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Alone in the Mind: Review of Research Examining the Link Between Loneliness and Dementia

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ABSTRACT

This narrative review focused on research investigating the impact of loneliness on the prevalence of dementia and its relationship with other risk factors. A comprehensive and rigorous search was conducted using a variety of scientific databases with specific keywords to identify all prior studies that examined the correlation between dementia and loneliness. The inquiry was confined to articles published in English from January 2017 to March 2024. The narrative review identified a consensus regarding the role of loneliness in enhancing the risk of all-cause dementia, with a particular emphasis on the subjective perception of loneliness. This phenomenon may be caused by the sensations of exclusion, discrimination, and alienation that are typically associated with low self-esteem and low life satisfaction, which may contribute to cognitive impairment and depressive symptoms. This finding was obtained despite the absence of robust evidence regarding the involvement of loneliness in the pathogenesis of dementia. Existing research has not yet identified a correlation between hereditary factors that influence the development of dementia and feelings of loneliness. However, loneliness is strongly associated with depression, which is a potential risk factor for dementia. Previous studies have reported a moderate correlation between depression and loneliness, as individuals who are isolated and lack a sense of community exhibit higher levels of depression. Meditation, social cognitive training, and social support are three strategies that have been implemented to address loneliness and are reported to be the most effective interventions. A strong correlation exists between dementia and loneliness. Although such strategies are unlikely to impede the progression of the disease if cognitive deterioration is already underway, understanding these associations can assist in the development of strategies to alleviate the effects of loneliness on vulnerable individuals.

1 | Background

Engaging in meaningful relationships and social interactions is a natural tendency among humans. As a species, we tend to seek comfort and emotional fulfillment in connecting with others. This tendency can be challenged by isolation caused by living conditions or disabilities, or by the loss of social network members through death or abandonment. Such challenges can elicit negative cognitive outcomes and reveal major problems in society [1].

A distinction must be made between loneliness and social isolation, as the former is a subjective distressing feeling that can develop independently of the number of people in one's

Abbreviations: AD, Alzheimer's disease; ADRD, Alzheimer's disease and related dementia; ApoE4, apolipoprotein E 4 allele; CTRA, conserved transcriptional response to adversity; HPA, hypothalamus-pituitary axis.

social circle, whereas the latter is an objective lack of relationships, which may or may not be associated with feelings of distress [2].

Although loneliness and social isolation impact individuals differently, both can predict morbidity and mortality, especially in older individuals; physical aging and decreased resilience increase the likelihood of objective isolation and feelings of dysphoria, causing prolonged neuroendocrine stress responses that may lead to several cognitive disorders, including dementia [3].

Dementia is an umbrella term that encompasses several neurodegenerative disorders characterized by progressive brain damage and subsequent deterioration of cognitive abilities [4]. Alzheimer's disease (AD) is the most prevalent subtype of dementia, especially among older people, accounting for approximately 70% of cases [5].

Increased understanding of the epidemiological and clinical aspects of dementia, as well as its economic consequences, can provide valuable insights for healthcare and policymaking, and enable individuals and their families to make well-informed choices [6]. Furthermore, with increased population aging, there is an anticipated increase in the prevalence of dementia, which is an increasingly important mental health issue [7]. Research, particularly prospective cohort studies, can be helpful for building a framework of different factors that increase the likelihood of developing the diseases, subsequently facilitating their detection at an earlier stage and creating interventions to enhance overall quality of life [8].

Multiple indicators of dementia risk, including personal behaviors, lifestyle choices, physical and mental health, and societal factors, are associated with loneliness [9]. The correlation between loneliness and increased dementia risk, as well as the progression of AD and related dementia (ADRD), indicates a possible early pathogenetic role [10]. Loneliness is linked to diminished white matter injury, decreased total cerebral volume, impaired executive function, and a detrimental effect on neurocognitive indicators of AD susceptibility [9].

This narrative review focused on studies examining the effects of loneliness on the incidence of dementia and its relationship with other risk factors.

