



Palliative Medicine Review Article

Loneliness – Cancer of the Mind

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ABSTRACT

World is greying as the proportion of the ageing population increases and the demography is changing both in the developing and developed world. Contact between people is the central part of everyone's life and the glue that holds communities and society together. Lack of social relations is considered to cause loneliness and isolation for the individual and, simultaneously, on a societal level, leads to marginalisation, social disintegration and diminishing trust between people. This has come to sharp focus during the corona pandemic. Meaningful social connections are central to the physical and mental health of human beings. Off late, the deleterious health implication of social isolation and loneliness has increasingly been noticed, with a higher risk of premature death and accelerated risks of coronary heart disease, stroke, depression, and dementia. Worldwide, there is an increasing awareness regarding the alarming consequences of loneliness, especially among older adults. In response, 2018 saw the launch of a UK loneliness strategy and the first minister for loneliness in the world appointed.

Keywords: Loneliness, Alone, Ageing, Social isolation, Depression, Anxiety

INTRODUCTION

Loneliness is often stigmatised, trivialised or ignored, but — with the rapidly growing number of older adults in the developing and developed, the increased likelihood of premature mortality and the deleterious effects of loneliness that have been identified in animal studies and longitudinal studies in humans, loneliness is emerging as a major public health challenge. Loneliness is a common experience 80% of those under 18 years of age and 40% of adults over 60 years of age report being lonely at least sometimes with levels of loneliness gradually diminishing through the middle adult years and then increasing in old age (i.e., ≥ 70 years).^[1] Loneliness is perceived as social isolation, not necessarily as objective social isolation. People can live relatively solitary lives and not feel lonely, and conversely, they can live in a joint family and feel lonely nevertheless.

Loneliness is defined as a distressing feeling that accompanies the perception that one's social needs are not being met by the quantity or especially the quality of one's social relationships. It is a negative subjective feeling that arises as a result of a discrepancy between a person's desired and actual social relationships.

For more than a quarter century, epidemiological studies have consistently noted an association between objective measures of social isolation — typically operationalised as being unmarried, having less than monthly contact with friends and family and/or having no participation in organisations, clubs or religious groups and health outcomes. The most common explanation for this association is the social control hypothesis, which postulates that interactions with friends, family and congregations incline better health behaviour, which in turn decreases risks for morbidity and mortality.

Each of us are capable of feeling lonely at times, and loneliness is an equal opportunity tenant for good reason. We can say that loneliness is the social equivalent of physical pain, hunger and thirst; the agony of social disconnection and the craving for social connection motivates the desire and establishment of social connections that are imperative for the survival of our genes. For as many as 15–30% of the general population, loneliness is a chronic state.^[2] If untreated, loneliness has profound consequences on memory, emotion, behaviour and health. Feelings of loneliness can occur in all phases of the life course. How loneliness is experienced by the individual

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can vary depending on societal beliefs about what loneliness means and when loneliness may be expected to occur. Motivation and desires for social connections are affected by social practices and these can be age-related. Loneliness is a personal experience since there has to be an understanding in society regarding the likelihood of a relationship that is missing.

Loneliness has been acknowledged as a major factor contributing to morbidity and mortality in humans for well over two decades. The brain is the key organ of social connections and processes, however, and the same objective social relationship can be experienced as caring and protective or as exploitive and isolating.

LONELINESS AFFECTS ONES' PHYSICAL HEALTH AND QUALITY OF LIFE

Increasing evidence suggests that perceived social isolation or loneliness is a major risk factor for physical and mental illness in later life. There is mounting evidence from research indicating that social isolation predicts increased morbidity and mortality. The effects of loneliness seem to accrue over time to accelerate physiological ageing.^[3] Similarly, loneliness was associated with increased systolic blood pressure (SBP) in a population-based sample of middle-aged adults,^[4] and a follow-up study of these same individuals showed that a persistent trait-like aspect of loneliness accelerated the rate of blood pressure increase over a 4-year follow-up period.^[5] Social isolation and the fallout are clearly evident in a study of mortality in the health and retirement study, all-cause mortality over a 4-year follow-up was predicted by loneliness and the effect was greater in chronically than situationally lonely adults.^[6]

A meta-analysis done in 2010 revealed that the odds ratio for increased mortality for loneliness is 1.45, which is approximate twice the odds ratio for increased mortality for obesity and quadruple the odds ratio for air pollution.^[7]

