

Review

The Impact of Loneliness and Social Isolation on Cognitive Aging: A Narrative Review

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Abstract. Social concepts such as loneliness and social isolation are fairly new factors that have been recently gaining attention as to their involvement in changes in cognitive function and association with dementia. The primary aim of this narrative review was to describe the current understanding of how loneliness and social isolation influence cognitive aging and how they are linked to dementia. Studies have shown that there is an association between loneliness, social isolation, and reduced cognitive function, in older adults, across multiple cognitive domains, as well as a heightened risk of dementia. Numerous changes to underlying neural biomechanisms including cortisol secretion and brain volume alterations (e.g., white/grey matter, hippocampus) may contribute to these relationships. However, due to poor quality research, mixed and inconclusive findings, and issues accurately defining and measuring loneliness and social isolation, more consistent high-quality interventions are needed to determine whether studies addressing loneliness and social isolation can impact longer term risk of dementia. This is especially important given the long-term impact of the COVID-19 pandemic on social isolation in older people is yet to be fully understood.

Keywords: Aging, Alzheimer's disease, cognition, dementia, loneliness, social isolation

INTRODUCTION

Over the past few decades, life expectancy of the elderly population has risen, coined the 'worldwide aging phenomenon' [1, 2]. This peak in life expectancy is also associated with an increased prevalence of non-communicable diseases (e.g., heart disease, diabetes mellitus, Alzheimer's disease)

which pose a threat to economic and health resources [3–5]. In recent years, we have observed a heightened prevalence of dementia, which is associated with the progressive decline of cognitive function [6]. Currently, there are approximately 55 million people living with dementia worldwide, which has been projected to rise to 78 million by 2030 [7].

In attempt to minimize this trend and better understand the causes of dementia, studies have focused on uncovering protective and risk factors. Some risk factors can be modified to influence cognitive deterioration, with the endeavor of slowing or delaying

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decline. The Lancet Commission into dementia [8] identified 12 potentially modifiable risk factors (e.g., smoking, depression, social isolation, physical inactivity) and investigated their contribution to dementia development and diagnosis. Modifiable risk factors were attributed to 40% of worldwide cases of dementia, insinuating that almost half of dementia diagnoses are potentially preventable. This highlights the utility of investigating risk factors for dementia prevention strategies.

Loneliness and social isolation are concepts which define different experiences and have independent associations with health outcomes [9, 10], yet have both been associated with cognitive decline [11]. Loneliness refers to one's perceived emotional and social state, whereby a disparity exists between ideal and actual quality/quantity of social connections [12, 13]. Older people are at a heightened risk of loneliness due to lifestyle factors (e.g., living alone, deceased friends and partners, chronic illnesses), in turn, putting them at risk for negative health outcomes associated with loneliness (e.g., poor immune function, mental health risks, heart disease) [14, 15]. A negative relationship between loneliness and cognitive function has been reported [16, 17]. In addition to impacting cognitive function, loneliness has been labelled a serious public health concern due to an observed increase in feelings of loneliness globally [18, 19] which has led to some researchers claiming we are amidst a 'loneliness epidemic' [20, 21]. Moreover, as loneliness is a risk factor for numerous negative health outcomes including enhanced onset of dementia, the necessity for further investigation is crucial [9, 13, 22].

Social isolation is considered an objective physical separation from others, which can be quantified by the number of individuals in their social networks and frequency of interacting with others [23, 24]. Isolation is also considered a major public health issue [24] due to its association with negative physical and mental health outcomes [14], as well as poor quality of life [25] and an increased risk of dementia [15]. In particular, it was found that social isolation was associated with a 50% increased risk of dementia [15]. Although loneliness and social isolation are interrelated concepts, they are still distinct social experiences. People can be objectively socially isolated without feeling lonely or have numerous social connections and still experience negative feelings associated with loneliness [26]. The subjective nature of loneliness outlines that some people may find sufficient social contact with only a few connections, while others may crave

more, hence, feeling lonely. Furthermore, the subjective and objective nature of loneliness and social isolation, respectively, are key differences between the concepts and influence their distinct experiences [27].

A 2020 report examining rates of loneliness and social isolation in the United States found that one third of adults aged 45 years and older experience loneliness, and almost a quarter of adults aged 65 and older are socially isolated [15]. Moreover, older people are considered at a heightened risk of experiencing loneliness and social isolation as they tend to be less socially engaged due to lifestyle factors associated with aging [28]. Older people may not have as many opportunities for social interactions [24] as the tempo of life can differ greatly from younger years. Lifestyle changes such as retirement [10], children moving out and experiencing the 'empty-nest syndrome' [29], spouses or friends passing away, and living alone can greatly limit the amount of social interaction throughout the day [16, 30]. Additionally, health-related issues such as reduced mobility, frailty, sensory and perceptual difficulties, and chronic illness [28] can also have an isolating effect on individuals, as their ability to go out and engage in social activities may be compromised.

