Master's Thesis

Associations between Social Isolation, Loneliness, Cognition, and Dementia: Implications for Clinical Practice, Social Engagement Interventions, and Public Policy

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ABSTRACT

Background: Social isolation and loneliness have been found to be common among older adults. The absolute number of individuals experiencing social isolation and loneliness will rise dramatically as a large proportion of the population reaches old age. Numerous studies have found associations between social isolation, loneliness, cognition, and dementia. However, the findings regarding these associations have been mixed.

Methods: This review aimed to clarify these associations. A search of the literature identified a total of 1,070 related articles. After deduplication by title, removal of articles based on exclusion criteria, and the addition of one article published shortly after the initial search that met inclusion criteria, a total of 27 articles using longitudinal cohort data remained. Each article was reviewed for associations between social isolation, loneliness, and cognitive functioning in older adults.

Results: Four main relationships emerged: 1) social isolation and cognition, 2) social isolation and dementia, 3) loneliness and cognition, and 4) loneliness and dementia. Social isolation and loneliness were found to be significantly associated with declines in cognitive performance, and loneliness was found to be associated with an increased risk of dementia. However, the association between social isolation and risk of dementia was found to be non-significant in all studies reviewed. Further, it was found that key covariates, such as age, gender, and depression, may have moderating effects on cognitive performance.

Discussion: This review has important implications for cognitive aging and public health. Further clarifying these associations through the standardization and harmonization of study design and methods will help identify targets for clinical practice, social engagement interventions, and public policy to help older adults optimize their cognitive health.

INTRODUCTION

Over the coming decades, a large demographic shift will greatly alter many aspects of public health. By 2050, the number of older adults in the US is anticipated to more than double from 40.2 million in 2010 to a projected 88.5 million (US Census Bureau, 2010). This trend is also occurring on a worldwide scale. The projected worldwide population for individuals over 65 years old in 2050 is expected to reach 1.6 billion, up from 617 million in 2015 (He et al., 2016). In addition, the proportion of the aging population will more than double, while the total population will grow by 34 percent (He et al., 2016).

In the US, more older adults are living alone and preferring to age in place (Wiles et al., 2011). Social relationships decline for a variety of reasons, including family and friends moving away, death or disability of peers, and other personal factors, such as retirement or declines in physical or cognitive health (Cudjoe et al., 2018). As a result, community-dwelling older adults tend to have smaller networks with fewer contacts as they age (McPherson et al., 2006), potentially increasing their risk for social isolation and loneliness, and the absolute number of older adults experiencing social isolation and loneliness is expected to rise.

The mounting health, economic, and societal costs of social isolation and loneliness among older adults has been identified as a unique public health challenge which warrants special attention (Fried et al., 2020). Social isolation and loneliness have also been found to increase risk for lower cognitive function, mild cognitive impairment, and Alzheimer's disease (Boss et al., 2015; Lara et al., 2019a; Lara et al., 2019b; Sundstrom et al., 2020; Snorri et al., 2020; Sutin et al., 2020; Wilson et al., 2007). A lack of public health efforts to address the needs of socially isolated and lonely older adults may increase long-term, cognitive health risks for this population.

However, the constructs of social isolation and loneliness are complicated and present many conceptual and measurement problems. Social isolation and loneliness are two closely related constructs, but they also differ phenomenologically (Hughes et al., 2004). While social isolation is an objective state of solitude, loneliness is a subjective feeling of solitude. An individual may be content while socially isolated, and another individual may experience loneliness, despite the presence of others. These differences may have important implications for developing public health interventions and policies to reduce the risk of cognitive decline and dementia.

Background

There are many terms that are used in the literature to characterize individuals' social connections. In addition to social isolation and loneliness, researchers have also used terms such as social relationships, social connectedness, social support, social engagement, social interaction, etc. Each of these terms may describe a slightly different aspect of our social world, but these sematic differences are largely attributable to different disciplines or fields of study. For this review, social isolation and loneliness will be the focus, which are the terms that have been found to be the most prominent in both epidemiological and cognitive aging research.

Social isolation

Nicholson (2009) describes a socially isolated individual as one who lacks engagement with others and has a minimal number of social contacts. The National Academy of Science and National Institute on Aging (2015) defines social isolation as simply the physical separation from others. Social isolation tends to be described as a measurement of the quantity, over quality, of one's relationships.

Social isolation is a common phenomenon among the aging. Cudjoe et al. (2020) found that 7.7 million community-dwelling older adults were socially isolated by national estimates based on a weighted, sample analysis. The most severely isolated older adults comprise four percent of the total population, representing an estimated 1.3 million individuals (Cudjoe et al., 2020). These figures are expected to rise as the population ages.

In addition, Cudjoe et al. (2020) found that socially isolated older adults were more likely to be male, have lower education, and have lower income. Both males and females who do not have a close partnership due to widowing, separation, divorce, or never being married were also found to be more socially isolated. Lastly, the authors found that Black and Hispanic older adults were less likely to experience social isolation than Whites.

Because social isolation is conceptualized as a lack of social contacts, and due to its objective nature, this construct tends to be measured quantitatively (Beller & Wagner, 2018). While measures of social isolation may be based on self-report, more objective measures have also been used, such as in the Berkman-Syme Social Network Index (BSNI), which incorporates marital status, close ties, church attendance, and social participation (Cudjoe et al., 2020). However, the treatment of these quantitative measures during analysis tends to vary between studies.

Loneliness

Social isolation should not be confused with "perceived social isolation", which is generally regarded as synonymous with loneliness (Caccioppo et al., 2012). The key distinction between social isolation and loneliness is that loneliness causes dysphoria, which is an unpleasant emotional experience reported by an individual. A consensus definition of loneliness has not been established, but it has been described as "a painful feeling of social isolation that accompanies perceived deficiencies in the number or quality of one's social relationships" (Peplau & Perlman, 1982, as cited in Hawkley et al., 2008, p. S375). A socially isolated person may not feel lonely, and a lonely person may not be socially isolated.

The total number of older adults experiencing loneliness is also expected to rise as the Baby Boomer generation ages (Hawkley et al., 2019). Loneliness across the lifespan peaks in young adulthood, recedes during midlife, then spikes in very old age (Luhmann & Hawkley, 2016). In a 2018 survey by the American Association of Retired Persons (AARP), it was found that one in three adults age 45 and older are lonely (AARP, 2018). In the literature, it was also found that 19.3% of older adults over 65 years of age report feeling lonely much of the previous week (Theeke, 2009, as cited in Masi et al., 2011) and 50% of those over 80 years of age report frequent loneliness (Hawkley, 2015).

Loneliness is typically captured though self-report measures. The most commonly used measures are one item from the Center for Epidemiologic Studies Depression Scale (CES-D) and the 3-Item UCLA Loneliness Scale, also referred to as the Hughes Loneliness Scale, which have demonstrated both reliability and validity (Devins et al., 1988; Hughes et al., 2004). These scales are typically used in surveys as part of large cohort studies because they are brief and easy to administer (Hughes et al., 2004). As a result, many cohort studies have effectively utilized these scales to help characterize populations that may be at greater risk for experiencing loneliness.

Known vulnerabilities to loneliness include "low socioeconomic status, depression, poor martial quality, infrequent contact with friends and family, few social roles, lack of participation in voluntary organizations, physical health symptoms, and physical limitations" (Hawkley et al., 2008 & Savikko et al., 2005, as cited in Cacioppo et al., 2010, p. 453). Those with the greatest risk for loneliness include older adults, residents of disadvantaged neighborhoods, and groups experiencing disproportionate losses. Groups that have been found to have elevated levels of

loneliness among older adults include low-income adults, unpaid caregivers, and individuals who identify as LGBTQ (AARP, 2018).

Alzheimer's disease

Public health efforts have added approximately 30 years to life expectancy over the last century (Fried, 2012). However, this extension of life will have a profound effect on the number of individuals who will be living with age-related diseases. Alzheimer's disease (AD) is listed among the top five causes of death worldwide (World Health Organization, 2018). The number of deaths due to Alzheimer's disease has risen 146.2% between 2000 and 2018, while other major causes of death, such as heart disease, stroke, and HIV, have declined (Alzheimer's Association, 2020).

Alzheimer's disease currently affects 5.8 million Americans age 65 years and older according to the Alzheimer's Association's 2020 Facts and Figures report. Due to a substantial demographic shift, an unprecedented number of individuals are entering the age-ranges associated with the greatest risk for Alzheimer's disease. Although age is not a cause of Alzheimer's disease, the prevalence of AD is age-related and affects 3% of people age 65-74, 17% of people age 75-84, and 32% of people age 85 and older (Alzheimer's Association, 2020). The total number of those diagnosed with Alzheimer's disease is expected to increase to 13.8 million Americans by 2050 (Alzheimer's Association, 2020), and the prevalence of AD in the US is expected to triple by 2060, as the rates of diagnosis for underrepresented groups are expected to accelerate (Matthews et al., 2018).