2 | Methods

Searches were conducted in UpToDate, Google Scholar, PsycINFO, Scopus, Web of Science, and PubMed for pertinent reviews, research articles, and books published post-2017 to March 2024. The following search terms were employed: loneliness, social isolation, dementia, Alzheimer's disease, dementia risk factors, vascular dementia, loneliness scale, apolipoprotein E, and depression. The inquiry was confined to articles published in English from January 2017 to March 2024. To guarantee the quality of evidence, the search was limited to studies employing randomized controlled trial, cohort or case-control designs relevant to the research question. A manual search for the reference lists of the included studies was conducted alongside the electronic database search to identify further pertinent articles. Specialists in the domain were additionally consulted to recommend supplementary resources and references. The search string was systematically refined through initial results and expert feedback to balance the inclusion of pertinent studies with the exclusion of irrelevant studies. Attempts were undertaken to incorporate gray literature, including conference proceedings, dissertations, and technical reports, via specialized databases and manual searches. Zotero citation tracking tools were employed to identify extensively cited articles and their subsequent citations.

Studies were required to utilize randomized controlled trials, cohort studies, case-control designs, systematic reviews and meta-analyses, or cross-sectional designs to be considered for inclusion. We only included studies in which participants were adults of 18 years of age or older and who were either residing in the community or institutionalized. In the included studies, the primary exposure of interest was social isolation or loneliness, which was assessed using validated questionnaires or scales. AD and other forms of dementia were included in the primary outcome, which was dementia or cognitive decline. To further investigate the relationship between loneliness and other dementia risk factors, it was necessary to investigate the interaction between loneliness and variables such as age, sex, education, occupation, lifestyle factors, medical comorbidities, and genetic factors.

Case reports, case series, and animal studies were excluded from the review. Furthermore, studies that focused on pediatric populations or individuals with severe baseline cognitive impairment were excluded. Studies that failed to evaluate dementia or cognitive decline or did not explicitly measure loneliness or social isolation were also excluded. Finally, studies that were published in languages other than English were excluded.

3 | Etiology

Because there is no robust evidence for the involvement of loneliness in the pathogenesis of dementia, pathways linking the two in existing studies tend to be hypothetical. One proposed pathway is stress-related, suggesting that individuals with perceived loneliness are more vulnerable to chronic psychological stress and, consequently, to unceasing hypothalamus-pituitary axis (HPA) activation [11]. The resulting hypercortisolism may damage the frontal and limbic regions of the brain, which may eventually cause impaired cognitive function [12]. Furthermore, glucocorticoids regulate inflammation and promote the resolution of inflammatory responses, and prolonged exposure to glucocorticoids, which is thought to be caused by loneliness, may lead to persistent inflammation because of the development of glucocorticoid resistance and the subsequent loss of regulatory responses [13].

Another pathway proposes an indirect influence by factoring in behavioral hazards as triggers for general health decline, which may affect cognitive function. For example, numerous studies have shown that lonely individuals are more likely to engage in behaviors associated with health risks, such as smoking, heavy

drinking, consumption of unhealthy diets, and lack of physical activity [14, 15]. Such behaviors are risk factors for both cardiovascular and cerebrovascular diseases, which have been linked to the pathogenesis and progression of dementia, as they influence and promote cognitive impairment reportedly through β-amyloid (Aβ) accumulation around cerebral vessels [16]. This intraneuronal accumulation arises when Aβ production and elimination are unbalanced, resulting in amyloid angiopathy in most AD patients. However, it remains to be determined whether the accumulation of Aβ is the root cause of AD or if it is a consequence of cerebral vascular disease in AD patients. Thus, Aβ may serve as an exacerbating factor only [17].

A third pathway links loneliness to the increased expression of pro-inflammatory gene expression, as the conserved transcriptional response to adversity (CTRA) has been identified in the immune cells of people exposed to chronic social adversity. The upregulation of CTRA gene expression was reported to be associated with decreased expression of antiviral and antibody-related genes, which, in addition to contributing to neurodegenerative diseases, may also leave the patient vulnerable to a myriad of infectious diseases [18, 19]. An interesting finding within some randomized controlled trials is that positive psychological interventions such as group therapy, gratitude journaling, positive affirmation, and mindfulness meditation can lead to down-regulation of CTRA gene expression [20–22].