In light of the COVID-19 pandemic and lockdown mandates in 2020 and 2021, social isolation became the living norm and an integral strategy to limit the spread of the virus [31, 32]. Opportunities for physical social interactions were drastically decreased, as everyday activities which usually permitted social engagement (e.g., appointments, shopping, exercising) were conducted remotely, and at-home visitors were prohibited [33, 34]. It was also suggested that the lockdown restrictions had a disproportionate impact on the elderly [35]. As to be expected, studies have reported feelings of loneliness magnifying as a result of the extended restrictions and lack of social interactions [36, 37]. This is a major concern for the well-being and neurocognitive health of older individuals, as little is known about the long-term ramifications of the extreme measures.

However, the relationship between loneliness, social isolation, and cognitive function is less well established within the literature compared to other biological and health behavior risk factors. As loneliness and social isolation are social constructs, they are considered more challenging to observe and assess compared to other factors such as smoking, diet, or exercise which can be quantitatively measured [38]. Additionally, separating and isolating interconnected

concepts is also challenging, as there is substantial overlap between loneliness and isolation, yet they are still distinct social phenomena with independent influences on health outcomes [9, 38, 39]. The preliminary findings of previous studies have highlighted the importance of investigating social factors when exploring cognitive aging and deterioration; however, a greater understanding is required to comprehend the pervasiveness of social risk factors on cognitive function and dementia development.

This narrative review will present the key literature exploring the role of loneliness and social isolation in poor cognitive decline and dementia risk. The link between loneliness and mental health outcomes, the role of recent interventions, and involvement of COVID-19 lockdowns will be described. Additionally, possible biomechanisms will be considered.

WHO IS MOST AT RISK OF LONELINESS AND SOCIAL ISOLATION?

Certain populations have exhibited an increased propensity of experiencing loneliness and social isolation. A Dutch cross-sectional analysis investigated how risk factors of loneliness and social isolation impact different age groups within adulthood (early adulthood: <30 years, middle adulthood: 30–64 years, late adulthood: >64 years) [40]. Correlation analyses revealed that living alone, lower education, immigrant status, inadequate financial resources, having a physical disability, or anxiety and depression were significantly associated with loneliness in late adulthood. Separating adulthood into three separate provides greater insight into the experiences of older adults who are at particular risk of loneliness and social isolation due to factors associated with aging (e.g., retirement, death of spouse/friends) [24, 28].

Gender differences in loneliness and social isolation risk have also been uncovered. A cross-sectional analysis of Japanese older adults found that loneliness was more prevalent among men, and that living alone has a greater association with loneliness for men compared to women [41]. This has been corroborated by other studies, including a US investigation of a national sample of older adults, who found living alone was associated with greater loneliness among men than women [42]. Additionally, the BBC Loneliness Experiment that compared data from participants living across 237 countries also found men reported more loneliness than women [43]. Similarly,

men also tended to be more socially isolated than women [44–46]. Hence, it is important to consider the impact of gender within loneliness and social isolation research.

Poverty is a relevant risk factor for social isolation [47]. A cross-sectional analysis of Danish residents living in deprived neighborhoods compared to a nationally representative control sample investigated the relationship between loneliness, social isolation, and socioeconomic status (SES) [48]. Low-SES residents exhibited a higher prevalence of both loneliness and social isolation compared to medium/high-SES participants. Additionally, an Australian cross-sectional study investigated the impact of the COVID-19 lockdowns across rural and urban areas [49]. Interestingly, rural Australians exhibited greater feelings of worry regarding loneliness compared to urban residents. Moreover, rural Australians worried about becoming lonely were also reportedly less happy than Australians living in major cities, suggesting that living in rural regions may be a risk factor for loneliness. This finding has been replicated by other studies [50, 51]. Moreover, the stress of financial instability, being unable to afford certain experiences or necessities, and can contribute to isolating from others. These associations highlight the importance of interventions being designed specifically to target lower SES related loneliness and social isolation [48]. Identifying characteristics that put individuals at greater risk of experiencing loneliness and social isolation has the potential to inform future studies and interventions designed to help vulnerable groups.

DOES LONELINESS AND SOCIAL ISOLATION IMPACT COGNITIVE FUNCTION?