Alzheimer's disease is a neurodegenerative condition, which causes a gradual decline in global cognitive functioning. Although dementia is most commonly associated with memory loss, there are also other symptoms, such as impairments in planning, decision making, and abstract thinking, as well as language difficulties and motor problems in the later stages of the disease. Alzheimer's disease can appear with or without neuropsychiatric symptoms.

Known associations

Beller and Wagner (2018) noted that few studies have compared the effects of social isolation and loneliness on cognition. Although these constructs are closely related, they have been found to be independently associated with various health outcomes (Cacioppo et al., 2010). For example, researchers have found that social isolation is a better predictor of mortality than loneliness. In the literature, loneliness has been more frequently studied in relation to mental

health, while social isolation has been more frequently studied in relation to cognitive and physical health (Beller & Wagner, 2018).

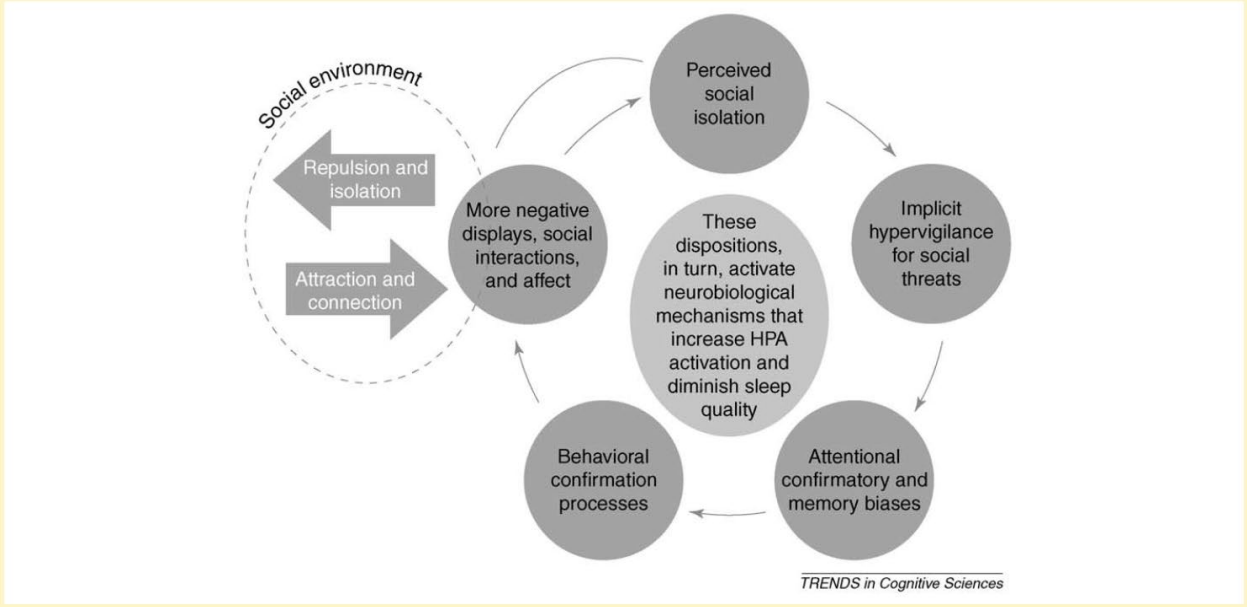
Social isolation and loneliness have been linked with several poor health outcomes and are independently associated with declines in physical, psychological, and cognitive health (Buchman et al., 2010; Cacioppio et al., 2010; Wilson et al., 2007). In addition, decreased socialization during late-life is also associated with greater cognitive decline (James et al., 2011). Other associations have been found between loneliness and cognitive performance, dementia due to Alzheimer's disease, and neurodegenerative biomarkers (Donovan et al., 2016; Donovan et al., 2017; Snorri et al., 2020; Sundstrom et al., 2020; Sutin et al., 2020; Wilson et al., 2007).

Theory

Cacioppo and Hawkley (2009) proposed a potential model for the effects of loneliness on human cognition (Fig. A). This regulatory loop is driven by evolutionary forces, but has a maladaptive effect in modern society. The authors discuss several possible mechanisms that could explain the effect of loneliness on cognition, including increased inflammation, decreased neuroplasticity, decreased social cognition, lower cognitive stimulation, increased cognitive load, elevations in depression, reductions in physical activity, reduction in social interactions, impairments in learning, and disrupted sleep.

Figure A

Cacioppo & Hawkley (2009) – Model of loneliness and human cognition



Hawkley and Cacioppo (2010) attempted to revisit these possible mechanisms and better explain the link between the loneliness model (Fig. A) and mechanisms for cognitive health outcomes. The proposed mechanisms from Figure A were lumped into three broad categories: a) decreased healthy behaviors, b) disrupted sleep patterns, and c) dysregulated physiological functioning, which implicate endocrine, genetic, and immune pathways (Hawkley and Cacioppo, 2010).

Cacioppo and Hawkley (2009) and Hawkley and Cacioppo (2010) base the loneliness model of cognition on the following premise:

> Perceived social isolation is tantamount to feeling unsafe, and this sets off implicit hypervigilance for (additional) social threat… Negative social expectations tend to elicit behaviors from others that confirm the lonely persons' expectations, thereby setting in motion a self-fulfilling prophecy…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 behavioral mechanisms that contribute to adverse health outcomes. (Hawkley & Cacioppo, 2010, p. 220)

While this premise describes the psychological state and resulting behavior of lonely individuals, similar effects in cognition have been observed in socially isolated individuals who may not experience the feelings and behaviors described in the passage above (Lara et al., 2019a). If this is the case, an alternative explanation or theory would have to account for similar cognitive changes seen in the socially isolated, as opposed to the lonely.

Interventions

Transitioning from a lonely to a non-lonely state offers several benefits, such as better self-rated health, lower family strain, and more frequent socializing (Hawkley & Kocherginsky, 2018). In addition, increases in socialization during late-life are associated with less cognitive decline (James et al., 2011). These benefits demonstrate that sustained social engagement contributes to successful aging, as outlined by Rowe and Kahn (1997).

To understand the true effect of interventions, many methodological issues must first be addressed. For example, the measurement of loneliness has been inconsistent across studies and has yet to be standardized. An initial review of intervention studies on loneliness reveals a lack

of rigorous design, poor representative sampling, and inconsistent measures and outcomes (Fried et al., 2020; Masi et al., 2011). Researchers must clarify the impacts of social isolation and loneliness on cognitive health to understand, operationalize, and effectively integrate this knowledge into clinical practice, social engagement interventions, and public policies to mitigate risks of cognitive decline and dementia-level impairment in older adults.

Significance of the Study

This review discusses the similarities and differences found in the existing literature between the associations of social isolation, and of loneliness, on cognitive functioning, Alzheimer's disease, and dementia. Discrepancies between major types of associations are outlined with a focus on describing aspects of methodology that may explain these discordant results, such as cohort effects, variations in the selection or treatment of independent and dependent variables, the inclusion or exclusion of key covariates, or variations in the methods of statistical analysis.

The results can inform a public health approach in addressing the risks to older adult cognition associated with social isolation and loneliness. Understanding the relationship between these factors may inform clinical practices, social engagement interventions, and public policy. The review summarizes what has been found with regard to the effects of social isolation and loneliness, on cognition and incident dementia.

AIMS

A review of empirical findings reported in peer-reviewed, published literature was conducted to compare similarities and differences between social isolation, loneliness, cognition, and dementia in older adults.

Aim 1: Review associations between social isolation and cognitive functioning in older adults.
Aim 2: Review associations between loneliness and cognitive functioning in older adults.
Aim 3: Compare the findings from Aim 1 and Aim 2 and discuss similarities and differences.

METHODS

Search databases and terms

Databases used for this review included Web of Science, Scopus, EBSCOhost, and ProQuest. During a preliminary search of the literature, several search terms were found to be effective at gathering articles related to Aims 1 and 2 above. These search terms were then

formatted into a search string to optimize the resulting articles: ("social isolation" OR "perceived social isolation" OR "loneliness") AND ("Alzheimer's disease" OR "dementia" OR "cognitive impairment" OR "cognitive decline" OR "cognitive functioning" OR "cognitive function" OR "cognitive reserve" OR "cognition").

Operational definitions

Establishing operational definitions of key variables of interest aided in both the search of the literature and the analysis of the results. Articles were not required to adhere strictly to the operational definitions set forth below. Rather, these definitions were used to help clarify and categorize articles into the appropriate subsections contained in the results section.