Social isolation has been identified as an independent risk factor for dementia. Previous studies have reported that socially isolated individuals have a higher likelihood of developing dementia, with hazard ratios indicating a significant increase in risk [23, 24]. This association persists even after adjusting for other factors such as loneliness and depression [24].

4 | Loneliness Versus Social Isolation

While both loneliness and social isolation are linked to dementia, their impacts differ. Some studies suggest that feelings of loneliness may be more strongly associated with dementia onset than with social isolation itself [25].

However, other studies have indicated that social isolation independently contributes to dementia risk, separate from loneliness [23, 24].

5 | Quantifying Loneliness: Exploring Measurement Approaches

Because of the subjective nature of loneliness and the fragmented data related to its repercussions on health outcomes, measuring the extent and distribution of this condition is challenging [26]. Many scales have been developed and implemented for this purpose; these scales encompass single and multi-item measures; some ask directly about loneliness, while others assess feelings that are commonly associated with loneliness, from which a multifarious evaluation of loneliness can be inferred [27].

One such scale is the University of California, Los Angeles Loneliness Scale, which was first developed in 1978 and most recently updated in 1996. This scale encompasses 20 items concerned with participants' feelings and their relationships with people around them. Ratings on a scale from 1 (never) to 4 (often) are utilized to compute subjective feelings of loneliness [28]. Another widely used scale is the De Jong Gierveld Loneliness Scale, which was developed in the early 1980s through qualitative research and survey explorations. Scores on this scale ranged from 0 (not lonely) to 11 (extremely lonely). There are three versions of the scale: the original version consisting of 11 items, and two shorter versions, one consisting of six items for measuring emotional loneliness and another consisting of five items for measuring social loneliness. All versions clearly distinguish between loneliness and social isolation [29].

A myriad of other scales have been developed and implemented over the years. A retrospective analysis conducted in the United States examining the association of loneliness with 10-year all-cause dementia risk used the Center for Epidemiologic Studies Depression Scale which measures loneliness using depression symptoms [9]. A glaring issue with this scale is that loneliness and depression are independent of one another, both conceptually and in terms of statistical applications, and using the symptoms of one of them to gauge the other is likely to yield misleading results [30, 31].

A longitudinal cohort study conducted in Sweden, examining the connection between perceived loneliness and all-cause dementia, AD, and vascular dementia, used a single-item scale to measure loneliness with one direct question: “Do you often feel lonely?” [32]. Although a single closed-ended question may seem ostensibly unreliable as a measure in and of itself, a cross-sectional study conducted in Germany indicated otherwise. The study results supported the reliability and validity of a single-item loneliness scale, and the scale was credited as a useful and informative tool compared with an established three-item loneliness scale [33].

6 | The Interplay Between Loneliness and Other Dementia Risk Factors

One of the most significant genetic risk factors for AD is the apolipoprotein E (APOE) ε4 allele (ApoE4). ApoE4 is one of the three alleles of the APOE gene (ApoE2, ApoE3, and ApoE4), and serves as a biomarker to measure susceptibility to the disease. Although approximately 25% of people are ApoE4 carriers, the percentage of AD patients who carry at least one copy of the ε4 allele is approximately 40% [34]. People who carry one copy of this allele are 3–7 times more likely to develop AD, whereas people who carry two copies of the allele are 12 times more likely to develop AD [35]. The involvement of this particular allele is likely to be related to its association with increased synthesis and accumulation of Aβ peptide, eventually leading to

the so-called "amyloid-β cascade" [36]. Multiple published studies have reported an association between Aβ burden and loneliness, particularly in carriers of ApoE4. A cross-sectional study conducted in the United States found that amyloid-positive participants were 7.5 times more likely to be lonely, as determined by the three-item UCLA scale, compared with amyloid-negative participants, and this association was stronger in carriers of ApoE4 [37]. Additionally, a prospective cohort study conducted in China found a strong connection between leisure activities and dementia, especially among carriers of ApoE4 [38]. Another study explored data from the aging, demographics, and memory Study module of the health and retirement research and implied that a supportive social environment and more engagement with family and friends may protect against the increased risk of AD among ApoE4 carriers [39]. Contrary to these findings, several other studies reported no association between ApoE4 and loneliness, and no significant reduction in ApoE4 risk of dementia in the presence of strong social networks [40–42].

