Loneliness and Social Isolation: Determinants of Cardiovascular Outcomes

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Abstract: One in three Americans report experiencing loneliness in everyday life, a number that has grown exponentially over the last few decades. As we respond to the SARS-COV2 pandemic with quarantine and social distancing, social isolation and feelings of loneliness are increasing among people of all ages. This presents as an opportune time to recognize the public health impact of these important psychosocial determinants. Loneliness and social isolation are associated with a higher incidence of CVD, higher healthcare utilization and worse outcomes even after controlling for conventional risk factors of CVD. In this review, we discuss loneliness and social isolation as determinants of cardiovascular outcomes, the pathophysiology of this association, and its implications in clinical practice. We discuss some of the shortcomings in the assessment of loneliness and social isolation while identifying the most commonly used rating scales for the same. Finally, we suggest modifications to interventions for loneliness and social isolation during the COVID-19 pandemic.

Keywords: Loneliness, social isolation, cardiovascular outcomes, psychosocial risk factors, COVID-19, pathophysiology.

1. INTRODUCTION

Cardiovascular diseases (CVD) continue to be the leading cause of death in the United States, and mitigation of risk factors has been the mainstay in improving CVD outcomes. CVD cost about $351 billion in terms of healthcare expenditure annually and claim more than 650,000 lives [1]. Conventional risk factors such as dyslipidemia, high blood pressure, smoking, high fasting blood glucose, and high body mass index are the major contributors to the global CVD burden [2]. Intensive blood pressure control, tight control of low-density lipoprotein (LDL) level, and advocating smoking cessation are now considered the standard of care in the treatment as well as prevention of CVD [3, 4]. While the emphasis on the management of these conventional risk factors has led to a decline in the number of deaths from CVD by 12.5% over the last decade, this decline has plateaued, implying a limitation in predicting CVD outcomes based purely on the conventional risk factors [2, 5, 6]. Further, these risk factors do not explain the CVD risk in all patients. Thus, the search for other modifiable risk factors continues.

2. PSYCHOSOCIAL STRESS AND CVD

The next frontier for CVD risk factor reduction is focused on psychological depression. Depression and anxiety play a critical role in the incidence and outcomes of CVD beyond that explained by conventional risk factors. One of the early studies found that the risk of incident coronary heart disease (CHD) was over 70% higher in depressed individuals relative to non-depressed individuals [7]. A number of meta-analyses reported that clinical depression or depressive symptoms increased the risk of CHD from 30% [8] to 60% [9-13]. The risk continued to be significant even after adjustment for other conventional risk factors, particularly cigarette smoking and physical inactivity [12], establishing depression as an independent risk factor for incident CHD as well as increased cardiovascular mortality [14, 15]. Furthermore, the increase in the risk of developing CVD is correlated with both the severity and recurrence of depression [16].

Similarly, anxiety disorders have been linked with higher incidence and poor outcomes of CVD, independent of conventional risk factors [17, 18]. Association between CVD and other psychosocial disorders, such as specific phobia, panic disorder, post-traumatic stress disorder and alcohol use disorder, unveil the breadth of psychopathology’s impact on CVD outcomes, prompting clinicians to explore other psychosocial risk factors [19]. Loneliness and social isolation are important determinants that have recently received growing attention as modifiable predictors of CVD risk.

3. LONELINESS AND SOCIAL ISOLATION: IMPACT ON HEALTH OUTCOMES

Loneliness and social isolation have reached epidemic proportions and are increasingly linked with poor health out-
comes. Loneliness is a subjective feeling of unhappiness or dissatisfaction which stems from being alone. Social isolation is a complete or partial lack of contact between an individual and the society. While the two terms differ in definition, they are often used interchangeably in the literature. A significant association has been noticed between loneliness, social isolation and all-cause mortality [20-23]. A 2015 meta-analysis of 70 relevant studies found that social isolation, loneliness, and living alone corresponded to an average increase in mortality by 29%, 26%, and 32%, respectively [24]. When compared to conventional risk factors for mortality, this increased risk was greater than that from light smoking (less than 15 cigarettes per day), obesity, and physical inactivity [23]. On the other hand, strong social relationships can increase the likelihood of survival by as much as 50% [23]. In this review, we discuss the prevalence of social isolation and loneliness in the US and its impact specifically on the pathogenesis of CVD and its outcome.