- Social isolation – An objective measure of an individual's interactions with others (e.g., number of contacts, frequency, duration, etc.) – this concept is interpersonal.
- Loneliness – A subjective, dysphoric feeling related to a disagreement between an individual's expectations and their perceptions of their social relationships (e.g., quality, quantity, etc.) – this is a psychosocial factor at the individual level.
- Cognitive decline – Lower performance on cognitive tasks compared to an individual's previous level of functioning. These changes may, or may not, be clinically meaningful.
- Mild cognitive impairment – Clinically meaningful declines in at least one objective measure of cognition (e.g., memory, executive functioning, language, etc.). This is a clinical diagnosis that does not necessitate a specific biomarker profile.
- Alzheimer's disease – Functional definition – A meaningful impairment in two or more domains of cognitive functioning that interferes with daily life. The functional definition of AD may, or may not, relate to a specific biomarker profile of disease.
- Alzheimer's disease – Biological definition – Biomarkers may consist of blood, imaging, cerebrospinal fluid, etc. These biomarkers are understood within the AT(N) framework (Jack et al., 2018). The biological definition can be ascribed across all functional stages, including prodromal disease, mild cognitive impairment, and dementia-level impairment.
- Dementia – A functional diagnosis that does not specify disease etiology. Similar to the functional definition of Alzheimer's disease described above, it is a meaningful impairment in two or more domains of cognitive functioning that interferes with daily life. However, it does not specify a disease phenotype or biomarker profile.

- Older adults – This term will be defined by chronological age (i.e., years of life). Typically, a benchmark of 65 years old has been established as an arbitrary timepoint that is more aligned with benefit payments in the US, as opposed to human development.

Inclusion Criteria

This review included articles that were peer-reviewed publications beginning January 1, 2000, published in the English language, and focused on longitudinal cohort studies in older adults. The review also includes results from cohort studies done in other countries to highlight any cultural differences or similarities to extend the generalizability of the findings.

Exclusion Criteria

Studies that focused exclusively on loneliness or social isolation in early- or mid-life were excluded, as well as those focusing on older adults living in structured, community settings (e.g., assisted living settings or nursing homes). Additionally, articles were excluded that focused on the COVID-19 pandemic, because extenuating circumstances during the pandemic may confound the natural relationships between the variables and outcomes of interest. To exclude COVID-19 articles, the following alteration was made to the search string: ("social isolation" OR "perceived social isolation" OR "loneliness") AND ("Alzheimer's disease" OR "dementia" OR "cognitive impairment" OR "cognitive decline" OR "cognitive functioning" OR "cognitive function" OR "cognitive reserve" OR "cognition") NOT ("COVID-19").

Search Results

An initial search of the literature was conducted in December 2021 and included four databases: Web of Science, Scopus, EbscoHost, and ProQuest. The primary search string was limited to articles that included the search terms in the title only and during the period dated January 1, 2000 through December 31, 2021.

The search results yielded a total of 1,070 articles (Web of Science = 159, Scopus = 138, EbscoHost = 521, ProQuest = 253). If applicable, search filters on each search engine were then used to refine results according to inclusion/exclusion criteria. The filters used are as follows:

- Web of Science – No search filters available based on the inclusion/exclusion criteria.
- Scopus – No search filters available based on the inclusion/exclusion criteria.
- EbscoHost – academic journals [439], aged: 65+ years [71], aged (65 years & older) [47], aged 80 and over [39], very old (85 years & older) [16].
- PROQUEST - Source type: Journals, Document type: Article, Language: English.

The number of articles yielded after the application of search engine filters totaled 504 (Web of Science = 159, Scopus = 138, EbscoHost = 121, ProQuest = 87). Filtered results from all search engines were exported into Microsoft Excel, and 317 articles were excluded using the remove duplicates feature applied to the title column. The remaining 187 article titles and abstracts were reviewed individually for inclusion/exclusion criteria. Upon abstract review, articles were excluded for the following reasons:

- Not applicable (magazine articles, poster summaries, etc.) – 40
- Animal models – 23
- Caregiver sample – 13
- Non-community dwelling adult sample – 8
- Sensory impairment as primary exposure – 7
- Other conditions as primary exposure – 6
- Interventions – 9
- Early- or mid-life sample – 5

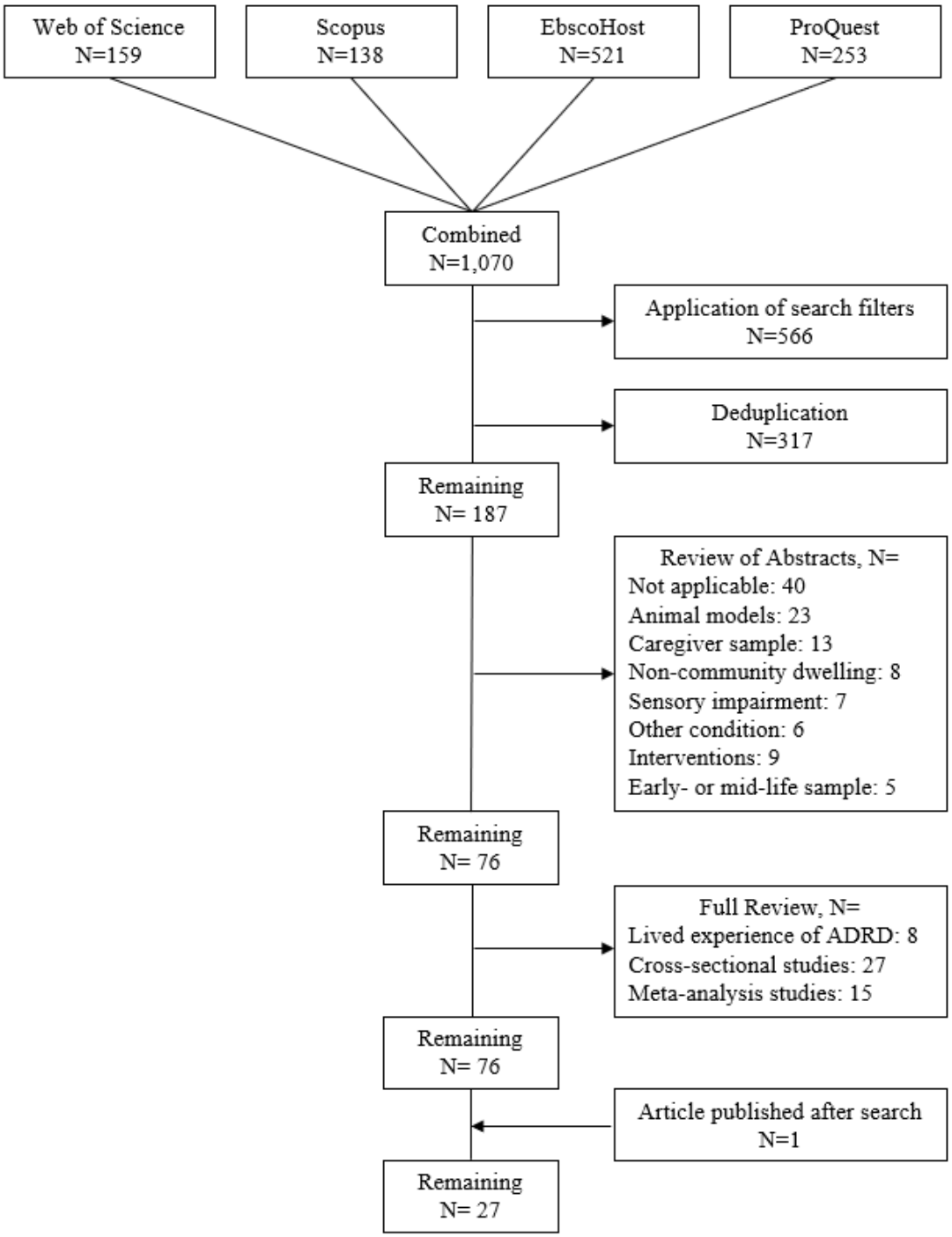
In addition, eight articles were found to describe the experience of loneliness in those diagnosed with MCI, AD, and dementia. The experience of loneliness or social isolation in those living with neurocognitive conditions is an important question with its own implications for standards of care and public health. However, this question is beyond the scope of this review.

Similarly, 27 articles used a cross-sectional study design or had other methodological issues. While these articles were reviewed for additional information that might add to the understanding of associations between social isolation and loneliness in cognitive aging, cross-sectional analysis is not a reliable way to establish causation between exposure and outcome, and may be subject to reverse causation and other issues of directionality. Instead, this review focused on longitudinal, prospective cohorts, which provides the best design for identifying potential causal associations between exposures (i.e., social isolation and loneliness) and outcomes (i.e., cognitive decline, Alzheimer's disease, and dementia).

Lastly, 15 articles were either review articles or a meta-analysis of the literature, as opposed to articles presenting original research. Additionally, Salinas et al. (2022) was published shortly after the initial search and was added to the results because it met the inclusion criteria for this review, which brought the final article count to 27. Each article was reviewed and any data relevant to Aim 1 and Aim 2 were extracted.

Figure B

Diagram of search results and exclusion process



RESULTS

A table describing key details for each study can be found in the Appendix. The summarized information includes first author and year of publication, cohort location, name of cohort, interval of assessment (if available) and duration of study, total number of participants, age of participants (i.e., minimum, mean, standard deviation, and range, if available), percent female, measures used for the independent variables and dependent variables, covariates, and method of analysis.