Loneliness represents a potential risk factor for poor cognitive function within otherwise healthy older individuals. This has been observed among several cognitive domains, including immediate and delayed recall [16], memory [2], verbal fluency, composite cognitive scores [11], global cognition, and processing speed [52]. Other studies have examined loneliness as a predictor of cognitive impairment [53] as loneliness has been associated with accelerated cognitive decline over time [2, 54]. Similar findings have been linked to studies investigating the cognitive impact of social isolation, whereby there was a significant association between social isolation

and decreased verbal fluency, immediate recall, and delayed recall over 4-year period within a healthy older adult sample in England [16]. This was corroborated by a recent study, which observed a significant association between loneliness and reduced cognitive function over a 3-year follow-up within a Spanish older adult sample [11]. This was exhibited via lower composite cognitive scores, reduced verbal fluency and forward digit span tasks.

Despite these findings, loneliness and social isolation studies have yielded relatively mixed and conflicting results. Several studies have failed to find a significant association between the social concepts and reduced cognitive function [55, 56], while others found associations with some cognitive functions but not others [52, 57]. The lack of significant findings may be attributed to a small sample size [55], low power, possible unmeasured confounding variables (i.e., SES, rurality, other health conditions) [56], or failing to consider possible gender differences within the sample [57]. One systematic review uncovered that only 8 of 33 studies employed validated measures to assess loneliness [39]. There has also been criticism of studies which employed a single-item question to measure the level of loneliness within the sample [22], as a single item may not be effective in obtaining a well-rounded assessment of how the person's experience [39]. This makes it unclear how loneliness and social isolation interact with cognitive function, highlighting the necessity to further delineate this association.

Increased attention for research concerning loneliness and social isolation as risk factors of cognitive decline is positive; however, more research is required to gain a stronger insight into how loneliness and social isolation influence cognition.

LONELINESS AND SOCIAL ISOLATION AS DEMENTIA RISK FACTORS

The literature pertaining to loneliness and dementia risk has revealed that individuals experiencing loneliness are at heightened risk of developing dementia-related disorders compared to non-lonely individuals. This association has been observed via declining Mini-Mental State Exam (MMSE) scores [58], increased diagnoses of dementia-related disorders [59], and transitioning from mild to severe cases of dementia [60]. A longitudinal study of 12,030 participants aged 50 and older from the Health and Retirement Study found loneliness was associated

with a 40% increased risk of dementia after controlling for effects of social isolation and risk factors (clinical, behavioral, and genetic) [9]. This was supported by a retrospective analysis of prospective data collected from the Framingham Study population-based cohorts who were dementia-free at baseline [61]. Researchers uncovered a 3-fold greater risk of dementia for participants who experienced loneliness, were below the age of 80, and did not present *APOE* ϵ 4 alleles. Additionally, a meta-analysis of 10 studies observing healthy adults aged 50+ years revealed that prolonged loneliness and social isolation was associated with a 49–60% higher risk of developing dementia than individuals who do not experience loneliness or social isolation [31]. However, as loneliness and social isolation are distinct concepts and experiences, it is important to examine them separately.

Recent studies have shown more consideration for the distinction between loneliness and social isolation, as they have taken the time to analyze them separately; however findings have been mixed. A recent cohort study using the UK Biobank investigated how loneliness and social isolation differently contribute to genetic risk for dementia [62]. The cohort consisted of 502,656 individuals aged 60 years and older, of which 5.5% reported feeling lonely, and 8.6% were socially isolated. Interestingly, social isolation, but not loneliness, was associated with an increased risk of dementia. Similar findings were reported in a study of 462,619 participants (mean age at baseline: 57) from the UK Biobank [63]. Researchers found social isolation, independent of loneliness and depression, was associated with a 1.26-fold increased risk of dementia (when using Cox proportional hazard models) over a mean follow up of 11.7 years. However, loneliness was not significantly associated with a heightened risk of all-cause dementia. In contrast, the Amsterdam Study of Elderly (AMSTEL), that observed 2,173 healthy elderly community-dwellers failed to find a significant association between social isolation and dementia risk [64]. While participants experiencing loneliness were more likely to develop dementia than non-lonely individuals, the findings suggest that the feeling of loneliness contributed a greater risk for developing dementia rather than being objectively alone. Suggesting that our perceptions of social interactions could have a greater influence than being physically isolated from others [9].