In the national health and nutrition survey, women with chronic high-frequency loneliness (>3 days/week at each of two measurement occasions about 8 years apart) were prospectively associated increase incidence of coronary heart disease (CHD) over a 19-year follow-up in analyses that adjusted for age, race, socioeconomic status, marital status and cardiovascular risk factors.^[8] Low mood symptoms that are seen with loneliness have adverse health outcomes, but loneliness continued to predict CHD in these women after also controlling for depressive symptoms. Loneliness has also been shown to increase the risk for cardiovascular mortality, individuals who reported often being lonely exhibited significantly greater risk than those who reported never being lonely.^[9]

MENTAL AND COGNITIVE FUNCTION

Several studies also indicate that loneliness is a risk factor for cognitive decline and dementia. A couple of

longitudinal studies addressed this question. Tilvis *et al.*^[10] measured cognition by the mini-mental state examination and the clinical dementia rating at baseline and at 1-, 5-, and 10-year assessments of a population-based sample of 75–85-year-old individuals. Results of the 10-year follow-up assessment revealed that two biological measures and loneliness independently predicted cognitive decline. In a larger prospective study, Wilson *et al.*^[11] assessed 823 older adults free of dementia at enrolment. Participants completed an extensive battery of cognitive measures to assess global cognition, episodic memory, semantic memory, working memory, perceptual speed and visuospatial ability. Participants who experienced more loneliness, the poorer their cognitive performance in all domains at baseline. Furthermore, loneliness was correlated with increasing cognitive declines in all domains except working memory and episodic performance.

HOW DOES LONELINESS UNRAVEL

Loneliness posits^[12] that perceived social isolation is tantamount to feeling unsafe and this sets off implicit hyper-vigilance for social threats in the environment. Unconscious surveillance of social threats produces cognitive biases, relative to non-lonely people, lonely individuals see the social world as a more threatening place, expect more negative social interactions and remember more negative social information. Negative social expectations tend to elicit behaviours from others that confirm the lonely persons' expectations, thereby setting in motion a self-fulfilling prophecy in which lonely people actively ostracise and stay away from people that could be potential social partners as they perceive that the cause of the social distancing is attributable to others and they cannot do anything about it. This self-reinforcing loneliness loop is accompanied by feelings of hostility, stress pessimism, anxiety and low self-esteem and represents a dispositional tendency that activates neurobiological and behavioural mechanisms that contribute to adverse health outcomes.

HOW DOES IT AFFECT OUR HEALTH BEHAVIOUR?

The effect of loneliness is implicit vigilance for social threats and a diminished capacity for self-regulation. The capacity to control one's thoughts, emotions and behaviour is vital to attaining personal goals or adhering to social norms. Feeling socially isolated impairs the capacity to self-regulate and these effects are so automatic as to seem outside of awareness for self-regulation of lifestyle behaviours. Regulation of emotion can enhance the ability to regulate self-control behaviours,^[13] as is evident from research showing that positive affect predicts increased physical activity. In middle-aged and older adults, greater loneliness was associated with less effort applied to the maintenance and optimisation of

positive emotions.^[14] Compromised regulation of emotion in lonely individuals explained their diminished likelihood of performing any physical activity and loneliness also predicted a decrease in physical activity over time. Physical activity is a well-known protective factor for physical health, mental health and cognitive functioning, suggesting that poorer self-regulation may contribute to the greater health risk associated with loneliness through a diminished likelihood of engaging in health-promoting behaviours.

Besides the behavioural issues, there are neurobiological mechanisms^[15] that include age-related changes in neuroendocrine, cardiovascular, inflammatory stress responses, elevated vascular resistance, blood pressure, hypothalamic-pituitary-adrenocortical (HPA) activity, leukocyte glucocorticoid resistance reflecting aberrant ratios of circulating white blood cells, lower inflammatory control and diminished immunity.

Cognitive performance has also been suspected as a potential mechanism in the loneliness-health rapport. For example, severe and continual feelings of loneliness have been shown to affect executive functioning, increased sensitivity to negative social stimuli and undermine interpersonal trust.

SLEEP

Countering the physiological effects of the challenge of daily emotional, cognitive and behavioural experiences, sleep offers physiological restoration. Loneliness is associated with impaired sleep (e.g., shortened sleep duration, poor sleep efficiency, and greater daytime tiredness) in later adulthood. Moreover, findings from two longitudinal health surveys of older adults^[16] suggest that loneliness predicts decrements in subjective sleep quality, which, in turn, feed-forward to further exacerbate subsequent loneliness, suggesting a bidirectional causal relationship.