The relevant results of each study are discussed below in sections organized by study aim. The findings for Aim 1 and Aim 2 have each been divided into two subsections that address a specific aspect of each aim (i.e., cognition and dementia). In Aim 3, the results of Aim 1 and Aim 2 are discussed in subsections devoted to exploring cognition (i.e., social isolation v. loneliness) and dementia (i.e., social isolation v. loneliness).

Aim 1: Associations between social isolation and cognitive functioning

Social isolation and cognition

In all the studies included in this review, higher baseline social isolation was correlated with lower baseline cognitive performance (Evans et al., 2019; Griffin et al., 2018; Shankar et al.; 2013; Zhong et al., 2017). Several studies also found that greater social isolation was associated with lower cognitive function over time (Griffin et al., 2018; Shankar et al.; 2013, Zhong et al., 2017). Griffin et al. (2018) also found that rate of cognitive decline among those who were more socially isolated was steeper ($\beta = -0.09$, 95% CI [−0.16, −0.01]) in participants over 65 years old in the US Health and Retirement Study (HRS) over a 6-year period with evaluations every two years.

Some cognitive associations with social isolation were found to be specific to certain domains of cognitive functioning. For example, in the English Longitudinal Study of Ageing (ELSA), an indexed score of contact frequency, participation in group activities, and number of close relationships was used by Shankar et al. (2013). The authors found that social isolation at baseline led to decreases in verbal fluency, immediate, recall, and delayed recall at 4-year follow up ($\beta = -0.05$ to -0.03, $p < .001$).

Over a 4-year period, with assessment every two years, participants in the Cognitive Function and Ageing Study-Wales (CFAS-Wales) were administered the cognitive test Cambridge Cognitive Exam (CAMCOG), as well as the Lubben Social Network Scale (LSNS-6)

for social isolation. In a study of 1,524 participants over 65 years old, Evans et al. (2018) found that those who were less socially isolated at baseline had better cognitive scores at follow-up (R^2 = 0.17, F (7, 2216) = 64.67, $p < .001$). The results led the author to conclude that loneliness independently accounted for 17% of the cognitive change after adjusting for several covariates, namely age, gender, education, and cardiovascular risk factors.

Additionally, in a study of 1,691 participants from Spain, Lara et al. (2019a) also found that social isolation was associated with lower cognitive scores of verbal fluency, digit span, and composite cognitive scores over a 3-year period. These effects remained significant after removing individuals with depression. This finding supports results discussed above from Evan et al. (2018) that effects from depression are not driving the relationship between social isolation and observed declines in cognitive performance.

Similar findings have been found in non-western cohorts as well. Yu et al. (2020) studied social isolation and cognitive decline in older adults participating in the China Health and Retirement Longitudinal Study (CHARLS) over a 4-year duration. In 7,761 participants, more socially isolated individuals, based on and index score of marital status, contact frequency, and group participation, exhibited lower cognitive functioning across episodic memory ($\beta = -0.05$, $p < .001$) and global cognition ($\beta = -0.03$, $p < .01$), which remained significant after adjustment for the covariates age, gender, education, residence, health behaviors, chronic diseases, and depression.

Gou et al. (2021) reported a similar finding for the CHARLS cohort of Chinese adults 50 years of age and older in regard to episodic memory ($\beta = -0.06$, $p < .001$) across the same duration of time. However, when stratified by gender and controlling for several other covariates, such as age, education, etc., the authors found that for depressed, older Chinese women the association between social isolation and memory remained ($\beta = -0.08$, $p < .001$), while the association did not remain significant in depressed, older Chinese men ($\beta = -0.03$, $p = 0.350$).

Joyce et al. (2021) also observed a gender difference in their study of Australian older adults, ages 70-94, in the ASPREE Longitudinal Study of Older Persons (ALSOP). The authors found that socially isolated women with low social support had poorer cognitive performance outcomes ($\beta = -1.17$, $p < .001$) compared to men on three tests of cognition: the Controlled Oral Word Association Test (COWAT), the Symbol Digit Modalities Test (SDMT), and the Hopkins

Verbal Learning Test-Revised (HVLT-R). However, the authors did not find an association between social health and longitudinal, cognitive decline over a mean duration of 3.1 years.

Social isolation and dementia

In a seminal paper, Wilson et al. (2007) reported on a study of 823 participants in the Chicago area who were enrolled in the Rush Memory and Aging Project (MAP) and found that greater social activity was associated with a lower risk of developing Alzheimer's Disease (RR = 0.52, 95% CI [0.34, 0.79]), but that social network size was not associated with Alzheimer's disease risk (RR = 1.01, 95% CI [0.97, 1.05]). While social activity and social network size may, or may not, be appropriate proxies for social isolation, several additional studies have taken up the specific question regarding the association between social isolation and dementia risk.

In a study of 2,173 participants in the Amsterdam Study of the Elderly (AMSTEL), Holwerda et al. (2014) found no association between dementia risk and the social isolation index used in their multivariate analysis. The social isolation index consisted of living situation, marital status, and social support. Dementia status was determined by family report, via the Geriatric Mental State (GMS) questionnaire and a battery of computerized neuropsychological tests, known as the Automated Geriatric Examination for Computer Assisted Taxonomy (AGECAT).

Zhou et al. (2018) studied 7,867 participants from the Chinese Longitudinal Health Longevity Study (CLHLS). They measured dementia by self- or proxy-report, in response to two questions: 1) Are you suffering from dementia? 2) Have you been diagnosed by a physician? If both questions were answered in the affirmative, the case was categorized as incident dementia. Measures of social isolation included living alone, marital status, and social support. The authors found no significant associations between social isolation and dementia when fully adjusting for covariates in the model.

Joyce et al. (2021) also found that there was no predictive relationship between any measure of baseline social health and later dementia over a mean of 4.4 years of follow-up. Social health consisted of social support, social isolation, and loneliness. Social isolation was derived from the LSNS-6, which includes self-report on frequency of community engagement and contact with relatives and friends. In this large study of 11,498 Australians, social isolation at baseline produced a hazard ratio that conferred no additional risk for developing dementia (HR = 1.00, p = 0.99). The authors also note that no differences were observed when depressive symptoms were removed from the model.

Lastly, in a study of 6,677 participants in ELSA, Rafnsson et al. (2021) also examined the relationship and possible association between social isolation and dementia. The authors found that an indexed score of social isolation, which was assessed by the frequency of contact with family and friends, was not associated with dementia, as measured by self- or proxy-report, over an average duration of 6.25 years from baseline.

Summary of Findings:

The impact of social isolation appears to differ in its relationship to cognitive performance and risk of dementia. While social isolation was significantly associated with declines in cognitive performance, there were no reported significant associations between social isolation and incident dementia. Although, the associations between social isolation and cognition were all in the same direction (i.e., social isolation was associated with cognitive decline), the effect sizes for these associations were generally small. Key covariates in the associations between social isolation and cognition were gender and depression, which resulted in mixed findings for two studies (Gou et al., 2021; Joyce et al. 2021). No key covariates were identified in studies examining social isolation and incident dementia.

The associations between social isolation and cognition suggest that effects may be domain specific, as the results of domain specific testing were mixed (e.g., verbal fluency). In addition, these studies did not provide information about transient versus chronic social isolation, which may have differential cognitive health outcomes. This is may be especially important gap in knowledge for public health policy and interventions, given the practice of social distancing during the COVID-19 pandemic to mitigate risks of infection. Lastly, mild cognitive impairment (MCI) was not studied as a specific outcome in either studies of cognition or dementia, which may have helped further contextualize cognitive outcomes in terms of clinical relevance.

Aim 2: Associations between loneliness and cognitive functioning

Loneliness and cognition

Loneliness was found to be associated with lower cognitive performance at baseline in a majority of the studies reviewed, as well as future decline, and a steeper rate of cognitive decline (Hajek et al., 2019; Lara et al., 2019a; Luchetti et al., 2019; Shankar et al., 2013; Wilson et al., 2007; Yin et al., 2019; Zhong et al., 2017; Zhou et al., 2019). It was the most frequently reported association in the literature, as it was found in over half of the articles in this review.

In 823 participants that were part of the Rush Memory Aging Project (MAP), Wilson et al. (2007) found that the primary areas of cognition affected by loneliness were semantic memory, processing speed, visuospatial perception, and global cognition. Cognition was evaluated by the annual administration of 20 cognitive tests, including the Mini-Mental State Examination (MMSE); tests of episodic, semantic, and working memory; and executive function. The assessment of loneliness was evaluated using a modified version of the de Jong-Gierveld Loneliness Scale, which includes five items: "I experience a general sense of emptiness", "I miss having people around", "I feel like I don't have enough friends", "I often feel abandoned", and "I miss have a really good friend." Loneliness was found to have a significant association with cognitive decline based on each of the cognitive measures ($p < .01$).