However, it is unclear how loneliness and social isolation distinctly operate as dementia risk factors

due to mixed findings. A lack of association between loneliness, social isolation, and dementia risk has also been reported in older Australians [56]. The study included a large healthy sample of the general Australian elderly population, of which only 5% reported feeling lonely and 2% were socially isolated. Yet, it is estimated that 13% of people aged 65 and older experience loneliness [65] and 19% of elderly Australians are socially isolated [66, 67]. Notably, the initial data collection for the analysis was conducted from 2010–2014, and represents a pre-pandemic experience, however, the levels of loneliness and social isolation reported in the study also vary greatly from the national average at the time. Similarly, a genetically informed longitudinal study also failed to establish a link between loneliness and dementia risk in older adults [68]. The study comprised of 1,632 pairs of twins from the Swedish Twin Registry who participated in one of the three previous longitudinal studies. Loneliness was measured via a single-item question at 5-6 time points throughout the longitudinal studies, while cognitive testing and *APOE* ϵ 4 allele status were employed as dementia indicators. Changes in loneliness over time did not correlate with dementia risk even when both genetic and environmental factors were considered. These contrasting findings make it difficult to generalize findings to the broader population as the association between loneliness, social isolation, and dementia risk is unclear.

Possible attributors to the mixed findings within the literature include discrepancies in measures of loneliness, social isolation, and dementia across studies, additionally, failing to account for the impact of covariates. A systematic review conducted by Victor [22], outlined several challenges when evaluating the relationship between loneliness and dementia, including how predictors and outcomes are defined, conceptualized, and measured, namely that previous studies investigating the relationship between perceptions of loneliness and dementia risk have numerous methodological differences, which have ultimately led to discrepancies in findings [39, 52, 60, 69]. Notably, the inconsistency of loneliness and dementia measurement tools across studies may be attributed to variability of findings [22]. Hence, it is crucial especially when investigating complex conceptual variables to employ validated measures which are consistent with other studies to be able to compare findings.

Additionally, covariates are highly important to consider within dementia research due to the mul-

tidimensional nature of the diseases which are simultaneously influenced by numerous factors. Victor [22] outlined five covariate domains which encompass the factors that can exert an influence over loneliness and dementia (i.e., socio-demographic, social health, health behaviors, physical health, and mental health). It is evident in past research that some studies have omitted key covariates, such as depression, educational level, and marital status [70–73], all of which have been significantly associated with loneliness [22]. Hence, future studies should aim to include at least one covariate for each domain suggested by [22], to ensure a degree of control is sustained. Although, future research would benefit by consistently including the same covariates to allow potential generalizability of significant findings. The loneliness and social isolation research discipline is still in its early stages, as evident via the mixed and inconclusive findings. Understanding the associations between loneliness, social isolation, and dementia risk, when validated measures are used, may be valuable in informing the creation or refinement of risk assessment tools.

THE IMPACT OF THE CORONAVIRUS (COVID-19) ON LONELINESS, SOCIAL ISOLATION, AND COGNITION

The COVID-19 lockdown restrictions disrupted the structure, function, and quality of social interactions across all ages [24]. Mandates outlining the distance one could travel from home, number of visitors, and hours people were permitted to leave home all significantly reduced social interactions [33]. As opportunities for social interaction already derive from limited sources for elderly people (e.g., shopping, appointments, family visits) [16, 30], it is important to investigate the impact of these emergency measures on loneliness, social isolation, and cognitive function.

Recent research has focused on investigating the ramifications of the COVID-19 lockdowns in producing an environment with a heightened risk of loneliness and social isolation. Studies worldwide have reported an increase in perceived loneliness since the beginning of the pandemic [74–77]. This includes a recent Australian white paper [78] that found that 50% of Australians reported feeling lonelier since the onset of the COVID-19 pandemic. However, this is contrasted by Luchetti et al. [53] who found no increase in feelings of loneliness com-

pared to pre-pandemic loneliness levels within a sample of American adults. Hence, at this stage it is unclear whether loneliness has increased as a result of the COVID-19 pandemic, and further research is required.

It is difficult to generalize findings from COVID-19-loneliness studies to the broader adult population as both loneliness and lockdown restrictions are personal multidimensional experiences. There was a wide variance in the severity of lockdown restrictions and durations between countries and regions, which were ultimately linked to population density, number of confirmed COVID-19 cases, and vaccine rollout. Victoria, Australia holds the title for longest lockdown worldwide (over 260 days) [79], juxtaposed to Austria, which spent 29 days in lockdown in 2020, and Sweden refusing to mandate COVID-19 restrictions [80]. Hence, it is plausible that some citizens may have felt the sting of loneliness more so than others, depending on their country's lockdown mandates and durations. These between country differences were considered by researchers who conducted a cross-country comparative study which examined the impact of social distancing restrictions on people living in Norway, USA, UK, and Australia [81]. The researchers found significant differences between countries in terms of mental health, quality of life, and loneliness. It was uncovered that Norwegian participants exhibited lower levels of loneliness and poor mental health, as well as higher quality of life compared to participants residing in the USA, UK, and Australia. Though the COVID-19 pandemic was a universal health threat across the world, the measures instated by each country and individual experiences were unique. Hence, there is value in understanding between country differences in loneliness experience following the various lockdown periods.