Sleep deprivation has adverse effects on cardiovascular functioning, inflammatory status and metabolic risk factors.^[17] In addition, short sleep duration has been associated with risk for hypertension,^[18] incident coronary artery calcification and mortality.^[19]

Sleep quality is underappreciated as an important factor in accomplishing sleep's restorative effects. Non-restorative sleep (i.e., sleep that is non-refreshing despite normal sleep duration) results in daytime impairments such as physical and intellectual fatigue, role impairments, and cognitive and memory problems. It has come to light that loneliness exacerbates feelings of vulnerability and involuntary vigilance for social threat, implicit cognitions that are contrary to relaxation and sound sleep. Indeed, loneliness and poor quality social relationships have been associated with self-reported poor sleep quality and daytime dysfunction (i.e., low energy and fatigue), but not with sleep duration.^[20] Loneliness was associated with greater daytime dysfunction in a 3-day diary study of middle-aged adults, an association that was independent of age, gender, race/

ethnicity, household income, health behaviours, body mass index, chronic health conditions, daily illness symptom severity, and related feelings of stress, hostility, poor social support and depressive symptoms.^[16]

PHYSIOLOGICAL FUNCTIONING

Chronic social isolation, rejection and/or feelings of loneliness in early childhood, adolescence and young adulthood cumulated in a dose-response fashion to predict cardiovascular health risk factors in young adulthood, including elevated blood pressure.^[21] In our study of young adults, loneliness was associated with elevated levels of total peripheral resistance (TPR), TPR is the primary determinant of SBP until at least 50 years of age,^[22] which suggests that loneliness-related elevations in TPR in early to middle adulthood may lead to higher blood pressure in middle and older age.

Loneliness was associated with elevated SBP in a population-based sample of 50–68-year-old adults in the Chicago Health, Aging and Social Relations Study.^[4] The association between loneliness and elevated SBP was exaggerated in older relative to younger lonely adults in this sample, suggesting an accelerated physiological decline in lonely relative to non-lonely individuals. These increases were cumulative such that higher initial levels of loneliness were associated with greater increases in SBP over a 4-year period. The imminent effect of loneliness on SBP was unconnected with that of age, gender, ethnicity, cardiovascular risk factors, medications, depressive symptoms, social support, perceived stress and estrangement.^[5] Increased SBP is an independent risk factor for chronic cardiovascular disease and these studies suggest that the effects of loneliness accrue to intensify the trajectory to jeopardise health.

NEUROENDOCRINE EFFECTS

Alterations in TPR levels are intrinsically influenced by a myriad of physiological processes, along with the activity of the autonomic nervous system and the HPA axis. The sympathetic branch of the autonomic nervous system plays a major role in maintaining basal vascular tone and TPR and elevated sympathetic tone is responsible for the development and maintenance of many forms of hypertension.^[23] To date, loneliness has not been shown to correlate with sympathetic nervous system activity in the myocardium but studies have shown that the concentration of epinephrine is higher in overnight urine collection of middle-aged and older adult samples.^[24]

Excitation of the HPA axis involves a sequence of signals that accomplishes the release of Adrenocorticotropic Hormone from the pituitary and cortisol from the adrenal cortex. Vascular integrity and functioning are obligated, in part, to the well-regulated activity of the HPA axis. Dysregulation of the HPA axis contributes to inflammatory processes that play a role in hypertension, atherosclerosis, and CHD.^[25]

Stephoe *et al.*^[26] found that chronically high levels of trait loneliness in middle-aged adults (M = 52.4 years) predicted greater increases in salivary cortisol during the first 30 min after awakening (i.e., cortisol awakening response) such that the cortisol awakening response in individuals in the highest loneliness tertile was 21% greater than that in the lowest tertile. In a study of middle-aged and older adults, day-to-day fluctuations in feelings of loneliness were associated with individual differences in the cortisol awakening response. The above study compiled everyday reports of psychosocial, emotional and physical states that were completed at bedtime on each of 3 consecutive days and salivary cortisol levels were measured at wakeup, 30 min after awakening and at bedtime each day.^[27]

The social evaluative threat is known to be a potent elicitor of cortisol and that loneliness is characterised by the chronic threat of hypervigilance for negative social evaluation is consistent with the finding that loneliness predicts increased cortisol awakening response. The relevance of the association between loneliness and HPA regulation is particularly noteworthy given recent evidence that loneliness-related alterations in HPA activity.^[28]

