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Research paper

Loneliness and Cardiovascular Disease

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Abstract

Loneliness is a silent social epidemic that affects more than one third of the US population. Cardiovascular diseases impart a huge morbidity, mortality, and financial burden on our society. The detrimental role of loneliness in cardiovascular diseases is being increasingly recognized. Besides having a direct molecular effect on cardiovascular diseases, loneliness also encourages poor compliance with healthy lifestyles, that play a significant role in preventing and improving cardiovascular diseases. This brief review highlights the ominous effects of loneliness on cardiovascular diseases.

Keywords: *Atherosclerosis; Cardiovascular Diseases; Coronary Artery Disease; Loneliness; Social Isolation.*

1. Introduction

Loneliness and social isolation are closely related, with loneliness being the subjective manifestation of social isolation (Cacioppo & Hawkley 2005, Heinrich & Gullone 2006). Loneliness is a worldwide phenomenon (Rico-Uribe et al. 2016), and its prevalence is on the rise(Madsen et al. 2019). It affects all population groups, from kindergarten students to senior citizens (Asher 1984, Cassidy & Asher 1992, De Jong Gierveld & van Tilburg 1999, Victor et al. 2005). A recent study in the United States of America (US) by Cigna, of adults aged 18 and older found that 46 percent reported "sometimes or always feeling alone" (Cigna 2018).
Loneliness imparts significant harm to our physical and mental systems (Richard et al. 2017). It is detrimentally associated with several disorders, including obesity (Lauder et al. 2006), cancer (Drageset et al. 2013), and cognitive decline (Wilson et al. 2007). It is associated with premature mortality (Rico-Uribe et al. 2014). Psychiatric dysfunctions affected include depression (Cacioppo et al. 2010), alcoholism (Akerlind & Hörnquist 1992), suicidal ideation (Akerlind et al. 2007), aggressive behaviors, and impulsivity (Cacioppo et al. 2014). Loneliness is also increasingly being pathologically implicated in all phases of cardiovascular diseases (CVD) (Valtorta et al. 2018).

2. Discussion

Cardiovascular diseases (CVDs) are common in the US, with the American Heart Association estimating that they affect about half the US population (Benjamin et al. 2019). With more than 650,000 Americans dying from CVDs each year, they are also the leading cause of death in the US (Roth et al. 2018). CVDs include hypertension (HTN), coronary artery disease (CAD) and coronary heart disease (CHD), cerebrovascular disease, heart failure (HF), rheumatic heart disease, congenital heart disease, cardiomyopathies, and peripheral vascular disease (WHO. int). HTN is a major public health problem in the United States. The recent decrease in its threshold to <130/89 mm/Hg has raised its prevalence to 45.4% of the US population (105 million adults) from 32.0% (74.1 million), based on 2014 guidelines (Bundy et al. 2018). It is associated with 25% of all CVD deaths and these represent more deaths than those from any other modifiable cause (Cheng et al. 2014, Danaei et al. 2009). CHD is present in 15.5 million Americans (Mozaffarian et al. 2016) and was associated with 366,000 deaths in 2017 (Healthline.com). Atherosclerosis is usually the underlying cause in these HTN related deaths (Hansson 2005). Stroke is also a major cardiovascular disease in the US (Go et al. 2014). Projections show that by 2030, an additional 3.4 million US adults aged ≥18 years (representing 3.88% of the adult population), will have had a stroke – representing a 20.5% increase in prevalence from 2012 (Ovbiagele et al. 2013). Stroke is the leading cause of serious long-term adult disability in the US (Roger et al. 2012). Based on data from NHANES 2013 to 2016, an estimated 6.2 million Americans ≥20 years of age suffer from HF (CDC 2019). Projections show that the prevalence of HF will increase 46% from 2012 to 2030, resulting in >8 million people ≥18 years of age being diagnosed with HF (Heidenreich et al. 2013). Elevated blood lipid concentrations, or dyslipidemia, currently affect 13% of the US population and are strong predictors of cardiovascular disease (Carroll et al. 2017). Diabetes Mellitus (DM) is a major disorder in the USA (Boyle et al. 2010). CVD affects 32.2% of all persons with type 2 DM and is the leading cause of death in this population (Einarson et al. 2018). Chronic kidney disease (CKD) is growing rapidly in the US (CDC 2020). CVD is common in patients with CKD and may affect 33% of the renal patients (Srivastava et al. 2017). It is the most common cause of death in these patients before the disease reaches an end-stage renal disease status (Schrier 2007). Metabolic syndrome has a prevalence of 33% in the USA with more women than men having this condition (Aguilar et al.