As a number of studies have reported increases in loneliness following COVID-19 restrictions, it is also crucial to consider the possible cognitive ramifications of the lockdown mandates. However, only a few studies thus far have investigated this association. In particular, one study investigating Italians living with dementia found cognitive decline was exacerbated compared to pre-pandemic cognitive function between 2019 and 2020 [82]. Other investigations into the ramifications of lockdown restrictions have yielded mixed results, with some supporting the aforementioned changes in cognition following the lockdowns [83, 84], while others contrasting these findings [85, 86]. A Portuguese study investigated the effect of lockdown restrictions on mental health

within a cognitively healthy adult sample and briefly examined the influence on cognition via employing the Montreal Cognitive Assessment (MoCA) and MMSE measures [87]. It was uncovered that the cognitive function abilities pre-pandemic were maintained within the sample. Interestingly, Portugal had the shortest lockdown of 15 days, juxtaposed to Italy, which spent 71 days in lockdown [80]. This may assist in explaining the discrepancy in results, as the aforementioned change in cognitive function identified by Tondo and colleagues [82] examined Italian individuals, and a lack of change was detected in the Portuguese sample [87]. Though the samples differed in terms of dementia diagnoses, it is plausible that longer lockdown restrictions may lead to worsened cognitive outcomes. Another study that obtained contrasting results was a recent population-based matched retrospective cohort study of Canadian adults (aged 65+ years) living in long-term care homes [88]. Researchers examined the impact of COVID-19 restrictions on 1-year incidence of cognitive decline via the Cognitive Performance Scale and compared cognitive decline between groups tested before the pandemic (pre-COVID-19 group) and during (COVID-19 group), with participants matched based on age, sex, cognition, and presence of end-stage disease. Interestingly, cognitive decline was lower for participants within the group tested during the pandemic juxtaposed to those tested before the pandemic. This may be attributed to a higher incidence of death within the COVID-19 group. It is important to note that many studies investigating the effects of the COVID-19 pandemic either focused primarily on mental health impacts or global health outcomes [37, 77, 83, 85], and oftentimes cognition was a secondary outcome [86, 87, 89]. Furthermore, this outlines a gap within the literature of studies directly focusing on the cognitive impact of social restrictions due to the pandemic. Longitudinal studies are required to understand the long-term cognitive effects of living in a heightened state of loneliness and prolonged periods of social isolation, and how these differ from potential cognitive deficits due to COVID infection [90].

ASSOCIATIONS BETWEEN LONELINESS, SOCIAL ISOLATION, AND MENTAL HEALTH OUTCOMES

When exploring the complexities of loneliness and social isolation, it is also important to con-

sider their interplay with mental health outcomes. Research has shown that loneliness and social isolation contribute significantly to the diagnoses of mental health disorders such as depression and anxiety [91], hence, are considered risk factors [92, 93]. Researchers have uncovered a strong association between loneliness and depression [9, 94–96], which has been speculated to be due to their shared symptomatology (e.g., helplessness, pain) [97]. The Health and Retirement Study (HRS) was a large longitudinal panel survey of a non-clinical sample of older adults that collected biennial data from participants from 2006–2016. Findings exhibited that loneliness strongly predicted depression, as well as the symptom cluster of pain, fatigue, and depression [98], supporting the concept of shared symptomatology. Social isolation has also been significantly associated with depression onset [99, 100]; however, there has been far less commentary on this relationship. Interestingly, a population-based study uncovered that both social isolation and loneliness were associated with depressive symptoms after controlling for demographic factors [99]. Yet, the association between loneliness and depressive symptoms was independent of and stronger than the association with social isolation, which has been replicated in other studies [101]. This may be attributable to the symptomatic similarities between loneliness and depression are stronger than with social isolation.

Akin to their symptomatologic similarities, mental health disorders, loneliness, and social isolation also share negative outcomes on cognitive function and are associated with an elevated risk of cognitive decline [9, 17, 102, 103]. Researchers have found that individuals suffering from depression exhibit changes in executive function [104], working memory [105], delayed memory [106], and attention [107]. Anxiety disorders have been characterized by similar cognitive deficits to working memory, delayed memory [106], executive function [108], processing speed, inhibition, and problem solving [109]. Such cognitive changes have also been observed for people experiencing loneliness [16, 52] and social isolation [16, 60]. Hence, it is crucial to consider how these multiple factors interact when attempting to understand the phenomena of cognitive decline, as mental disorders could account for some of the variance in cognition [2].

