slowly to affect beat-to-beat changes quickly (133). Therefore, HF-HRV directly measures parasympathetic control of the heart (45, 91).

Recent studies have suggested that positive social interactions have an effect on HF-HRV (45). Marriage was associated with greater HF-HRV (102), and happy marriages were associated with even greater HF-HRV (123). One study of 2066 male civil servants in the United Kingdom (the Whitehall cohort) found a correlation between smaller HF-HRV and low social integration (56). Similarly, the effect of social integration on autonomic nervous system function was demonstrated in a recent study of students who had moved to a foreign country. The lack of social integration within the initial 5 months in the host country was correlated with a higher heart rate and lower HF-HRV (45). The results suggested that changes in autonomic nervous system function, measured by HF-HRV, may be an important link between social integration and health (45).

Studies in animal models of social isolation have suggested that HRV may be regulated by the social environment. Socially isolated prairie voles had lower HF-HRV compared with socially paired voles at baseline and during exposure to stress (46, 47). Exogenous oxytocin administration increased the HF-HRV of socially isolated voles to a level similar to socially paired voles (47).

Similarly, oxytocin administration to healthy young adults significantly increased both sympathetic (indexed by pre-ejection period) and parasympathetic (indexed by HF-HRV) autonomic cardiac control (91). Importantly, the level of loneliness negatively predicted alterations in autonomic control of cardiac function induced by oxytocin treatment, which was independent of anxiety, depression, and serum markers. Lonelier individuals had lower response to oxytocin-induced effects on HF-HRV (91). Because simultaneous activation of

the parasympathetic nervous system mitigates the potentially deleterious effects of heightened sympathetic output (91, 133), loneliness may cause a potentially healthy response (autonomic coactivation) to become harmful (selective activation of the SNS).

Hence, one mechanism by which social isolation may negatively impact health outcomes is *via* altered autonomic nervous system function (45). Indeed, a lower HF-HRV has been correlated with adverse health outcomes (45), including reduced cognitive function, depression, CVD, and all-cause mortality (73, 132, 134, 137).

### The immune system

Social isolation and socioeconomic stress have been associated with the conserved transcriptional response to adversity (CTRA) in leukocytes, characterized by upregulation of proinflammatory gene expression and downregulation of antibody- and antiviral immunity-related genes (25, 26, 101). Human myeloid-derived antigen-presenting cells such as dendritic cells, monocytes, and B cells have been identified by transcript origin analyses as the major cellular contributors of the transcriptional response of the immune system to loneliness (24).

In lonely individuals, SNS activation (101), rather than circulating levels of cortisol, causes the shift between pro- and anti-inflammatory signaling (25, 101). Loneliness also has been correlated with elevated levels of norepinephrine metabolites (but not epinephrine) in urine (23). SNS activation enhanced myelopoiesis (55, 101) and concurrently regulated CTRA-related gene expression (23).

Reciprocal regulation of the leukocyte transcriptome may result in two distinct functional consequences: enhanced inflammation and an impaired antiviral response.

Monocytes are the main source of the proinflammatory function of the CTRA (101), which results from immature CD14<sup>+</sup>/CD16<sup>-</sup> monocyte subset expansion (23) and upregulated proinflammatory gene expression (24). While the number of total circulating leukocytes (24) was not significantly changed in lonely individuals, the percentage of circulating monocytes was increased and CTRA-associated gene expression was upregulated (23). Upregulation of CTRA-related gene expression in human resulted likely from selective expansion of the immature CD14<sup>+</sup>/CD16<sup>-</sup> classical monocyte subset rather than the total CD14<sup>+</sup> monocyte population (23). Similarly, macaques with high PSI also showed upregulated circulating monocyte frequencies and percentages. Within the monocyte population, classical CD14<sup>+</sup>/CD16<sup>-</sup> monocytes were expanded, and nonclassical CD14<sup>+</sup>/CD16<sup>+</sup> monocytes were unchanged (23). Analogous to high-PSI humans, high-PSI macaques showed upregulated CTRA-related gene expression in the classical CD14<sup>+</sup>/CD16<sup>-</sup> monocytes from the PBMC population (23). Moreover, circulating lymphocytes from high-PSI humans (24, 25) and macaques (23) showed glucocorticoid resistance, including downregulated GR expression and upregulated NF- $\kappa$ B expression (23).