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2015). This clustering of risk factors is associated with an increased risk for CVD morbidity and mortality (Gami et al. 2007). Mottillo and his group determined that the increased risks faced by these individuals include a 2-fold increase in major cardiovascular outcomes and a 1.5-fold increase in all-cause mortality (Mottillo et al. 2010). Obesity affects 42.4 percent of Americans 20 years old or older, and the prevalence has been steadily rising (Craig et al. 2020). Both overweight and obese individuals are at an increased risk for CVD compared with those with normal body weight (Asad et al. 2018). Psychosomatic stress, often a part of loneliness, also has significant negative repercussions on CVD morbidity and mortality (Nabi et al. 2013). Depression is common and affects nearly 16 million people in the US (Liu et al. 2015). It is strongly linked with CVDs such as angina, myocardial infarction, heart failure, and CHD related mortality (Poole et al. 2019). A meta-analysis estimated that depression was associated with a 30% excess risk for coronary heart disease and its presence resulted in a poorer prognosis (Gan et al. 2014, Blumenthal et al. 2014). Co-morbid CHD and depression result in a 2-fold increase in cardiac and all-cause mortality (Dickens et al. 2006). Sleep disturbances have also been linked to an increased CVD risk (King et al. 2008).

2.1 Impact of loneliness on CVD and its major risk factors

In a study of 5397 adults, Valtorta and his group found that loneliness had a 27% increased risk of cardiovascular disease over a mean follow-up of 5.4 years (Valtorta et al. 2018). Men living alone appear to have a worse prognosis from CVD than women (Gandhi et al. 2019). Chronic loneliness also increases CVD mortality (Holt-Lunstad et al, 2015), independent of other risk factors (Holt-Lunstad et al. 2010), such as HTN, smoking, and obesity (Xia & Li 2017).

Loneliness is a risk factor for HTN, and this association strengthens with increasing age (Hawkley et al. 2006). Lonely people also face higher blood pressure if they are diabetic (Kobos et al. 2020). Loneliness decreases pulse pressure reactivity and increases vascular resistance and lowers the cardiac output (Hawkley & Cacioppo 2003, Hawkley et al. 2003, O'Donovan et al. 2007). Hawkley and his group estimated that systolic blood pressure in lonely individuals would increase by 3.6 mmHg per year when compared with the least lonely individuals (Hawkley et al. 2010). Diastolic blood pressure elevations are also influenced by acute mental stress in women (Steptoe et al. 2004). Loneliness and social isolation exacerbate atherogenesis in animal studies (Bernberg et al. 2008). In humans, they also impact atherogenesis and are independent risk factors for CVD (Holt-Lunstad & Smith 2016). Increased coronary artery calcification, a marker of atherosclerosis, has been noted in socially isolated individuals (Kop et al. 2005). In a meta-analysis done in 2016, Valtorta and his group found that in 11 longitudinal studies on cardiovascular diseases, social isolation was associated with 29% excess risk of incident CHD (Valtorta et al. 2016). Subsequent studies have confirmed that loneliness is associated with an increased risk for CHD (Hakulinen et al. 2018). Lack of social support in patients after a myocardial infarction is also a marker of poor prognosis, with increased readmission, and re-infarction rates, and higher mortality (Glozier et al. 2013). Hakulinen and group found that social isolation was associated with a 1.5-fold increased risk of mortality after an acute myocardial infarction (Hakulinen et al. 2018). In patients following coronary artery bypass grafting, verbalizing the term “I feel lonely”, increased mortality, both at 30 days and at 5 years after the surgery (Herlitz et al. 1998). In a meta-analysis done by Valtorta and his group, there was a 32% increase in the relative risk of stroke in individuals with poor social relationships or loneliness across nine independent studies, involving 2577 events (Valtorta et al. 2016). Lonely individuals experience poor recovery and greater functional decline following a stroke (Boden-Albala et al. 2005). They also have a higher risk of recurrent stroke and greater disability (Boden-Albala et al. 2005). On the other hand, stroke patients with high levels of social support or large social networks have a more rapid and extensive functional recovery after the event (Boden-Albala et al. 2005). Stroke patients suffer from several impairments (Hilari et al. 2010, Theeke et al. 2014) and it is not surprising that they face increased depression (Jongenelis et al. 2004) and loneliness (Ebrahim et al. 1987). This leads to a further decrease in theit quality of life (Theeke et al. 2012). Women who are widowed or unmarried and living alone are 3.5 times more likely to be institutionalized following a stroke (Petrea et al. 2009). Lonely stroke individuals also suffer from increased mortality (Tilvis et al. 2011). Loneliness is common in heart failure patients (Löfvenmark et al. 2009). They experience more dyspnea, and greater dyspnea with lower social support (Seo et al. 2014). They also have more depression (Brouwers et al. 2014). They are more likely to visit the emergency room and have an increased risk of hospitalization (NASEM, 2020). Lonely heart failure patients end up spending more days in the hospital and are more likely to get readmitted (Löfvenmark et al. 2009). They tend to be less compliant with health care recommendations, especially those given for regular exercise, daily weighing, and restricted sodium intake (Jankowska-Polańska et al. 2020). Women with loneliness and heart failure experience a poorer quality of life (Burström et al. 2012). Lonely heart failure patients also over-utilize healthcare resources (Löfvenmark et al. 2009). Loneliness is associated with a nearly 4 times increased risk of death in these patients (NASEM, 2020). Loneliness-induced psychosomatic stress also increases the risk of sudden cardiac death (Kuller et al. 1987, Palacios-Ceña et al. 2018).