Shankar et al. (2013) found that while loneliness led to lower immediate ($\beta = -0.05$, $p < .001$) and delayed ($\beta = -0.03$, $p = .02$) memory scores, changes in verbal fluency did not reach significance. These associations were assessed in 6,034 participants in ELSA over a duration of four years. Loneliness was measured by a frequently used, 3-item modification of the UCLA Loneliness Scale (Hughes et al., 2004). Out of the many measures of cognitive function in ELSA, the authors chose to focus on an immediate and delayed list learning task for memory and a semantic, verbal fluency task, which they considered a measure of executive functioning.

Yin et al. (2019) also found that loneliness was associated with cognitive decline over a 10-year period, independent of depression. In their study of 5,885 UK participants in ELSA, assessments were completed every two years, which included list-learning and semantic fluency tasks as a measure of cognition and the 3-item Hughes Scale as a measure of loneliness. Yin et al. (2019) found that loneliness predicted a faster rate of decline for memory ($\beta = -0.07$, SE = 0.01, P = .001). However, in contrast to Shankar et al. (2013), individuals who were lonelier were found to have a greater rate of decline in verbal fluency ($\beta = -0.09$, SE = 0.03, $p = .003$).

The cognitive measure used by Hajek et al. (2019) was unique. This study of 6,420 participants, age 40 years and older (M = 61.37) from the German Ageing Survey, utilized the digit symbol test. Although the digit symbol test is a common measure of processing speed and perceptual motor speed used in cognitive research, it was the only study in this review that used it as a cognitive outcome. However, as with other studies, the association between greater loneliness and poorer cognitive performance was found to be significant ($\beta = -1.13$, $p < .01$) and remained significant when adjusting the model for depressive symptoms and other covariates.

In the CLHLS, Zhong et al. (2016) studied 2,995 Chinese participants, age 65 years and older. The authors examined both transient and chronic loneliness, using a single-item question of loneliness from the Center for Epidemiologic Studies Depression Scale (CES-D) over six years, and found both to be related to lower MMSE scores compared to non-lonely participants. They found that older adults who experienced chronic loneliness had greater declines in cognitive performance than those who experienced transient loneliness. For individuals who were chronically lonely versus transiently lonely, the authors found an effect 2.59 times greater (chronic loneliness: $\beta = -1.017$, $p = .003$; transient loneliness: $\beta = -0.392$, $p = .041$). The effect size was reduced when the authors controlled for potential confounders, but remained significant (chronic loneliness: $\beta = -0.640$, $p = .035$; transient loneliness: $\beta = -0.389$, $p = .029$).

Zhong et al. (2017) then expanded on the work of their previous study, incorporating CLHLS data from a much larger sample of 14,199 Chinese participants, age 65 years and older, over nine years with assessment every three years. Loneliness was measured using a single-item question and cognitive outcomes were evaluated using the MMSE. They found that severe loneliness was significantly correlated with future cognition ($p \leq .023$) and associated with future cognitive decline ($\beta = -0.045$, $p < .001$) in Chinese older adults ($M = 84$; range 65-100).

In the US, Donovan et al. (2017) studied 8,382 participants in HRS. Participants had assessments every two years, which consisted of single-item question on loneliness and two measures of cognition (i.e., the Telephone Interview for Cognitive Status (TICS) and proxy-rated scores on the Informant Questionnaire of Cognitive Decline in the Elderly (IQCODE)). When controlling for covariates, the results demonstrated that loneliness was an independent risk factor for cognitive decline, which accounted for an approximately 20% faster, relative rate of decline compared to those who did not report loneliness over a 12-year duration.

The authors also found an interesting association between loneliness, cognition, depression, and time. When controlling for depression over time, the effect size of loneliness on cognitive decline remained significant, but was reduced. Loneliness alone was a significant predictor of future cognitive decline ($\beta = -0.2$, 95% CI [−0.3, −0.1], $p = .002$), but adding depression to the model resulted in half the predictive value ($\beta = -0.1$, 95% CI [−0.2,0.1], $p = .08$).

Similar findings were observed in a large European cohort of 14,114 participants in the Survey of Health, Ageing, and Retirement in Europe (SHARE). Luchetti et al. (2019) found that,

after controlling for age, there was a 31% increased risk of cognitive impairment (HR = 1.31, 95% CI [1.19,1.44]) for participants that reported loneliness on a single-item question. When using a 3-item loneliness scale, the increased risk of developing cognitive impairment was over 50% (HR = 1.56, 95% CI [1.32, 1.84]) for those reporting any loneliness. Among those who reported frequent loneliness, the risk for cognitive impairment was more than double, compared to those who were never lonely (HR = 2.07, 95% CI [1.46, 2.95]). The authors also found a 50% reduction in the effect size between loneliness and cognitive impairment when adjusting for covariates such as depression, but the association remained significant.

Zhou et al. (2019) found a gender effect among 6,898 older adults in China over three years. While the unadjusted association, including both men and women, was found to have a 30% increased odds ratio for cognitive impairment given loneliness (OR = 1.30, 95% CI [1.01, 1.69]), the observation held for men (OR = 1.30, 95% CI [1.01, 1.69]), but not women (OR = 0.98, 95% CI [0.81, 1.19]), when adjusted for covariates. To summarize, the authors state that although loneliness is more commonly reported in older Chinese women, the impact of loneliness on cognition may be more meaningful in older Chinese men.

Lara et al. (2019a), found an association between loneliness and lower cognitive scores, over a three-year time period, in a nationally representative Spanish cohort. The study utilized the 3-item Hughes Loneliness Scale and a battery of cognitive tests. The authors found significant declines in delayed recall, digit span, and a composite score of cognitive functioning ($\beta = -0.01$ to $\beta = -0.11$, $p < .05$). The authors also found in a sensitivity analysis that the effect of loneliness on cognition was still significant when individuals with depression were excluded from the study. They concluded from this that the effect of loneliness on cognition is not merely a proxy for effects driven by depression.

Power et al. (2020) attempted to further clarify the role of depression by running a mediation analysis between loneliness and cognitive functioning. In a study of 7,433 participants in the Irish Longitudinal Study on Aging (TILDA), the authors found that in addition to the direct effect of loneliness on cognition ($\beta = -0.103$, $p < .001$), there is also a pathway through depression ($\beta = -0.020$, $p < .005$). Importantly, they did not observe the same indirect effect via anxiety ($\beta = -0.000$, $p = .958$). As a result, the authors conclude that depressive symptoms account for 19.4% of the direct effect observed between loneliness and cognitive impairment. The measures used in this study were a 5-item version of the UCLA Loneliness Scale and list

learning (i.e., immediate and delayed), verbal fluency (i.e., animals), and global cognition (i.e., MMSE) tasks for cognition.

A minority of studies had conflicting findings, which challenge the associations between loneliness and future cognitive decline (Griffin et al., 2018; Kyrolainen et al., 2021; Wang et al., 2020; Yu et al., 2020). For example, in a study of 6,654 US participants in HRS who were followed over six years, with assessments every two years, Griffin et al. (2018) found a baseline correlation between loneliness and cognition, but found that loneliness was not correlated with future cognitive decline ($p = .9051$). The authors noted that their findings challenged previous findings, especially given that their study used the same cohort as Donovan et al. (2017). They suggest that the different findings may be due to selection of the loneliness instrument (i.e., the 3-item Hughes Loneliness Scale used in Griffin et al., 2018, vs. the single-item loneliness question in the CES-D used in Donovan et al., 2017).

In unadjusted models, Yu et al. (2020) found a significant association between loneliness and cognition that predicted cognitive decline over four years in lonely individuals. The cohort consisted of 7,761 Chinese participants from CHARLS, who were assessed for loneliness with a single-item question and cognitive index score consisting of the TICS, orientation, constructions, and serial sevens. However, after adjusting to covariates, the association failed to remain significant.

Wang et al. (2020) found that loneliness was not significantly associated with cognitive decline over a 20-year follow-up period. This study included 713 UK participants from the Cambridge City Over-75 Cohort (CC75C), which was confined to the oldest-old ($M = 86$). Cognitive measures used the MMSE and loneliness was assessed via a self-reported single-item question. The authors propose that this discordant finding is due to adjustment for cohort effects, follow-up time, and other covariates. However, it also raises a consideration if age may play a more fundamental role in the associations between social loneliness and cognition.

The same was true for Kyrolainen et al. (2021). A large study of 12,320 participants in the Canadian Longitudinal Study on Aging (CLSA), evaluated loneliness based on a single-item question and determined cognitive outcomes based on a battery of tests, such as the Rey Auditory Verbal Learning Test (RAVLT), Mental Alternation Test (MAT), semantic fluency (animals), phonemic fluency (FAS), prospective memory test, and the Stroop test. The results

also found an association between loneliness and future cognitive decline in unadjusted models, which failed to remain significant after adjusting for age, gender, living area, education, etc.