Based on these data, Cole *et al.* proposed a mechanistic model in which loneliness results in an SNS-mediated expansion of myeloid-lineage cells characterized as immature, proinflammatory, and glucocorticoid resistant (23). Upregulation of proinflammatory gene expression in lonely people may be explained by glucocorticoid resistance even with

concurrently elevated cortisol levels, as the anti-inflammatory effects of endogenous glucocorticoids are diminished because of impaired GR signaling (23). The resulting long-term inflammation may represent a key mechanism in the development of loneliness-associated chronic diseases such as atherosclerosis, cancer, and neurodegeneration (23).

The other part of the leukocyte CTRA, namely, reduced type I interferon activity and reduced antibody-related gene expression, likely comes from dendritic cells, which produce interferon, and B lymphocytes, respectively (23, 24). This may lead to impaired immunity as the functional consequence. At baseline, high-PSI macaques showed down-regulated PBMC mRNA levels of interferon genes compared to controls. After infection with SIV, interferon gene expression was significantly upregulated in controls but not in high-PSI animals. High-PSI macaques also showed weaker suppression of SIV gene expression in PBMCs, increased viral load in plasma and cerebrospinal fluid, and decreased titers of anti-SIV IgG antibodies (23).

Importantly, CTRA gene expression may reciprocally affect loneliness. In lonely individuals, the immature proinflammatory monocytes can traffic into the brain, leading to anxiety and altered social behavior. Moreover, release of proinflammatory cytokines in the brain may promote “sickness behaviors,” which include affective, perceptual, and motivational processes that could augment loneliness and decrease the desire for social interaction, creating a vicious cycle (22, 23). As mentioned above, this positive feedback loop involves trafficking of monocytes to the brain (80, 143, 147).

#### Oxidative stress

Disturbed redox homeostasis in oxidative distress may represent a key molecular link from chronic psychosocial stress to CHD (116). Social isolation induces oxidative stress in the brain and in peripheral tissues. In the brain, oxidative stress was shown to be a crucial mechanism triggering HPA activation. In the periphery, oxidative stress may be the result of social isolation-induced changes in the HPA, SNS, and the immune system as detailed above. Indeed, a large-scale study involving 2858 subjects showed that markers of the HPA axis, SNS, and inflammation were associated with oxidative damage in a dose-response manner (9).

Social isolation rearing of rats (individual housing starting at the age of 21 days) led to an increase in oxidative stress in the hypothalamus and the prefrontal cortex (20, 109). Importantly, the elevation in oxidative stress markers in the

hypothalamus after 2 weeks was an early pathological event that preceded the increase of corticotropin-releasing factor levels in the hypothalamus and adrenocorticotropic hormone levels in the plasma at 4 weeks, and increased corticosterone levels in plasma and saliva after 7 weeks (20). Thus, the early increase of oxidative stress likely triggered the stress response and HPA-axis activation (20).

NADPH oxidase (NOX) enzymes comprise a family of membrane proteins that generate reactive oxygen species (ROS) (108). Among the NOX enzymes found in the brain (NOX1, NOX2, NOX3, and NOX4), NOX2 has a critical role in social isolation (20, 108). Social isolation in rats led to upregulation of NOX2 and its components (p22phox, p67phox, p47phox, and p40phox) in the brain (109). Treatment of rats with the antioxidant/NOX inhibitor apocynin (starting after 4 weeks of social isolation) stopped the progression of HPA-axis activation induced by social isolation (20). Rats that had a loss-of-function mutation in the NOX2 subunit p47phox were completely protected from changes in the neuroendocrine profile and behavior induced by social isolation (20). These results suggested that NOX2-derived oxidative stress in the hypothalamus was a causal factor in social isolation-induced HPA activation and in the development of anxiety-like symptoms.

The relationship between oxidative stress and the HPA axis in social isolation seems to be bidirectional. As mentioned above, NOX2-mediated oxidative stress in the hippocampus lies upstream of social isolation-induced changes in the HPA axis. On the contrary, glucocorticoids derived from the HPA axis also have an impact on NOX expression and activity (108). In hippocampal neurons, glucocorticoids have been shown to upregulate the expression (151) and activity (66) of NOX. There is also evidence that social isolation may induce oxidative stress in the prefrontal cortex and hippocampus by inhibiting antioxidant enzymes (39, 108). However, these results are inconsistent (Table 1).