4. LONELINESS AND SOCIAL ISOLATION: PREVALENCE BEFORE AND DURING COVID-19

The prevalence of loneliness amongst adults in the US is thought to have doubled over the last decade, and about a third of the population reports feeling lonely according to recent estimates [25, 26]. The prevalence is as high as 49% in some groups [27]. While conventionally thought an affliction of old-age, the prevalence is seen to be growing amongst the younger age groups. In a multi-state study in 2017, 33% of respondents aged <25 years reported loneliness compared to 11% of those aged >65 years [28].

The prevalence of loneliness and social isolation has more recently been impacted by the onslaught of the COVID-19 pandemic and the extensive changes in lifestyle brought about by social distancing and self-isolation measures. Observations from the SARS outbreak of 2003 predict an ominous trend of adverse mental health outcomes [29]. In a survey, all participants who were placed in quarantine in 2003 reported a sense of isolation, particularly due to lack of physical contact with family members, and long-term consequences included reduced direct contact with other people and avoidance of public places [30, 31]. In the current pandemic, with >90% of the population following "sheltering-in-place" orders, the rates of loneliness are as high as 43.8%, which is significantly higher than the previously reported prevalence of 38% [32]. Some populations are particularly hard hit by COVID-related loneliness and social isolation, such as college students and those residing in nursing homes [33]. In a survey of Chinese college students (N=992), COVID-related isolation worsened a myriad of psychological symptoms, including depression, fear, hypochondria, and obsessive-compulsive disorder [34]. Most nursing homes have essentially been on lockdown due to the increased risk of contagion during the current pandemic. There have been reports of many residents stopping to eat and giving up without family visits, making it imperative to focus on the consequences of this burning issue at hand.

5. LONELINESS AND SOCIAL ISOLATION: RELATIONSHIP WITH CVD

Loneliness is known to play an independent and critical role in the incidence, healthcare utilization, and outcomes of CVD.

5.1. Incidence

A meta-analysis investigating the incidence of CHD and stroke in high-income countries concluded that poor social relationships increased the risk of incident CHD by 29% and that of stroke by 32% [35]. Table 1 summarizes some representative studies investigating the incidence of CHD, MI, and death due to CHD in an otherwise healthy population [36-44].

5.2. Health-Care Utilization

Loneliness and social isolation also lead to greater health-care utilization amongst patients with cardiovascular disease. In a study of 1,681 respondents with heart failure, the group that experienced a higher degree of social isolation was reported to have 26% more out-patient and 57% more emergency room visits when compared to those with low levels of social isolation. The rate of hospitalization was 68% more in subjects with a high degree of social isolation than in those with a low degree of social isolation [45].

5.3. Outcomes

In addition to increased incidence and higher healthcare utilization, patients lacking social support have worse outcomes after cardiovascular events [46]. Berkman et al. observed that lack of emotional support after MI increased the odds of 6-month mortality by 2.9 times after controlling for severity of MI, comorbidities, risk factors such as smoking and hypertension, and sociodemographic factors [47]. In a study of 1,290 patients undergoing coronary artery bypass grafting, the ratings on the statement “I feel lonely” predicted survival at 30 days and 5 years after surgery, even after controlling for preoperative factors known to increase mortality [48].

6. GAPs IN LITERATURE

There are some limitations when considering loneliness and social isolation as risk factors for CVD. Most of the studies in the field are descriptive and observational analysis. While a significant association is seen between CVD and an umbrella of terms related to social support and social isolation, lack of a single validated measure is a major problem precluding a systematic analysis. Some studies have employed previously tested tools like the Berkman-Syme Social Network Index, which measures social integration, and Duke Social Support Index, which measures social interaction and subjective support [49, 50]. Similarly, several outcome measures are used for social isolation; the UCLA-Loneliness score has been used in multiple national and international reports [51]. However, most studies related
to CVD outcomes have implemented independent questionnaires. The variability in determinants studied poses a problem in comparison and reproducibility of results, weakening the strength of association.