Loneliness and Dementia

Wilson et al. (2007) found that loneliness was associated with the clinical diagnosis of Alzheimer's-type dementia, over a 4-year period with annual assessments. For every point increase on the 5-item de Jong-Gierveld scale for loneliness, the risk of AD increased by 51% (RR = 1.51, 95% CI [1.06, 2.14]). Those who endorsed the single-item loneliness question on the CES-D were found to be 86% more likely to develop AD (RR = 1.86, 95% CI [1.10, 3.14]). The difference in risk for future AD between someone reporting high loneliness versus low loneliness was over two times greater. The authors also found that the risks associated with loneliness and developing AD remained significant when controlling for race/ethnicity, income, disability, vascular risk factors, and social isolation. However, controlling for depression decreased the risk of AD by 16%.

Holwerda et al. (2014) also found that when controlling for vascular risk, depression, and other covariates, older adults who experience loneliness, compared to those that do not endorse such feelings, have increased odds for developing dementia (OR = 1.64, 95% CI [1.05, 2.56]) over a 3-year period. Similar results were found by Zhou et al. (2018) in the CLHLS cohort of older adults in China. Those over the age of 65 who were experiencing loneliness at baseline had increased odds of developing dementia (OR = 1.31, 95% CI [1.11, 1.56]) over a 3-year period, after controlling for various demographic, lifestyle, and health factors.

These findings were once again confirmed by Sundstrom et al. (2018) in a study of 1,905 Swedes who participated for up to a 20-year duration in the Betula Prospective Cohort Study. The authors found that when controlling for covariates (i.e., sociodemographic, medical and psychiatric conditions, activities of daily living, etc.) the increased risk for developing dementia for lonely individuals was more than 50% higher for all-cause dementia (HR = 1.51, 95% CI [1.01, 2.25]) and 150% higher for Alzheimer's disease (HR = 2.50, 95% CI [1.44, 4.36]).

Sutin et al. (2020) conducted a large study of 12,030 US participants in HRS with evaluations every two years over a 10-year duration of time. Loneliness was evaluated using the 3-item Hughes Loneliness Scale and cognitive status was assessed using a composite score calculated from three items on the TICS. The authors found that for every one-point increase in loneliness, it conferred a 40% increased rick of dementia (HR = 1.40, 95% CI [1.26, 1.56]). This

association was independent of genetic risk (HR = 1.30, 95% CI [1.16, 1.46]). They also found that these results were preserved when accounting for race, ethnicity, gender, education, and depression. Only age produced a differential effect on developing dementia, as younger-lonely individuals were found to have more risk for dementia than older-lonely individuals.

An ELSA study of 6,677 older adults in the UK over 6 years, conducted by Rafnsson et al. (2021), also used the 3-item Hughes Loneliness Scale, but relied on self- or proxy-report to capture dementia status. The authors found that for every point increase in loneliness there was a 40% increased risk of dementia (HR = 1.40, 95% CI [1.09, 1.80], p = .008). These results remained significant after controlling for possibly confounding factors, such as age, sex, race/ethnicity, and education.

The findings of Kim et al. (2021), in a study of 2,476 Swedish participants in the Swedish Twin Registry, also reflect the nuance of age, changes in loneliness over time, and dementia risk. For this study, the authors used a single-item question for loneliness and an expert consensus panel for dementia diagnosis. When their models were based on intake and centered at age 60, even mildly elevated levels of loneliness at baseline conferred a greater risk of developing dementia (HR = 1.43, 95% CI [1.33, 1.52]).

As an interesting caveat, the authors found that the difference between baseline loneliness and loneliness at the last assessment was statistically significant ($p < .001$). This led the authors to suggest that loneliness tends to increase with age. When they accounted for this change in their model, their conclusion was that change in loneliness with age did not significantly correlate with dementia risk, regardless of environmental and genetic confounds.

However, Akheter-Khan et al. (2021) found in a sample from 2,880 US participants in the Framingham Heart Study (FHS), that persistent loneliness was an independent risk factor, when controlling for genetic, apolipoprotein E (APOE) status and depression. Loneliness was assessed using a single-item questions from the CES-D and dementia status was determined by expert consensus. The difference between older adults who report persistent loneliness (HR = 1.91, 95% CI [1.25, 2.9]; $p < .01$) versus transient loneliness (HR = 0.34, 95% CI [0.14, 0.84], $p < .05$) is over five times the risk.

Lastly, Salinas et al. (2022) studied 2,308 participants in FHS over a 10-year period. The exposure to loneliness was measured using a single-item (CES-D) and dementia outcomes were assessed using the MMSE, a battery of neuropsychological tests, and diagnosis by expert

consensus. In addition, the authors also included MRI of the head to examine any brain changes that may be associated with underlying pathology, based on volumetrics and white-matter hyperintensities. Covariates that were selected for the study included age, sex, education, depression, social isolation, vascular risk factors, and APOE status.

For the analysis, Salinas et al. (2022) first stratified the sample into two groups by age (i.e., age less than 80 and age 80 and older) because it is known that amyloid and tau, hallmarks of Alzheimer's disease, have a greater neuropathological burden in older adults. They also relied on previous literature which suggested that associations between loneliness and risk of dementia may vary between young-old adults and old-old adults. These age-related effects of pathology and loneliness on cognition, may have resulted in skewed outcomes. Therefore, the authors stratified participants by age.

They found that there was no association between loneliness and participants in the 80-and-older group, but in the under-80 group the risk of dementia given loneliness was over twice as likely (HR = 2.27, 95% CI [1.32, 3.91]). In addition, they also found that lonely, APOE e4 non-carries in the under-80 group had three times the risk of developing dementia (HR = 3.03, 95% CI [1.63, 5.62]). Lastly, in a subset of 1,611 with MRI data, lonely participants were found to have lower, total cerebral volume and more white-matter hyperintensities. This study is the first to present compelling data linking loneliness to dementia risk via biological pathways (i.e., genetic risk and brain atrophy).

Summary of Findings

Loneliness in older adults was associated with both cognition and dementia. The evidence over the course of the entire review was most abundant for the association between loneliness and cognition, but the results of loneliness on cognition were somewhat mixed. A majority of studies reported that increased levels of loneliness were associated with decreased cognition, while a minority of studies either found a non-significant relationship or an association that failed to remain significant when covariates were considered. Key covariates that emerged for loneliness and cognition were age, gender, and depression. Effect sizes varied from small to moderate for significant associations between loneliness and declines in cognition.

However, the associations between loneliness and dementia demonstrated a much larger effect than any other relationship reviewed across all studies. The associations between loneliness and dementia were also robust, remaining significant even after controlling for several

covariates, such as depression, education, gender, etc. The only covariate of note was age, which drove a differential effect between the young-old and old-old in Salinas et al. (2022). These findings, regarding the associations between loneliness and dementia, seem to be the most important and consequential, given their effect size and very serious implications.

As in the summary for Aim 1, a similar gap in the literature was found for Aim 2 regarding a lack of diagnostic classification for MCI. This is important for contextualizing what cognitive declines associated with social isolation and loneliness may mean clinically. The literature also offers little information on disease pathology. Other than Wilson et al. (2007) and Salinas et al. (2022), no other studies using longitudinal cohorts included measures of AD pathology or biomarkers. However, this has been explored in cross-sectional studies, such as Donovan et al. (2020), which found that cortical amyloid burden was 7.5 times more likely in lonely versus non-lonely groups. Future research incorporating measures of brain pathology via biomarkers in longitudinal cohorts will further explain underlying mechanisms.

Aim 3: Compare findings from Aim 1 and Aim 2

Cognition (social isolation v. loneliness)

Both social isolation and loneliness at baseline were correlated with lower baseline cognition. Additionally, both predicted future declines in cognitive performance and a faster rate of decline. The effect sizes of associations between social isolation and loneliness on cognition were both sensitive to the addition of covariates, namely age, gender, education, and depression, typically leading to smaller effects or differential outcomes. For example, both Yu et al. (2020) and Joyce et al. (2021) found that socially isolated women – age 50 years and older and age 70 years and older, respectively – had poorer cognitive outcomes than men. However, Zhou et al. (2019) found that loneliness in Chinese participants, age 65 years and older, had a greater effect on cognition in men than in women, despite the fact that loneliness was more commonly reported by women in their study and in the general population.

Associations between loneliness and cognition may be more robust than between social isolation and cognition. In general, the associations between loneliness and cognition had larger effect sizes and were less likely to be meaningfully changed by the addition of demographics and other covariates, including depression. Additionally, adding loneliness into models built for social isolation resulted in a lower effect size, while adding social isolation into models built for loneliness did not substantially impact effect size.

Out of the seven studies that provided information about associations between social isolation and cognition, five found a statistically significant association (Evans et al., 2018; Griffin et al., 2018; Lara et al., 2019a; Shankar et al., 2013; Yu et al., 2020) and two had mixed results (Gou et al., 2021; Joyce et al., 2021). In the two studies that did not find an association, gender was a key covariate. Joyce et al. (2021) did not find an association initially, but did when stratifying by gender. Gou et al. (2021) also had mixed results when stratifying by gender, finding an association between social isolation and cognition in Chinese women, but not men. Of the seven total studies, two of three studies focusing on depression found that associations remained when adjustments were made for depression, while one provided a mixed result.