Social isolation-induced oxidative stress also has been observed in the vasculature. For example, individually caged Watanabe heritable hyperlipidemic rabbits have a higher NOX activity in the aortic arch (86). As NOXs are the main producers of ROS in the vasculature (42, 71, 72), the increased vascular activity of NOX may promote atherosclerosis development by inducing oxidative stress. Mechanistically, social isolation-induced HPA activation, GR resistance, SNS activation, and inflammation, as described above, may all contribute to vascular oxidative stress. Although a short incubation for 24 h with glucocorticoids was reported to reduce p22phox expression in human smooth muscle cells, chronic

TABLE 1. REPORTED CHANGES IN ANTIOXIDANT ENZYMES IN THE HIPPOCAMPUS OF SOCIALLY ISOLATED RATS

<i>Animals</i>	<i>Age at isolation</i>	<i>Duration of isolation (weeks)</i>	<i>Antioxidant systems</i>	<i>Reference</i>
Male rats	3 weeks	8	SOD↓; catalase↓; GPx↓	(114)
Male rats	2–3 months	3	SOD1↔; SOD2↔	(38, 40)
Male rats	2.5 months	3	GSH↓; MDA↔; SOD↔	(152)
Male rats	3 months	3	SOD↑; catalase↑	(95)
Male rats	3 months	3	SOD↔; catalase↔; GPx expression↔;	(32)
			GPx activity↓; GLR expression↑; GLR activity↔	
Male rats	3 months	3	GCLM↑; GSTA3↔; GLR↔	(31)

GCLM, glutamate cysteine ligase modifier subunit; GLR, glutathione reductase; GPx, glutathione peroxidase; GSTA3, glutathione S-transferase A3; MDA, malondialdehyde; SOD, superoxide dismutase; ↓, reduction; ↑, increase; ↔, no significant changes.

dexamethasone treatment has been shown to upregulate NOX1 expression in rat smooth muscle cells (77, 118).

Exogenous administration of the sympathetic neurotransmitter norepinephrine in rats was shown to increase systemic ROS production by stimulating circulating leukocytes (110). Conversely, ROS stimulated central and peripheral SNS activity (16). Treatment of freshly isolated human PBMC with norepinephrine increased the gene expression of NOX components and intracellular superoxide production, effects that are preferentially mediated by  $\alpha_2$ -receptors (30). Moreover, norepinephrine treatment also enhances adhesion of CD14<sup>+</sup> monocytes to endothelial cells (30). These results are consistent with the observation in humans that loneliness results in an SNS-mediated increase of proinflammatory immature monocytes (23). Indeed, proinflammatory monocytes may have a crucial role in CVD pathogenesis by infiltrating into the vascular wall, causing local inflammation and oxidative stress, as shown in the mouse model of angiotensin II-induced hypertension (144).

Thus, it is possible that environmental stressor-stimulated pathways, triggered by social isolation, traffic noise, or air pollution (84, 85, 145), may converge into a common mechanism, that is, inducing vascular dysfunction and CVD by causing vascular oxidative stress and inflammation.

### Interventional and Therapeutic Strategies

Because of the detrimental effects of loneliness on physical and mental health and the growing prevalence, there is an urgent need for the development of interventional and therapeutic strategies. Currently, there is no pharmacological treatment for loneliness (14). There are, however, approaches that can mitigate loneliness or alleviate the damaging effects of loneliness on health.

#### *Interventions to reduce loneliness*

When Engel proposed the biopsychosocial model of disease 40 years ago, the dominant model of disease at that time was biomedical, leaving no room within its framework for the social, psychological, and behavioral dimensions of illness (36). Nowadays, the contribution of such factors to disease is well accepted in the scientific community. Moreover, corresponding intervention strategies have been developed in the past decades. As early as in 1983, Ornish *et al.* showed that a short-term intervention consisting of stress management training and dietary changes could improve cardiovascular status in CHD patients (93).

In particular, interventions aimed to mitigate loneliness include strategies to improve social skills, enhance social support, increase opportunities for social contact, and address maladaptive social cognition (15). A recent meta-analysis demonstrated that the use of cognitive behavioral therapy to address maladaptive social cognition was most effective for reducing loneliness (78). Other approaches such as meditation, qigong, tai chi, yoga, and promoting purpose and meaning in life may reduce the detrimental effects of loneliness on health (22, 26, 29, 41).

#### *Interventions to reduce the health effects of loneliness*

Besides interventions to reduce loneliness, it also is important to develop therapeutic strategies to prevent the

detrimental effects of loneliness on health, because current loneliness reduction interventions are not always successful and are not equally effective for every individual. The following potential strategies are proposed based on the pathogenic mechanisms summarized above.