There has also been some concern of bias due to confounding of conventional risk factors, as the studies exploring the association of loneliness and social isolation with incident CHD have largely included unadjusted analysis. In a large cohort study from the UK, the risk of MI and stroke associated with social isolation was attenuated by 84% and 83%, respectively, when adjusted for other risk factors [46]. However, in more recent cohort studies, the association of loneliness with the difference in health determinants has been inconsistent [52, 53]. The effect of loneliness and social isolation on health behaviours and consequently worse health outcomes needs to be further explored with adequately powered studies before these can be ascertained to be independent CVD risk factors.

7. MECHANISMS LINKING LONELINESS AND SOCIAL ISOLATION WITH CVD

Several mechanisms have been proposed linking loneliness and social isolation to poor cardiovascular outcomes. Increased stress reactivity, autonomic dysregulation, and exaggerated inflammatory response have been implicated as important pathways [22, 52-54]. A pathophysiological model connecting loneliness and social isolation to atherogenesis and the development of CVD is summarized in (Fig. 1).

Lonely individuals are observed to have higher total peripheral resistance and these changes can be seen beginning early in life [52, 53]. A study by Cacioppo et al. comprising 89 undergraduate students with a mean age of 19.26 years, found that lonely young adults have higher total peripheral resistance in response to psychological stressors as compared to their non-lonely counterparts [53]. In the same study, non-lonely participants had a greater cardiac output than lonely participants. In the second part of the study, similar responses were observed in older adults (mean age 65 years) in addition to the observation that age-related increase in resting systolic blood pressure was higher in lonely adults as compared to non-lonely adults. A similar pattern was also seen in heart rate variability which is measured by the variation in beat-to-beat interval and is mediated by the autonomic nervous system. Low heart rate variability is associated with increased risk of CHD and cardiovascular mortality [55]. Lonely individuals tend to have lower heart rate variability in response to stress. Gouin et al. investigated the effect of social integration on heart rate in 60 students who were recruited to the study within 22 days of moving to a new country and found that lower levels of social integration at 5 months after recruitment were associated with higher resting heart rate and lower heart rate variability [56].

The role of hypothalamic-pituitary axis is somewhat more controversial. Persistent activation of the hypothalamic-pituitary axis was noted to be associated with loneliness in animal studies, leading to higher basal levels of corticosteroids and decreased glucocorticoid receptor sensitivity [22]. However, studies in humans do not show a significantly high cortisol level amongst lonely responders [53, 54]. Glucocorticoid resistance leading to chronic stress can mediate inflammation, which is an important part of the pathogen

Table 1. Studies investigating the incidence of coronary heart disease (CHD) and myocardial infarction (MI) or death due to CHD in populations without a known history of CHD.

| Study (First Author, Year) | Study Focus | Sample Size (n) | Mean Age or Age Range (Years) | Gender | Determinant Measured (Measure used) | Prevalence of Determinant |
|---------------------------|-------------|----------------|-------------------------------|--------|-----------------------------------|--------------------------|
| Hedblad, 1992             | Incidence   | 394            | 68                            | M      | Lack of emotional support         | -                        |
| Kawachi, 1996             | Outcome     | 32,624         | 42-77                         | M      | Social isolation (Berkman-Syme SNI) | 5.8% (SNI I)             |
| Eng, 2002                 | Outcome     | 28,369         | 55                            | M      | Social isolation (Berkman-Syme SNI) | 30% (SNI I & II)         |
| Strodl, 2003              | Incidence   | 10,432         | 70-75                          | F      | Low-fair social support (Duke Social Support Index) | 15%                     |
| Rosengren, 2004           | Incidence   | 741            | 50                            | M      | Low social integration and low emotional attachment | Low social integration 21.6% | Low emotional attachment 23% |
| Barefoot, 2005            | Incidence   | 9,573          | 57.5                          | M & F  | Social isolation (number and frequency of close contacts) | -                       |
| Lena André-Petersson, 2006| Incidence   | 414            | 68                            | M      | Unsatisfactory social support     | 34.1%                   |
| Thurston, 2009            | Incidence   | 2616           | 44                            | M & F  | Loneliness                        | -                       |
| Gafarov, 2013             | Incidence   | 870            | 25-64                         | F      | Social isolation (Berkman-Syme ICC & SNI) | 57.1 (Low ICC) 77.1% (SNI I & II) |