A total of 15 studies reported information about associations between loneliness and cognitive decline. Out of these 15 studies, 10 found a significant association between loneliness and cognitive decline (Donovan et al., 2017; Hajek et al., 2019; Luchetti et al., 2019; Shankar et al., 2013; Wilson et al., 2007; Zhong et al., 2016; Zhong et al., 2017), four did not find an association (Griffin et al., 2018; Kyrolainen et al., 2021; Wang et al., 2020; Yu et al., 2020), and one had mixed results (Zhou et al., 2019). Key covariates included depression, age, and gender, but the results of including these covariates were mixed.

Depression did not have an effect on significant associations between loneliness and cognition in six studies (Donovan et al., 2017; Hajek et al., 2019; Luchetti et al., 2019; Lara et al. 2019a; Yin et al., 2019; Power et al., 2020). Mixed results were found in Zhou et al. (2019) when controlling for gender and other covariates. Age, as a covariate, was also found to have mixed results. Luchetti et al. (2019) found that age did not affect a significant association between loneliness and cognition, while Wang et al. (2020) did not find an association of significance when incorporating age.

Dementia (social isolation v. loneliness)

Relatively few studies examined the association between social isolation and dementia risk. Of the five that were included in this review, all concluded that there was not a statistically significant association between social isolation and risk of incident Alzheimer's disease or dementia (Holwerda et al., 2014; Joyce et al., 2021; Rafnsson et al., 2021; Wilson et al., 2007; Zhou et al., 2018). These findings were not affected by adjusting for any covariates, including demographics, proxies for socioeconomic status (SES), depression, daily functioning, other medical conditions, etc.

However, the most compelling and consequential evidence regards the increased risk of Alzheimer's disease and dementia for lonely, older adults. Several studies examined the relationship between loneliness and dementia and found a significant and robust association, such that even when controlling for covariates, including demographics, depression, other health factors, etc., the association between loneliness and dementia remained significant with a relatively large effect size.

Of the eight studies examining associations between loneliness and incident dementia, six found an association (Akheter-Khan et al., 2021; Holwerda et al., 2014; Sundstrom et al., 2018; Sutin et al., 2020; Wilson et al., 2007; Zhou et al., 2018) and two had mixed results (Kim et al., 2021; Salinas et al., 2022). Key covariates included depression, age, and genetic status. Five studies found associations when controlling for depression (Akheter-Khan et al., 2021; Holwerda et al. 2014; Sundstrom et al., 2018; Sutin et al., 2020; Zhou et al., 2018). Controlling for age had mixed results in three studies (Kim et al., 2021; Salinas et al., 2022; Sutin et al., 2020). Genetic status supported associations in two studies (Akheter-Khan et al., 2021; Salinas et al., 2022).

DISCUSSION

In total, 27 longitudinal, cohort studies were included in this review. The results of this review clearly outline the relationships between social isolation, loneliness, cognition, and dementia. Given the findings, there are several recommendations for future research, public health interventions, and policy that can help close remaining gaps in knowledge, while also addressing concerns raised by the most compelling and supported evidence.

Future Research

Comparing results across longitudinal cohort studies proved to be challenging because several of the study components have not been standardized. Several points of interest below highlight these discrepancies in study designs and methods observed in this review, including nomenclature, follow-up period, covariates of interest, instrumentation, and methods of analysis.

Terminology

Aside from disagreements about the constructs of social isolation and loneliness, there also seems to be a disagreement about what terms should be used for each. Standardizing the naming conventions for each construct — i.e., social isolation and loneliness — would help clarify the literature a great deal. Naming that contributes to ambiguity includes "perceived

social isolation", "subjective social isolation", "objective loneliness", etc. Developing a standard definition for the two primary constructs would be helpful for future studies, especially considering the cross-cultural evidence of these phenomena.

Follow-up period

Unfortunately, the elapsed time between assessment of the independent and outcome variables is often not clearly reported in the literature. Most cohort studies use multiple waves of data collection, which produce varying timepoints for assessment. The time period between baseline and follow-up varied dramatically across studies from annually to once every two or three years. The range for study duration is even wider, as researchers selected cases from as little as two years of observation to up to 20 years of observation. Analyses involving time-to-event modeling are even more opaque, as a dementia diagnosis may occur outside of the designated follow-up period for assessments.

Such dramatic differences in follow-up period warrants further consideration, as time variance is not generally accounted for, with the exception of Griffin et al. (2018) and Wang et al. (2020). Ultimately, results may not be able to be compared to one another. Time variance is especially relevant because certain studies found an age-dependent effect that may change the strength of associations over time, depending on the age-range into which sub-groups fall within a cohort. Longitudinal studies will continue to produce data that can help explain time- and/or age-dependent effects, but intervals between assessments should be standardized and both the mean and range of time from initial assessment to outcome assessment should be reported.

Covariates

In this review, common covariates of interest emerged. Covariates that seemed to most reliably differentiate study results included age, gender, and depression. Notably, the studies reviewed included many other covariates in their models, but they did not typically yield differential findings. As a results, it may be best to prioritize collection of the three above and discard others that have not produced meaningful insights.

In addition, many of the studies did not report on race/ethnicity or proxies for socioeconomic status, such as occupation, income, education, etc. Of those that did, they did not find an association that would have led to a different outcome based on these factors (Luchetti et al., 2019; Sutin et al., 2020). However, the reporting of demographics should be standardized.

This would have several benefits, such as improving confidence in generalizability, allowing for stratified analysis, and exploring moderators that may be related to specific conceptual models.

Instrumentation

Kryolainen et al. (2021) highlighted that the CES-D single-item loneliness measure used in a majority of the studies reviewed may have low predictive validity and low test-retest reliability. The single-item CES-D measure asks if the participant felt lonely during the past week, which may not accurately capture a participant's experience in longitudinal studies that typically evaluate participants every 1-3 years. This may have an impact on the reliability of results in these studies.

In addition, the traditional use of validated instruments may not be valid in situations that challenge the traditional constructs of social isolation and loneliness. For example, during COVID-19 social distancing, many people would likely endorse two out of the three questions on the Hughes Loneliness Scale by the very nature of social distancing guidance, but this is not necessarily an endorsement of loneliness. Kim et al. (2021) recommends the use of a multivariate measurement of loneliness and suggests that it may more accurately reflect the construct and produce more reliable findings than a single-item measure.

Cognitive measures and clinical outcomes should also be standardized and harmonized across studies. Most of the cognitive measures used have been well-established and validated (e.g., MMSE, TICS, etc.). However, scoring can vary from study to study, which may lead to different outcomes between studies. In addition, many clinical outcomes for dementia were based on either a composite score of cognition or an expert consensus panel. Composite scores of cognition, which are unvalidated combinations of multiple test scores, may inaccurately reflect cognitive status, as domain-specific strengths and weakness are typically not captured. In addition, while consensus panels have been shown to be adequate for clinical research, there is inevitably disagreement and uncertainty that may not be captured, which may contribute to misclassification.

Method of analysis

The methods of analysis between studies varied, which may also prevent the comparison of results across studies. Strategies used for analysis included multiple linear regression, multiple logistic regression, lagged dependent variable regression, Cox proportional hazards, Kaplan-

Meier plots, generalized estimating equations (GEE), moderation analysis, imputation, etc. A full list of methods of analysis can be found in the Appendix.

Although the measures used in these studies have been found to be both reliable and valid (e.g., Hughes Loneliness Scale, CES-D, etc.), a wide range of methods were applied to the treatment of these scores for analysis that may fundamentally change the validity of the instrument. For example, many studies dichotomized the 3-item loneliness, as opposed to treating it as a continuous variable. Standardizing the treatment of validated measures would be valuable in cross-study comparisons.

Lastly, information regarding loss-to-follow-up was not typically reported. However, this information may have important implications, as loss-to-follow-up may also be meaningfully related to social isolation, loneliness, cognition, dementia, and all-cause mortality. As a result, analysis and reporting should also incorporate information about loss-to-follow-up.

Public Health Implications

Studies in this review have demonstrated that loneliness is more significant for incident dementia in the young-old compared to the old-old. These findings may provide a counterfactual to the Wilson et al. (2007) conclusion that loneliness is not associated with disease pathology, because the authors' conclusions were drawn based on an autopsy series of advanced AD cases with a mean age of 86.1 years old.

Fifteen years after Wilson et al. (2007) found that loneliness was not associated with the underlying, biological hallmarks of Alzheimer's disease (i.e., amyloid deposition and tau), there may be renewed interest in exploring the neurobiological link between loneliness and dementia, as reintroduced by Salinas et al. (2022). These findings can help inform clinical practice, social engagement interventions, and public policy, regardless of underlying mechanisms.

Clinical practice

Many of the studies reviewed suggested that loneliness may be a prodromal feature of dementia (Donovan et al., 2017; Holwerda et al., 2014; Lara et al., 2019a; Sundstrom et al., 2019; Zhong et al., 2017). Sundstrom et al. (2019) urge health professionals to pay attention to reports of loneliness by older adults. In addition, Lara et al. (2019a) recommends that screening for loneliness in clinical settings could identify older adults at high risk for cognitive decline. Similarly, Donovan et al. (2017) envisions loneliness as an easily measured clinical marker that may be etiologically linked to cognitive decline and dementia.