Indeed, the relationship between loneliness, social isolation, and mental health outcomes is likely bidirectional. In a recent population-based longitudinal

study, loneliness was found to predict the development of severe common mental disorders (e.g., mood disorders, anxiety disorders, substance-abuse disorders) in a Dutch general population [110]. Moreover, baseline severe mental disorder symptomatology predicted onset of loneliness at three-year follow up for participants who were not previously experiencing loneliness. A longitudinal study in a population-based US sample also found similar bidirectional associations; while depression and anxiety symptoms were associated with small significant increases in loneliness, loneliness was strongly associated with depression and anxiety symptoms at an 8-week follow up [111]. This was corroborated by an additional longitudinal study, that uncovered a bidirectional association between loneliness and likelihood of suffering from depression or anxiety; however, the association has been observed stronger with loneliness as the origin [50]. Whereas the association between social isolation and subsequent likelihood of depression and anxiety was unidirectional, reinforcing the importance of examining loneliness and social isolation separately. Furthermore, it is likely that mental health symptoms may exacerbate feelings of distance, and lack of connections with others, however, feelings of loneliness may perpetuate withdrawal from others, resulting in social isolation, and subsequent poor mental health symptoms.

POTENTIAL MECHANISMS UNDERLYING THE ASSOCIATION BETWEEN COGNITION, LONELINESS, AND SOCIAL ISOLATION

It has been theorized that loneliness and social isolation are associated with underlying biomechanisms which may be responsible for stimulating changes in cognitive function that have been documented in past research. Dementia is characterized by neural structural changes including atrophy which has been linked to common functional deficits (i.e., memory decline, altered executive function) [112, 113]. Hence, the decline in cognitive function associated with loneliness and social isolation may have a biological foundation.

A commonly explored biomechanism of loneliness is the biological stress response and association with the hypothalamic-pituitary-adrenal (HPA) axis [55]. It has been suggested that feelings of loneliness stimulate a biological stress response designed

to propel us towards behaviors that enhance our reconnection with others [114, 115]. The negative sensation associated with loneliness indicates that social needs are not being met (i.e., perceived social threat), which is hypothesized to stimulate a person to connect with others to alleviate the negative feeling [116]. Additionally, there is evidence that lonely individuals experience cortisol dysfunction, resulting in heightened secretion of the hormone, in turn, dysregulation of the HPA axis [114, 117]. Overtime the prolonged activation and dysregulation of the regulatory mechanism, paired with hypercortisolism, can cause damage to the system and manifest into poor health outcomes (e.g., inflammation, metabolic disorders, psychiatric disorders) [52, 114], which may explain the plethora of health conditions associated with loneliness. Additionally, as the hippocampus is particularly sensitive to stress hormones, which can disrupt functioning, chronic HPA axis activity may be responsible for the observed reduction in memory processing capacity [118]. Furthermore, heightened cortisol secretion has been associated with deleterious effects on the brain such as neurodegeneration [119], which is notable given higher cortisol levels have been observed in dementia patients [118]. Researchers have also uncovered that elevated cortisol has been linked to poor cognitive outcomes. One study investigated a dementia-free cohort in the United States and uncovered higher cortisol levels was associated with poorer memory and visual perception [120]. This was corroborated by another study that examined the effects of cortisol as a mediator between loneliness and cognitive function within a sample of healthy older adults which found that loneliness was not directly associated with deficits in cognitive function [55]. However, when examining the association with bedtime cortisol levels as the mediator, a significant relationship was found between loneliness and poorer performance on executive function, attention, processing speed, and verbal memory immediate recall. These findings further reinforce the hypothesis that maladaptive HPA axis function mediates the relationship between loneliness and decreased cognition and contributes to dementia pathology. Several studies have uncovered various brain regions associated with loneliness that have exhibited structural and functional differences compared to non-lonely individuals [116]. These include abnormal grey and white matter distributions within the prefrontal cortex [116], hippocampus and amygdala [121], posterior superior temporal cortex [116, 122], and increased cerebral white matter volume

[123]. The visual, attentional, and limbic regions have also been implicated in loneliness, due to their association with loneliness behaviors (e.g., attentional bias for negative stimuli, reduced cognitive flexibility) [124]. Moreover, those who scored high on loneliness scales exhibited reduced grey matter within these regions compared to low scorers, which may help explain associated loneliness behavioral tendencies. One study hypothesized that loneliness would be associated with neural regions responsible for social processes, which was investigated using voxel-based morphometry and the University of California (UCLA) Loneliness Scale [125]. They found that lonely individuals brains exhibited less grey matter within the left posterior superior temporal sulcus, a region that is implicated in social perception. Loneliness was also significantly correlated with objectively measured social perception skills (i.e., eye gaze perception), which suggests that loneliness may be associated with deficits in basic social perception skills. However, these findings are limited by heterogeneity of study methodologies and cohorts, outlining the need for further investigations.