**Allopregnanalone.** Given the important role of the HPA axis activation in chronic loneliness, modulation of the HPA axis may represent a rational strategy to treat loneliness-associated disorders. Animal studies have demonstrated that 3 $\alpha$ , 5 $\alpha$ -tetrahydroprogesterone (allopregnanalone [ALLO]) decreased stress-induced activation of the HPA axis and facilitated recovery from stressful events (14).

ALLO is a progesterone-derived, endogenous neuroactive steroid in the brain (14, 15). It is a potent modulator of the  $\gamma$ -aminobutyric acid (GABA<sub>A</sub>) receptor complex and has powerful antianxiety, anesthetic, and anticonvulsant properties (14). Whereas acute stress increases ALLO levels, repeated stress results in decreased serum levels of ALLO, which suggests that the chronic stress-induced hyperactivation of the HPA axis is partly attributable to a downregulation of ALLO synthesis (14). Indeed, ALLO specifically regulates the functions of the HPA axis (8).

Recent reports in animal models demonstrated that ALLO has an important role in social isolation. Individual housing of adult male mice reduced ALLO levels, which was attributable to downregulation of the rate-limiting enzyme 5 $\alpha$ -reductase type I in ALLO biosynthesis. Downregulation occurred specifically in selected neurons of the basolateral amygdala, hippocampus, and medial prefrontal cortex (2, 34, 98). Importantly, administration of exogenous ALLO can normalize social isolation-induced HPA dysfunction (8, 103) and behavioral effects (37, 88, 98, 99). Similar results have been obtained with ganaxolone, a synthetic analog of ALLO (100).

Interestingly, the social isolation-induced behavioral effects can also be normalized with some selective serotonin reuptake inhibitors at doses far below those required to block serotonin reuptake (37, 88, 90, 98, 99). These results indicate that such drugs may lead to improvement in behaviors not by inhibiting serotonin reuptake, but rather by elevating corticolimbic levels of ALLO.

Based on the animal studies, Cacioppo *et al.* hypothesized that ALLO has an important role in loneliness in humans (14, 15). The potential of ALLO, ALLO precursors, and ALLO analogs as novel treatments for loneliness needs to be tested in clinical studies (14).

**$\beta$ -Blockers.** Direct SNS innervation of the spleen and primary and secondary lymphoid organs links behavioral processes to regulation of the immune system (120). Epinephrine and norepinephrine stimulate receptors belonging to two major subclasses: the  $\alpha$ - and  $\beta$ -adrenergic receptors (48). Most immune cells have  $\alpha_1$  and  $\beta_2$  receptors, which typically exert opposite effects (Table 2). Under homeostatic conditions, the signals mediated by  $\beta_2$  receptors usually predominate (5). Activation of  $\beta$ -adrenergic receptors by catecholamines increases the production of proinflammatory cytokines in several cell types (48).  $\beta_2$  receptor activation in mouse macrophages has been shown to upregulate IL-1 $\beta$  and IL-6 expression, which promotes a proinflammatory immune response (131).



TABLE 2. EXPRESSION AND FUNCTION OF ADRENERGIC RECEPTORS IN IMMUNE CELLS

Cell type	$\beta_2$	$\alpha_1$	Reference
Neutrophils	↓ neutrophil interaction with endothelial cells; ↓ phagocytosis; ↓ lysosomal enzyme release; ↓ respiratory burst	↑ neutrophils release into the circulation	(5, 106)
Monocytes/ macrophages	Both pro- and anti-inflammatory effects reported	Proinflammatory effects (monocytes acquire $\alpha_1$ receptor after homing)	(5, 106)
NK cells	NK cell in blood (↑ acutely, ↓ chronically); both increased and decreased NK activities have been reported	↑ NK cytotoxicity	(5, 106)
DC	↓ Ag protein cross-presentation; ↓ IL-12; shift from Th1 to Th2-type immune response	Stimulation of DC migration	(5, 106)
Th0 cells	↑ IFN- $\gamma$ and Th1-cell differentiation (in the presence of TNF- $\alpha$ and IL-12); ↑ Th2-cell differentiation (in the presence of IL-4 and IL-10)	—	(5)
Th1 cells	↓ IFN- $\gamma$ (negative feedback)	—	(5)
Th2 cells	— (epigenetic loss of $\beta_2$ receptors)	—	(5, 17)
B cells	Dependent on activation state of B cell (↑ IgG1/IgE production during Ag processing; ↑ IgG2 after Ag processing; ↓ Ab production by plasma cells)	—	(5)

DC, dendritic cells; NK, natural killer.