Abbreviations: a: Age-range is provided if the mean population age was not measured.; b: Most studies either included males (M) or females (F). For studies that included both genders, the percentage of females has been noted; c: Determinant measured is the psychosocial factor studied. The measurement instrument used is mentioned for studies using a validated tool: Berkman-Syme Social Network Index (SNI) and Duke Social Support Index; d: Percentage of population that reported the presence of determinant; e: Relative risk (RR) along with the 95% confidence interval (CI).
Fig. (1). Hypothesized model of loneliness and social isolation affecting cardiovascular outcomes. Loneliness and social isolation can impact health-related behaviors. It also leads to an exaggerated autonomic response to stress and sympathetic nervous system hyperactivity. These conditions are associated with increased total peripheral resistance (TPR) and reduced heart rate variability (HRV), contributing to hypertension, ischemic heart disease and poor cardiac output. In animal models, social isolation has been associated with higher resting glucocorticoid levels from overactivation of the hypothalamic-pituitary-axis (HPA), leading to chronic inflammation and glucocorticoid resistance (receptor desensitization). It also increases the vasoconstrictive effects of catecholamines and decreases nitric oxide (NO) synthesis at the level of endothelial cells. There is evidence linking renin-angiotensin-aldosterone-system (RAAS) to social isolation, which in turn contributes to increased TPR, platelet activation and endothelial dysfunction. Loneliness has also been associated with increased circulating natural killer (NK) cells, fibrinogen and other inflammatory mediators, e.g., interleukin-6 (IL-6), IL-1β and tumor necrosis factor-alpha (TNF-alpha). This may be due to increased glucocorticoid levels or direct action on myelopoiesis. This state of chronic inflammation, along with endothelial dysfunction and platelet activation, leads to accelerated atherosclerosis. (A higher resolution / colour version of this figure is available in the electronic copy of the article).

Social isolation and stress have been shown to accelerate atherogenesis in cynomolgus monkeys independent of serum lipids or preponderance to atherosclerosis [62]. In Prairie Vole, social isolation may impair the normal release of protective anti-atherosclerotic factors like NO from the vascular endothelium [63]. In a study of 4,643 men and women stratified according to familial risk for CHD, a combination of low social support and high hostility significantly increased the odds of carotid artery lesions among high-risk women even after controlling for other risk factors. High-risk women showed significantly reduced odds of carotid artery lesions with high social support [64].

8. SCREENING FOR LONELINESS AND SOCIAL ISOLATION

As previously mentioned, multiple questionnaires have been used in literature to study the effects of loneliness. This poses a significant challenge to screening for loneliness in clinical practice. In an overview of 40 reviews of the public health impact of loneliness and social isolation, the authors came across 62 different self-reported questionnaires [65]. The R-UCLA-Loneliness Scale has been validated and deemed reliable [51]. The full version of the scale uses a 20-item questionnaire. An abbreviated 11-question scale has al-
so demonstrated factorability and internal reliability on a
two-factor model of “feeling isolated” and “available social
connections” [66]. The UCLA 3-item scale is validated for
telephone use, easy to administer, and it can be self-adminis-
tered. It is a fast and easy questionnaire that can be helpful if
incorporated into clinical practice and has gained a lot of
popularity and is the most commonly used loneliness scale
in the last decade [67]. However, the specific use of screening
for loneliness with regards to CVD incidence and out-
comes has not been studied. In present practice, screening
for loneliness and social isolation continues to be reliant on
a high index of suspicion amongst clinicians and self-report-
ing of patients.

9. POTENTIAL THERAPY OF LONELINESS AND SOC-
ICIAL ISOLATION WITH CVD

Multiple interventions have been studied at the individu-
aland the community level to mitigate loneliness. Some
models at the individual level include providing increased
opportunities for social contact, enhanced social support,
and behavioral interventions focused on social skills and ad-
dressing maladaptive social cognition. The latter has proven
to be most effective in studies so far [68]. Home visitation
and daily contact programs may be useful to address low so-
cial support amongst the elderly and people with disabilities
[69]. Telephonic helplines have proven to be a useful tool
that offers an opportunity to those suffering from loneliness
to reach out to those willing to help. England’s Silver Line
is one such example; lonely seniors can call to speak to an
operator about any topic of their choice [70]. This center re-
ceives about 10,000 calls a week.