Loneliness deleteriously impacts CVds by unfavorably affecting some major risk factors, primarily due to a poor compliance with healthy lifestyles by these individuals (Richard et al. 2017, Hackett et al. 2020). Major risk factors affected by poor lifestyles include dyslipidemia (Vargas et al. 2016, Richard et al. 2017, Floyd et al. 2017), diabetes mellitus (Lukaschek et al. 2017, Hackett et al. 2020), chronic kidney disease (Moorthi & Latham-Mintus 2019), metabolic syndrome (Henriksen et al. 2019, Kim et al. 2020), obesity (Rotenberg et al. 2017), psychosomatic stress (An et al. 2016), depression (Stickley et al. 2016, Matthews et al. 2016), and inadequate restorative sleep (Cacioppo et al. 2002).

Social isolation in rat pups subjected to periodic maternal separation has been associated with dyslipidemia (Vargas et al. 2016). Loneliness has also been linked with high cholesterol levels in humans (Richard et al. 2017). Individuals with higher social inclusion have lower low-density lipoprotein cholesterol levels (Floyd et al. 2018). Proper diet, physical activity, and desirable body weight greatly influence the lipid levels, and lonely individuals tend to be more non-compliant with these (Sorace et al. 2006). Loneliness is a risk factor for type 2 diabetes, both in animals (Nonogaki et al. 2007) and humans (Lukaschek et al. 2017). This link between loneliness and diabetes appears to be independent of other confounding factors, such as age, sex, ethnicity, wealth, smoking status, physical activity, alcohol intake, body mass index, HbA1c, hypertension, and known CVD (Hackett et al. 2020). Studies have demonstrated decreased social participation in adults with pre-dialysis chronic kidney disease (CKD) (Moorthi & Latham-Mintus 2019), those undergoing dialysis (Meltzer et al. 1989), and transplant recipients (Bailey et al. 2018). Smoking (Jo et al. 2020), drinking alcohol (Shankar et al. 2006). and obesity (Kovesdy et al. 2017) are reversible lifestyle factors that affect CKD and are more common in lonely individuals. Loneliness is also associated with metabolic syndrome (Whisman 2010). After analyzing data from the ‘Nord-Trøndelag Health Study’ involving 26,990 individuals followed for ten years, Henriksen and his group reported that individuals with higher levels of loneliness had a higher odd of developing metabolic syndrome (Henriksen et al. 2019). In a recently published study, metabolic syndrome was more common in individuals with a smaller social network (Kim et al. 2020). Social isolation in animals promotes the development of obesity (Nonogaki et al. 2007). In humans, lonely people tend to be more obese than non-lonely people (Lauder et al. 2006), and this is more prominent in older men (Hajek & König. 2019). Obesity further leads to more loneliness (Rotenberg et al. 2019). Behavioral modifications leading to a weight loss (as little as ≥5%

initial weight) among individuals with overweight/obesity improve several risk factors for CVD (LeBlanc et al. 2018). Low social support also results in chronic stress in adults (Steptoe & Kivimaki 2013). Loneliness is intricately associated with depression (Jaremka et al. 2014). This association has been seen in children (Qualter et al. 2010), adolescents (Stickley et al. 2016), young adults (Matthews et al. 2016), and older adults (Nyqvist et al. 2019). It prognosticates a worse course in these individuals with CVD (Ziggi et al. 2016). Loneliness is associated with poorer sleep quality, and the latter correlates negatively with CVD (Cacioppo et al. 2002, Hawkley et al. 2010). Depression in these individuals (Matthews et al. 2016), further aggravates sleep disorders (Wang et al. 2015). Diminished social support is associated with increased CVD morbidity (An et al. 2016). In a study by Barth and group, cardiac and all-cause mortality was 1.6-fold higher in patients with low social support (Barth et al. 2010).