Depression is another potential risk factor for dementia that may be intertwined with loneliness. It has been found that the incidence of dementia increases by 1.5-fold in individuals with diagnosed depression, and this association was found to be more significant when the onset of depression and the onset of dementia were no more than 10 years apart [43]. Three hypotheses have been proposed to explain the link between depression and dementia: (a) depression is not a risk factor but rather a prodromal stage of dementia; (b) the co-occurrence of depression and dementia is incidental, with the possibility that cognitive deficits caused by depression might lower the threshold for developing dementia; and (c) similar to loneliness, depression damages the hippocampus through a glucocorticoid cascade, causing the development of dementia [44]. Scales that measure the perceived feeling of loneliness and those that measure the burden of depression have some overlapping items, which implies a moderate level of association between the two [45]. Lonely individuals are reported to show greater depressive tendencies, as the lack of a sense of belonging can be a strong trigger for depression [46]. However, recent findings favor the separation between depression and loneliness when assessing their impact on cognitive function. Thus, depression and loneliness are considered to be conceptually and statistically independent as dementia risk factors [30, 31], and adjusting for depression does not appear to affect the level of association between loneliness and dementia, limiting the likelihood of shared mechanisms [47].

An association has been drawn between hearing loss and dementia, directly linking it to loneliness and social isolation, because hearing loss blocks a major stimulatory input, consequently hindering social interaction [48]. A prospective study in the United States reported a positive linear correlation between hearing loss severity and all-cause dementia. The results of this study support the direct involvement of loneliness and social isolation in this correlation because participants whose hearing threshold was below the level required for efficient verbal communication appeared to have a greater risk of developing dementia compared with those with less prominent hearing loss. However, it is still possible that vascular disease or genetic factors simultaneously cause both hearing loss and dementia [49].

7 | Association Between Loneliness and Dementia

Our narrative review revealed general agreement in the existing literature regarding the involvement of loneliness in increasing the risk of all-cause dementia. Previous research findings have characterized the relationship between loneliness in dementia-free adults and early cognitive and imaging measures of ADRD vulnerability, suggesting that the association between loneliness and dementia is partially related to the involvement of loneliness in the early neuropathogenesis of ADRD [9].

The subjective perception of loneliness is assumed to be more stressful than objective social isolation, and the feeling of exclusion, discrimination, and alienation is usually associated with low self-esteem and low life satisfaction, which may contribute to depressive symptoms and cognitive impairment [50, 51]. Previous studies have reported that older individuals who have a partner and do not live alone can still experience emotional loneliness. Consequently, the risk of dementia is still high, particularly among individuals who do not proactively communicate with friends and relatives. This highlights the possibility that frequent communication with others may satisfy the need for affection, reducing the risk of dementia [47].

This finding is consistent with the results of a previous longitudinal clinicopathological cohort study conducted in the United States, which found that cognition level at baseline was lower in lonely participants compared with persons who were not lonely. Additionally, during follow-up, a more rapid cognitive decline was observed in lonely participants compared with people who were not lonely. The study also suggested that social participation, rather than social network size, contributes to the risk of dementia [52]. However, it should be noted that differences in social and cultural backgrounds can influence how loneliness and social isolation are perceived [47].

Evidence linking the association between loneliness and dementia to sociodemographic factors is limited. A 3-year cohort study conducted in China indicated that lonely men were at an increased risk of dementia compared with lonely women [53]. Another study conducted in the United States found a significant interaction with the age of the participants; interestingly, the results suggested that advanced age may displace the negative impact of loneliness, and the results revealed a stronger association between loneliness and dementia among younger participants compared with that among older participants [54]. Similarly, a previous literature review revealed a stronger association between social deficit and mortality in individuals younger than 65 years [55].