Some countries have attempted to intervene on a commu-
nity level. The United Kingdom launched a “Campaign to
end loneliness” in 2011, which included designating a Min-
istry of Loneliness and a £22 million program to reach out to
9 million citizens who admitted to being lonely. The mea-
sures under this campaign focus on reaching lonely individu-
als and supporting those in need through volunteer activities,
neighborhood approaches, as well as policy changes across
public departments like housing and transport [70].

At present, there are no approved pharmacological
agents to reverse the pathological effects of loneliness. How-
ever, as more is learnt about the neurobiology of loneliness,
pharmacological targets like selective serotonin reuptake in-
hibitors (SSRIs), allopregnanolone, and oxytocin emerge as
important molecules to modify the downstream effects of
loneliness [71, 72]. Most of the present studies in this arena
are based on animal models which could offer promising tar-
gets in the management of adverse CVD outcomes of loneli-
ness and social isolation in the future.

10. SUGGESTED MODIFICATIONS FOR LONELI-
NESS AND SOCIAL ISOLATION INTERVENTIONS
DURING COVID-19

Although face-to-face visits are the gold standard in com-
bating loneliness and social isolation, several governmental
agencies and researchers have implemented modifications to
such contact to avoid the spread of COVID-19. The Centers
for Medicare & Medicaid Services (CMS) have recommend-
ed outdoor family visits for nursing home residents while en-
suring safe physical distancing and wearing a mask [73]. An
emergency waiver suspending the requirement for comply-
ing with the Health Insurance Portability and Accountability
Act (HIPAA) has increased the use of popular applications
for video chats, such as Apple FaceTime and Facebook Mes-
senger video chat for health care purposes [74]. Our team
has found improvement in behavioral problems of nursing
home residents with the use of Facetime with family mem-
bers [75]. Others have used drive-through contacts with fami-
ly members, parades, and therapeutic animal drop-ins
through the interventions to curb loneliness and social iso-
lation [33]. When family members are unavailable, research-
ers found telephone contact with medical students to be
meaningful both for the students and geriatric patients [76].
Judicious use of antidepressants and anxiolytics is also need-
ed for those that have new-onset or worsening of existing de-
pression and anxiety.

CONCLUSION

Loneliness is a public health problem that is associated
with an increased incidence of CVD incidence and poor out-
comes. However, most of the studies in this field are obser-
vational. Loneliness, by the nature of its subjectivity and in-
ter-person variability, is hard to identify and quantify, and
we have identified some well-validated rating scales used in
various studies. The impact of the current SARS-COV-2 pan-
demic, due to direct consequences of social distancing mea-
sures as well as its long-term implications from growing ill-
ness-anxiety and avoidance behavior, would be important
for the epidemiological investigation of loneliness and social
isolation. It is an opportunity to explore loneliness as an inde-
pendent risk factor for CVD. While governmental agencies
and researchers are modifying their approaches to combat
loneliness in vulnerable populations, adequately powered
studies are needed to factor for confounders like the differ-
eence in health-behavior and prevalence of conventional
CVD risk factors. Clinically validated screening tools, along
with greater awareness and social acceptability, are needed
to better identify those at risk and mitigate cardiovascular
risk. Future directions would then include studying the im-
 pact of treating loneliness in the prevention and outcomes of
CVD.

LIST OF ABBREVIATIONS

| Abbreviation | Description               |
|--------------|---------------------------|
| BMI          | Body Mass Index           |
| CHD          | Coronary Heart Disease    |
| CVD          | Cardiovascular Disease    |
| MI           | Myocardial Infarction     |
| NO           | Nitric Oxide              |

AUTHORS’ CONTRIBUTIONS

Dr. Sharma collected the data and wrote a preliminary
draft of the paper. Dr Mehta conceived the idea of the paper.
CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Implications in COVID-19 Era

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