A great part of our understanding of the neurobiological mechanisms of social isolation is based on animal studies, due to invasive techniques and ethical considerations when examining human cohorts [126]. For instance, a study investigated the impact of long-term social isolation on APP/PS1 transgenic mice in relation to environmental and genetic characteristics of Alzheimer's disease (AD) [127]. The researchers found that social isolated mice exhibited spatial working-memory impairment. In addition, the period of social isolation impacted memory-related regions of the hippocampus were and increased oxidative stress was observed. These findings suggest that environmental factors can manipulate genetic predisposition to accelerate the onset of AD symptoms. The impact of social isolation on female adult prairie vole neurology has also been investigated [128]. Following 6 weeks of social isolation researchers observed a reduction in cell proliferation (neurogenesis) and neuronal differentiation within limbic brain regions. Deficits in adult neurogenesis (particularly within the hippocampus) have been linked to cognitive impairments and has been implicated with AD risk and development [129]. Hence, the information yielded from animal studies provides insight relevant to human brain pathology which could be integrated into human studies [14]. However, the human experience of loneliness is com-

plex and involves perceptions of the quality and quantity of social interactions and connections to others, which cannot be investigated using animal models.

INTERVENTIONS TO ENHANCE SOCIAL CONNECTION

To combat the ‘loneliness epidemic’ [20, 21, 24], comprehensive public health action is required to minimize the negative impact of both loneliness and social isolation [130]. Interventions have been developed to assist community-dwelling and institutionalized older adults in alleviating loneliness, reduce social isolation, and promote social health [27]. Typically, interventions have involved either a group setting [131], or delivered one-on-one [27, 132] and varied concerning the type of service being provided, such as offering activities (e.g., physical programs, art classes) [133], support (e.g., discussion, therapy), internet training [134], and home visits [27]. Including a broad range of services and activities has been found to increase the likelihood of individuals finding a social program that they enjoy, in turn, motivating individuals to continue attending and engaging in these programs [27].

A meta-analysis of 50 articles attempted to quantify the effects of loneliness reduction interventions based on their primary intervention strategies [135]. Qualitative reviews have established four primary intervention strategies commonly applied to loneliness reduction interventions, including improving social skills, enhancing social support, increasing opportunities for social contact, and addressing maladaptive social cognition. Of these primary strategies, interventions that addressed maladaptive social cognition exhibited greater effect sizes compared to those focused on improving social skills, enhancing social support, or increased social contact. That is, the most successful strategy involved providing the psychological framework to combat maladaptive schemas and questioning one’s own perception of loneliness, opposed to providing instances of social interaction. The findings suggest that the individual perception of loneliness may be a strong contributor of loneliness outcomes and should be considered in future trials [9, 12, 13].

Another meta-analysis explored the effects of digital technology interventions in reducing loneliness within the older adult population [136]. The analysis included five clinical trials (i.e., four RCTs, one

quasi experimental study) and one pre-post study. However, the review found overall effect estimates were not statistically significant at any follow-up time point (i.e., 3-month, 4-month, 6-month); moreover, the quality of evidence in these trials was ranged from very low to moderate. Although digital technologies are increasingly being employed to manage health, an individual’s digital literacy and access to digital devices may limit the utility of such technologies [137–139]. This highlights the necessity to design and deliver intervention content in a way which is accessible and usable for older adults.

A recent systematic review investigated the effectiveness of existing interventions and uncovered that 55% of group programs, 25% of mixed interventions, and all three (100%) one-on-one programs reported at least one significant finding relating to loneliness or social isolation [130]. The included studies varied greatly in terms of the services being provided (e.g., fitness program, reminiscence therapy, computer literacy, leisure activities), and by the outcome measures included (e.g., psychological, physiological), while all employed either a loneliness questionnaire or social isolation measure. Interestingly, group programs did not produce as many positive effects on loneliness or social isolation compared to individual-based interventions. This suggests that loneliness and social isolation outcomes can be differently influenced by the mode of intervention (i.e., individual, group). This may be explained by group interventions fostering a sense of belonging and community, while individual interventions may offer an opportunity to develop a higher quality bond and deeper relationship with one other person [130, 140]. This links in with the individual perception of loneliness, whereby the quality of social relationships and interactions may take precedence over the quantity [12, 13]. Furthermore, the review’s findings emphasize the importance of considering the mode of loneliness/social isolation interventions as they can influence efficacy. However, the consensus between reviews is that existing interventions are limited by a weak quality of evidence, making it difficult to interpret the effectiveness of loneliness/social isolation programs [141–144].