The increased risk of ADRD is only associated with persistent loneliness, whereas transient loneliness does not appear to have the same effect. The rationale for these findings is that transient loneliness downregulates inflammatory responses by activating the HPA. Accordingly, persistent loneliness would be expected to cause prolonged activation of the HPA, which would lead to overactivity and eventually to the loss of efficiency and the loss of regulatory responses with the development of persistent inflammation [56]. This also explains why some studies that did not consider the duration of loneliness did not find a significant association between loneliness and dementia [57].

Different individuals respond differently to being socially isolated or feeling alone. However, the impact of subjective loneliness goes beyond genetic predisposition for dementia, because individuals who experience loneliness were reported to be more prone to developing ADRD than those with strong social circles, despite having similar levels of genetic risk [58].

Considering the observational nature of most of these findings, reverse causation should be considered. Early stages of cognitive decline may lead individuals to withdraw from relationships or, because of their altered mental status, they may face rejection from those around them, mistakenly leading researchers to infer an association between loneliness and dementia progression. Even when all risk factors are measured at baseline, it is possible that relevant processes may have started before these baseline measures were taken because dementia develops over the course of years. However, the Swedish cohort study mentioned earlier followed participants over 20 years, making it possible to assess reverse causation. In that study, participants whose onset of dementia was within 5 years of baseline were excluded, and their exclusion did not affect the association between loneliness and dementia [32]. Although this does not completely rule out reverse causation, it strongly diminishes its likelihood.

8 | Overcoming Loneliness: Pathways to Connection and Wellbeing

Loneliness is identified as an important public health issue, and addressing it requires the development of community programs, behavioral and environmental interventions, and online resources. Having good, healthy interactions and participating in different social activities can be helpful for maintaining cognitive reserve and can function as neural plasticity exercises that may prevent or delay cognitive deterioration [59].

Many interventions have been introduced to manage loneliness, with meditation, social cognitive training, and social support reported to be the most effective. Meditation involves visualization, listening to specific sounds, deep breathing, and reaching a state of calmness. Social cognitive training refers to understanding and processing social situations, people, and emotions. It should be noted that these interventions may engage specific populations and may not be as effective in others, so the target population is an important factor to consider when applying them [60]. In this sense, social support targets lonely people with disadvantageous circumstances, such as those living in distant or isolated locations [61].

Using technology to reduce loneliness was expected by specialists to make a significant difference, but the results of published studies have indicated otherwise. New connection methods such as social networking and video calls have not been found to significantly reduce the sense of loneliness in older adults [62]. However, using modern technology to assist people with disabilities, for instance, by using cochlear implants for people with hearing impairments, can significantly improve symptoms of loneliness [63].

It is important to understand that the pathophysiology of dementia cannot be reversed by addressing loneliness or by any other currently available intervention. Thus, managing loneliness, while it can be comforting, cannot reduce the incidence of dementia if cognitive deterioration is already in effect, particularly when considering the extent of the preclinical stage of dementia, which may be longer than 10 years, during which irreversible brain damage has often already taken place [64].

9 | Conclusion

The recognition of loneliness as a global health concern is accelerating with a recent upsurge in research. The consensus in relevant literature strongly suggests a significant association between loneliness and dementia, with the possibility of involvement of loneliness in the early neuropathogenesis of ADRD, although no robust evidence supports this possibility; therefore, further research is recommended in this area. Studies linking loneliness with other dementia risk factors are insufficient, and their results are inconclusive. However, available findings support the independence of loneliness as a risk factor. Understanding these associations can aid in developing strategies to mitigate the impact of loneliness on vulnerable individuals, although such strategies are unlikely to slow the progression of the disease if cognitive deterioration is underway.

Author Contributions

Ahmed Hussein Al-Samiry: conceptualization (equal), methodology (equal), writing–original draft (equal). **Samer Imad Mohammed:** conceptualization (equal), data curation (equal), methodology (equal), supervision (equal), writing–review and editing (equal). **Ahmed Majid Hameed:** methodology (equal), writing–original draft (equal). **Tayf M. Maryoosh:** methodology (equal), writing–original draft (equal).

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Ethics Statement

The authors have nothing to report.

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The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created.

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