The SNS upregulates production of immature, proinflammatory monocytes in the bone marrow, which is mediated via  $\beta$ -adrenergic receptors (48, 101). Moreover,  $\beta$ -adrenergic receptor-mediated mechanism is involved in social stress-induced glucocorticoid resistance (48, 101) and monocyte trafficking from the spleen (48, 80, 147).

When fed a cholesterol-containing diet and housed in periodically reorganized social groupings (*i.e.*, social disruption), highly aggressive and competitive (dominant) male cynomolgus monkeys developed exacerbated coronary artery atherosclerosis (62). Pharmacological treatment with the  $\beta$ -blocker propranolol prevented the exacerbation of atherosclerosis caused by the unstable social environment (62). Importantly, the antiatherogenic effects of propranolol on dominant male monkeys were independent of resting heart rate, blood pressure, and serum lipid concentrations (62).

Given the complex effects of  $\beta_2$  receptors in different immune cells and in other cell types, the therapeutic potential of  $\beta$  blockers for loneliness-associated diseases cannot be predicted at this stage, which warrants additional studies, especially in animal models of social isolation.

**Oxytocin.** Oxytocin is a neuropeptide produced in the hypothalamus, which promotes a strong desire for social affiliation (15). Besides the traditionally known role in uterine contraction, oxytocin is suggested to be a stress-responsive hormone that exerts a regulatory influence on the HPA axis (96). Moreover, the oxytocin receptor is expressed on major vascular cells, including endothelial cells, vascular smooth muscle cells and also macrophages (61, 129). *In vitro* experiments showed that oxytocin reduced NADPH-oxidase activity and inflammatory cytokine secretion by macrophages and endothelial cells (129). Chronic oxytocin administration attenuated atherosclerosis in Watanabe heritable hyperlipidemic rabbits (129, 130) and in socially isolated apolipoprotein E-knockout mice (87).

In humans, oxytocin administration promoted prosocial behaviors such as affiliation and trust, and influenced auto-

nomic cardiac control (15, 91). However, findings have been inconsistent and negative effects have been reported (15). Thus, additional research is required to examine the therapeutic potential of oxytocin in the treatment of chronic loneliness (15).

**NOX inhibitors.** As discussed above, oxidative stress is involved in different steps of social isolation-induced pathology. Oxidative stress triggers HPA activation (20), potentiates SNS activity (16), and promotes vascular damage. The role of antioxidant enzymes in this scenario is uncertain (Table 1). In contrast, NOX seems to play a key role. Therefore, NOX inhibitors may be of therapeutic interest.

Moreover, NOX inhibition may be a potential strategy to improve resilience. In this context, resilience explains how and why some individuals live in a state of chronic loneliness and yet do not develop mental illness (108). A loss-of-function polymorphism in the p47phox subunit of NOX completely prevented behavioral and neuroendocrine changes typically associated with social isolation in rats (20). Thus, NOX may be a crucial candidate target molecule for developing approaches to improve positive adaptation, and to maintain or regain mental health despite experiencing chronic loneliness or social isolation.

### Summary and Future Directions

Robust evidence supports the concept that loneliness and social isolation increase morbidity and mortality, and should be included as a risk factor for CVD. Chronic social stress is associated with activation of the SNS and the HPA axis resulting in selective expansion of proinflammatory monocytes, enhanced expression of cytokines, and glucocorticoid resistance. These mechanisms likely contribute to the increased risk of lonely individuals developing CVD. Their involvement, however, has not been proven so far and needs to be verified in future studies.

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**Abbreviations Used**

ALLO = allopregnanolone  
CHD = coronary heart disease  
CTRA = conserved transcriptional response to adversity  
CVD = cardiovascular disease  
eNOS = endothelial nitric oxide synthase  
GABA =  $\gamma$ -aminobutyric acid  
GR = glucocorticoid receptor  
HF-HRV = high-frequency heart rate variability  
HPA = hypothalamic–pituitary–adrenal  
HRV = heart rate variability

NO = nitric oxide  
NOX = NADPH oxidase  
PBMC = peripheral blood mononuclear cell  
PSI = perceived social isolation  
ROS = reactive oxygen species  
RSD = repeated social defeat  
SBP = systolic blood pressure  
SDR = social disruption stress  
SIV = simian immunodeficiency virus  
SNS = sympathetic nervous system  
TPR = total peripheral resistance