More recently in light of the COVID-19 pandemic, interventions have focused on the utility of employing technology to keep people connected while physically apart [142, 144]. When physical distancing was mandated, it was crucial to still maintain social connections with friends and fam-

ily during uncertain times, while complying with the government restrictions. A recent systematic review included a range of different interventions which were feasible to conduct during the COVID-19 restrictions and uncovered that psychological-based therapies (e.g., mindfulness activities, art discussion) yielded the strongest improvements in loneliness [144]. These activities could easily be conducted in online groups, hence, applicable while physical distancing measures were in place. However, when interventions are technology-based concerns are raised regarding the accessibility of computer devices (i.e., cost and socioeconomic status) and digital literacy of elderly participants [144]. A systematic review of technology-mediated interventions in enabling long-distance social interactions [142] found that few interventions were tailored specifically to older adults. Some studies have provided training in using technology and online programs to boost the confidence of older people when using the technology [142, 145]. However, it has been noted that a number of participants withdrew from these studies as they felt that learning how to use a computer was too difficult [146, 147].

Overall, the findings relating to loneliness and social isolation interventions have been underwhelming. Programs efficacy has varied greatly between studies and have been only of fair quality, which is not sufficient to establish conclusive remarks on their level of success [142–144]. Existing intervention studies have been criticized for how they attempted to define and operationalize loneliness and social isolation, which was associated with heterogeneity [27, 143]. Numerous interventions failed to distinguish between loneliness and social isolation, and viewed them synonymously, even though the constructs have separate definitions and experiences [27, 38, 143, 148]. This is particularly important when selecting the most appropriate and effective programs, so the individual can be matched to the most suited intervention based on their goals or needs [148, 149]. Additionally, Fakoya et al. [27] stated that as loneliness and isolation are individual experiences, this may cause difficulty in delivering and standardizing interventions. It has also been noted that the COVID-19 pandemic and restrictions have had a disproportionate effect on vulnerable groups with differing circumstances (i.e., women, low education, low income, rural), hence, loneliness and isolation may have been magnified for some populations [144]. Furthermore, it is crucial to consider these individual experiences when con-

structing interventions, to ensure they are targeting loneliness and isolation in the most effective manner [148].

Another criticism of past interventions is the use of a range of loneliness outcome measures which differed greatly between studies [143]. This causes particular difficulty when comparing effect sizes between interventions to determine their efficacy, as some measures have been deemed stronger than others. Moreover, the use of single-item tools raises concerns in terms of their validity and ability to capture an accurate representation of loneliness compared to multi-item measures [22, 39, 143].

In the context of cognitive impairment and dementia, very few interventions have focused on tailoring services to improve loneliness or social isolation related cognitive deficits. One study assessed the effectiveness of personal contact interventions in addressing loneliness in people diagnosed with dementia [150]. The researchers interviewed 25 family members, friends, and healthcare providers of people with dementia, to rate how well-suited they felt personal contact interventions would be for those diagnosed with dementia. The participants perceived the intervention as positive, with 80% rating the program as effective, logical, and suitable. However, there is currently no evidence suggesting this form of intervention is beneficial or effective in reducing loneliness for people with dementia, as it has not been empirically tested. No other studies have directly observed how interventions may improve cognitive function in relation to loneliness or social isolation or how dementia risk is influenced, which is a critical gap in the literature. Furthermore, accounting for socialization variables, within intervention studies targeted at improving cognition, may provide greater insight into individual responses to the intervention.

CONCLUSION

This narrative review has explored the current knowledge pertaining to loneliness and social isolation and their distinct roles in the decline of cognitive function and dementia risk. There is some evidence of an association between perceived loneliness, social isolation, and reduced cognitive function across multiple cognitive domains [2, 11, 16, 52] as well as a heightened risk of dementia development due to these social factors [9, 31, 58–60]. However, establishing a comprehensive understanding of the ramifications

of loneliness and social isolation is still ongoing. The magnitude of mixed and inconclusive findings, poor study designs, and in some cases low quality of evidence, limit the significant outcomes of successful studies [11, 56, 73, 85, 86]. Further, an overarching criticism of loneliness and social isolation research relates to defining and measuring the concepts, in particular, that the concepts have not been properly distinguished as they are two distinct experiences [22, 27, 38, 143, 148]. Ultimately, more consistent higher quality interventions are required to understand the importance of mitigating loneliness and social isolation to reduce dementia risk, particularly in this post-COVID world.

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CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

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