2.2. Mechanisms behind the harmful CVD effects of loneliness

Loneliness and social isolation activate the hypothalamic–pituitary–adrenal (HPA) axis (Cacioppo & Cacioppo 2015). resulting in higher cortisol levels (Doane & Adam 2010) and a flattened diurnal cortisol slope (Zilioli et al. 2017). Cortisol, the final product in the HPA axis chain, is characterized by a distinctive diurnal patterning, with concentrations highest in the mornings and progressively declining over the day (Adam & Kumari 2009). HPA axis dysfunction (Rosmond & Björntorp et al. 2000), abnormally high cortisol or a disturbed circadian rhythm are all associated with CVD (Crawford et al 2019). Loneliness also leads to an enhanced sympathetic nerve activity and an impaired parasympathetic function (McNeal et al. 2014). Loneliness in rats leads to increases in the plasma concentrations of both epinephrine and norepinephrine (Gavrilovi et al. 2010). Sustained activation of the sympathetic adrenal medullary system resulting in overexposure to epinephrine and norepinephrine contributes to the development of CVD (Lundberg 1999). Loneliness also raises the levels of three systemic inflammation biomarkers (Nersesian et al. 2018), interleukin-6, fibrinogen, and C-reactive protein (Smith et al. 2020). Studies have found alterations in inflammatory gene expression (Powell et al. 2013), with genes responsible for anti-inflammatory glucocorticoid response elements being under-expressed, and genes bearing response elements for pro-inflammatory NF-κB/Rel transcription factors, being over-expressed (Cole et al. 2007). Chronic inflammation plays a key role in all phases of CVD (Ross 1999). Loneliness also decreases immunity (Walker et al. 2019). Immunity, both innate and adaptive, is actively involved in atherogenesis (Frostegård et al. 2013). Loneliness also reduces healthy lifestyles. Lonely people have reduced self-regulation (Hawkley & Cacioppo 2010) and tend to lead unhealthy lifestyles (Shankar et al. 2011, Algren et al. 2020). On the other hand, individuals with stronger social connections are more likely to practice healthy lifestyles (Samuel et al. 2015). Lonely individuals are more likely to be non-compliant with recommended physical activity (Shiovitz-Ezra & Litwin 2012), follow an unhealthy diet (Locher et al. 2005), be overweight or obese (Whisman 2010), indulge in high alcohol intake (Shiovitz-Ezra & Litwin 2012), or smoke (Christakis & Fowler 2008). This is despite being aware of the documented benefits of healthier lifestyles on cardiovascular diseases (Perk et al. 2012). On the other hand, a good social support system results in decreased loneliness and much healthier lifestyles (Debnam et al. 2012). Lonely people often lack support from social networks, family members and neighbors and may also be non-compliant in accessing health care services or following treatment recommendations (Jankowska-Polańska et al. 2020). Unknown factors, such as genetic polymorphism may also play a role in the loneliness and its CVD connection.

2.3. Therapeutic interventions

Several therapeutic interventions have been developed to treat loneliness and include antidepressants, neuro-steroids, and oxytocin (Masi et al. 2010). Cognitive-behavioral therapy has shown to be beneficial in lonely individuals (Theeke et al. 2016). Multimodal behavioral interventions involving nutrition, physical activity, weight management, alcohol moderation, smoking cessation, and relaxation training, via healthcare counseling can also help promote healthy lifestyles in lonely individuals (Artinian et al. 2010).

3. Conclusion

The data is extremely persuasive regarding the ill effects exerted by social isolation and loneliness on cardiovascular morbidity and mortality. With the increasing prevalence of loneliness and the continuing harmful impact of cardiovascular diseases globally, it is imperative that this connection be recognized, and multimodal behavioral interventions aimed at reducing the ill effects of the former, are instituted. Given its significant effect on cardiovascular diseases, which may be comparable to those conveyed by smoking, obesity, and hypertension, loneliness should be considered as and labeled as a major risk factor for CVD. Besides the potential reduction in CVD, therapeutic interventions for loneliness should also help reduce several other chronic diseases and improve the quality of life in these patients.

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Conflict of interest

None

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