HOW DOES IT AFFECT OUR GENETICS AND IMMUNITY

Given that loneliness is associated with elevated cortisol levels, loneliness might be expected to reduce the risk for inflammatory diseases. Sense of loneliness and social isolation are linked with increased vulnerability to inflammatory disease. This finding may be attributable to impaired glucocorticoid receptor-mediated signal transduction failure of the cellular genome to 'hear' the anti-inflammatory signal sent by circulating glucocorticoids permits inflammatory processes to continue relatively unchecked.^[29] In a study of older taiwanese adults, this relationship was reflected in a positive correlation between cortisol levels and the ratio of neutrophil percentages relative to lymphocyte or monocyte percentages. However, in lonely individuals, this correlation was attenuated and non-significant, consistent with a diminished effect of cortisol at the level of leukocytes.^[30] The precise molecular site of glucocorticoid insensitivity in the pro-inflammatory transcription cascade has yet to be identified and additional longitudinal and experimental research is needed to ascertain the level to which chronic feelings of social isolation attribute to differential gene expression.

Social isolation effects on immunoregulation go beyond inflammation processes. Loneliness has been associated with impaired cellular immunity as reflected in lower natural killer cell activity and higher antibody titres to the Epstein Barr virus and human herpes viruses.^[31] We need more in-depth studies to analyse the role of loneliness, age, life stress context and genetic predispositions pan out to undermine immune functioning.

INTERVENTIONS

Six qualitative reviews of the loneliness intervention literature have been published since, and all explicitly or implicitly addressed four main types of interventions: (1) Enhancing social skills, (2) providing social support, (3) increasing opportunities for social interaction and (4) addressing maladaptive social cognition.^[32,33]

Only one of these reviews assured us that loneliness interventions can be successful, particularly interventions which targeted opportunities for social interaction. Implicit hypervigilance for social threat exerts a powerful influence on perceptions, cognitions and behaviours and that loneliness may be diminished by reducing automatic perceptual and cognitive biases that favour over-attention to negative social information in the environment. Interventions that intended to address deranged social cognition (e.g., cognitive behavioural therapy that implicated training to recognise automatic negative thoughts and elusive evidence, reduce biased cognitions and/or re-evaluate perceptions of loneliness and personal control) would be more useful than interventions that point to social support, social skills or social access.

HEALTH IMPLICATIONS OF ADDRESSING LONELINESS

Reducing feelings of loneliness and enhancing a sense of connectedness and social adhesion are desirable goals on their own merit, the vital question is whether altering perceptions of social isolation or connectedness has any impact on an individual's health. Will a timely intervention to lower loneliness produce a proportional advantage in the physiological mechanisms and alter physical health outcomes? A study which included 235 lonely home-dwelling older adults (>74 years) was randomly assigned to an intervention or control group. In the treatment arm of the study, closed small groups of 7–8 participants interacted with two professional coordinators once a week for 3 months to involve in group activities in art, exercise or therapeutic writing. The control group had ongoing interaction with regular community care. In contrast to the control group, participants in the treatment group became more socially engaged, made new friends and felt valued and wanted. This resulted in a significant difference in self-rated health, reduced doctor visits and reduce medical costs and an increased survival at 2-year follow-up.^[34]

CONCLUSION

In India, children usually continue to live with their parent's past adulthood, as they become financially and socially stable they tend to move out. In turn, as parents grow old, the younger generation provides emotional and economic support. Ideally, it is a rather beautiful system that inculcates close family ties across the generations. Unfortunately, no system is perfect and sometimes, the needs of ageing

and dependent parents are ignored, with the changing demography and ever-increasing proportion of nuclear families because of migration for jobs or education, older adults feel left out. Humans are such meaning-making creatures that we perceive social relationships where no objectifiable relationship exists (e.g., between author and reader, between an individual and god) or where no reciprocity is possible (e.g., in parasocial relationships with television characters). Conversely, we perceive social isolation when social opportunities and relationships do exist but we lack the capacity to harness the power of social connectedness in everyday life. Chronic perceived isolation (i.e., loneliness) is characterised by impairments in attention, cognition, affect and behaviour that take a toll on morbidity and mortality through their impact on genetic, neural and hormonal mechanisms that evolved as part and parcel of what it means to be human.

We need to educate and spread awareness among health-care professionals, the public about the devastating effect of loneliness. We need to impart the values of social cohesion and the importance of family to our younger generation. The western world has taken it seriously and trying to address this issue at various levels.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

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