Two recommendations for clinical practice, based on the results of the review and formed with the goal of identifying early-Alzheimer's disease, are listed below:

- Socially isolated and lonely older adults should receive a referral for a baseline neuropsychological evaluation, as a point of comparison for future cognitive changes.
- Severely and chronically lonely, older adults should be tested for Alzheimer's disease biomarkers to assesses the possible presence of early, neurodegenerative pathology.

This review has found that socially isolated and lonely older adults are at increased risk for declines in cognition, beyond normal age-related declines. Patients that report they are socially isolated or lonely to their primary physician should be given a referral to receive a neuropsychological evaluation. A referral would be beneficial for either transient or chronically, socially isolated or lonely older adults. This evaluation can serve several purposes, such as creating a detailed profile of cognitive strengths and weaknesses, serving as a baseline for future changes in cognition, and the evaluation of other psychiatric symptoms.

Reports of severe loneliness (e.g., coupled with depression) or chronic loneliness may be an important indicator of dementia risk that may warrant screening for Alzheimer's disease biomarkers. This is especially relevant for general practitioners and geriatricians, as older adults at the earliest stages of AD may not seek a full neurological assessment, or other testing for Alzheimer's disease, as cognitive changes like forgetfulness may be seen as normal, age-related changes. If biomarker results fall in a range that is concerning, the patient should receive a referral to a sub-specialty neurologist for a full diagnostic workup.

Social engagement interventions

Mitigation strategies, such as social engagement interventions, should be explored to prevent transient loneliness from becoming chronic loneliness in older adults. These strategies to reduce risk can be delivered through a number of ways. However, it is currently unknown what strategies may be most effective. An extensive review of social interventions designed to prevent loneliness in older adults has been published elsewhere (Masi et al., 2011). The authors found "… a small but statistically significant effect of loneliness reduction interventions…" (Masi et al., 2011, p. 259). Specific strategies include enhancing social support, increasing social engagement, and addressing deficits in social cognition.

Many of the studies reviewed discussed the need for public health interventions to benefit socially isolated and lonely older adults (Akheter-Khan et al., 2021; Donovan et al., 2017; Evans et al., 2019a; Lara et al., 209; Luchetti et al., 2019; Power et al., 2022; Shankar et al., 2013; Sutin et al., 2020; Yin et al., 2019; Yu et al., 2020; Zhong et al., 2016; Zhong et al., 2017; Zhou et al., 2019). Zhong et al. (2017) suggests that social interventions for older adults might not only improve cognitive health, but may also enhance emotional well-being. Additionally, social interventions have been found to enhance physical health (Fried et al., 2004). There may also be benefits beyond the individual level, extending to caregivers, friends, family and society (Zhou et al., 2019).

In addition to what interventions should be delivered, it is also important to consider who should receive these interventions. Shankar et al. (2013) highlights those interventions for those with lower education could be particularly beneficial. However, we also must consider what interventions will be most effective in a very heterogenous population. Given a variety of social factors, interventional approaches must be implemented without jeopardizing individual autonomy, or increasing levels of felt stigma, especially among older adults.

Previous work that has been done regarding the application of social prescribing in the clinic, suggests that it may be unethical to screen patients for their social needs without a plan for adequate and appropriate linkage to social programs, and that doing so could potentially result in harm and distrust (Alderwick et al., 2018). Even where social programs do exist, there may be many unmet needs caused by incongruous services, which are not culturally specific or may not offer services in the appropriate language. Before widespread incorporation of social questionnaires into standard practice in the clinic, these ethical concerns should be considered and researched, as unintended consequences of large-scale social screenings should be avoided.

Public policy

Older adults are a vulnerable group in regard to social isolation and loneliness, as the prevalence of each is much higher than in the general population. This review has highlighted increased risks for declines in cognitive performance in older adults who are socially isolated or lonely, as well as the increased risk of dementia in older adults who are lonely. Neurocognitive disorders can be very costly to individuals, families, and society. However, incorporating strategies to address social isolation and loneliness into public policy frameworks may help reduce the risks of developing these disorders and their associated costs.

Research priorities at the federal level (e.g., NIH/NIA) should support the standardization and best practices for future research on the effects of social isolation and loneliness on cognitive decline and incident dementia. Social engagement programs should also be a funding priority, so that the effects of these intervention models can be evaluated for both health and economic outcomes – or as Bickerdike et al. (2017) states, "… when, by whom, for whom, how well, and at what cost". These research objectives are synergistic with many others that are currently in place for longitudinal cohort studies, including a more rigorous collection of data pertaining to AD biomarkers, the social determinants of health, healthcare expenditures, etc.

For primary prevention, funding for organizations that attempt to prevent loneliness and social isolation in older adults should be increased and broadly distributed to community-based organizations (CBOs) on a city, state, and federal level. CBOs are often hamstrung by inadequate or inconsistent streams of funding, labor-intensive requirements in data tracking and reporting, as well as insufficient referral network due to a dearth of other support programs to which they could refer their constituents. Increasing funding for CBOs, refining the administrative work required of CBOs, and expanding the network of CBOs in underserved areas, will greatly improve their ability to reach older adults, and possibly prevent social isolation and loneliness.

It is also important to provide adequate infrastructure through healthcare reform to help address social isolation and loneliness. For example, the expansion of virtual conferencing may offer a novel way for older people to stay socially engaged, because virtual programming may have the ability to substantially improve access and reach for social engagement programs. However, resources needed for virtual, social engagement programming such as internet access, connected devices, and technology training are not provided under traditional entitlement programs. Older adults may have specific barriers that prevent them from accessing virtual programs, a disparity which is often referred to as the digital divide. Increased funding to improve internet access and connectivity should be provided to those in need as a health benefit.

For secondary prevention, patient-reported social isolation or loneliness should be accepted as a clinical indication associated with cognitive functioning. This indication should be incorporated into payment and reimbursement guidelines for cognitive screenings and assessments. Traditionally, coverage of neuropsychological testing is only provided when patients present with a cognitive complaint or functional impairment. However, older adults at the earliest stages of cognitive change, may not have a clear complaint that substantially differs

from cognitively healthy, older adults. Reports of social isolation or loneliness should count as a clinical indication that warrants further assessment in the service of early diagnosis given potential, disease-modifying interventions at the earliest stages.

Strengths and Limitations

This review had several strengths including the aggregation of results from 27 articles in peer-reviewed journals spanning 15 years, between 2007 and 2022. In addition, this review focused on using studies from longitudinal cohorts to reduce the possibility of reverse causation, which is an important methodological strength. Cohorts from various countries were included to examine any cross-cultural differences.

However, there were also some limitations that must be acknowledged. The search conducted was limited to articles written in English. Of the 27 studies reviewed, fourteen were based on European or Australian cohorts, seven were American or Canadian, and six were based in China, which may limit the generalizability of findings to other countries or cultures. Many studies were also inexplicit about their methods, and there was little standardization in measures used, time to follow-up, etc.

CONCLUSION

The prevalence of social isolation and loneliness is expected to rise as the absolute number of those entering old age continues to accelerate. As a result, it is important to understand previously reported associations between social isolation, loneliness, cognition, and dementia. Declines in cognitive performance and dementia-level impairment take a great toll on the public's health, affecting individuals, families, health systems, and society. There is also a large economic cost in caring for people with cognitive impairment, which – if avoided or delayed – could save an enormous amount of money in healthcare spending.

Of the articles reviewed, four main relationships emerged: 1) social isolation and cognition, 2) social isolation and dementia, 3) loneliness and cognition, and 4) loneliness and dementia. Some of these relationships had more supportive empirical evidence than others and some contained mixed evidence. Much of the evidence presented was subject to the addition of covariates. Variations in methodology made it difficult to directly compare results between studies, and a variety of other considerations may justifiably raise questions regarding validity, reliability, and generalizability.

However, the following general conclusions can be drawn from the review with a fair degree of confidence. Social isolation is associated with a small increase in risks for future declines in cognitive performance. On the other hand, social isolation was not found to be associated with an increased risk of incident dementia. Although results were somewhat mixed, loneliness was a robust predictor of future declines in cognitive performance, as the association between the two typically stayed significant when controlling for confounding factors, such as depression. The most convincing and consequential evidence is that loneliness is independently associated with an increased risk of incident dementia.

The findings from this review offer compelling evidence that both social isolation and loneliness may have deleterious effects on cognition, and that loneliness may be a prodromal indicator for the development of dementia. As a result, social isolation and loneliness may be viewed as modifiable risk factors for the optimization of cognitive health. Possible mitigation strategies include the following: 1) neuropsychological evaluation referrals for older adults who are socially isolated or lonely, 2) testing for Alzheimer's disease biomarkers in older adults who are severely or chronically lonely, and 3) the enhancement of social engagement interventions for older adults through funding and research.

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