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A review of studies on the impact of social isolation and loneliness on Alzheimer's disease

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Abstract:

Alzheimer's disease (AD), the most common neurodegenerative disease affecting the elderly, is on a continuous global rise in incidence and prevalence, placing a heavy burden on the individual, the family, and society. In recent years, more and more researches have revealed that social isolation and loneliness are important factors of risk for the development of AD. The purpose of this review is to systematically sort out the existing cohort research evidence on the impact of social isolation and loneliness on AD, to deeply explore the underlying neurobiological, psychological, and inflammatory response mechanisms, and to pay special attention to the gender specificity of the effects of social isolation and loneliness on AD, and to analyze the differences in cognitive decline, psychological problems, and disease progression between females and males, as well as their possible causes, with a view to providing new directions for future research and AD early prevention and intervention strategies for AD, with a view to providing new perspectives and theoretical basis for future research directions and early prevention and intervention strategies for AD.

Keywords: Social isolation, Loneliness, Alzheimer's disease, Cognitive decline, Gender differences

1. Introduction

Alzheimer's Disease (AD) is a neurodegenerative disease characterized by progressive cognitive dysfunction and behavioral abnormalities, and is the most prevalent kind of dementia. Due to the global population's aging trend, AD incidence and prevalence have significantly increased, and it has become an increasingly serious global public health problem. According to a prediction study by Yingquan Wang et al. (2019), the number of AD prevalence among Chinese people aged 60 years or older was 14.5 million in 2020, and it is anticipated to rise sharply to 30.03 million in 2050, which is 2.35 times higher than that of 2015, which suggests that the number of AD prevalence in China will increase dramatically in the next three decades if there are no effective preventive measures [1]. The China Blue Book on Alzheimer's

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Disease (2024) also points out that AD ranks fifth among the total causes of death among urban and rural residents in China, placing an increasingly heavy economic burden and caregiving pressure on individuals, families, and society [2]. Given that there are no drugs that can effectively reverse or cure AD, early identification of risk factors and preventive interventions are particularly important.

Among the many risk factors for AD, social isolation and loneliness, as psychosocial phenomena prevalent in the elderly population, are receiving increasing academic attention. Social isolation is usually defined as an objective lack of social connections, such as a small social network size and low participation in social activities; while loneliness is a subjective feeling, i.e., the gap between the quality or quantity of social relationships perceived by an individual and his or her expectations, and he or she may feel lonely even if he or she is in a crowd. These two states are particularly prevalent in the elderly population. For example, Zhang Yowen et al. (2024) found that up to 91.6% of older adults in the Shanghai community had moderate or higher levels of loneliness [3]. This high prevalence makes social isolation and loneliness a non-negligible factor affecting the health, especially cognitive health, of elderly.

This research review aims to provide insight into the available evidence, potential mechanisms, and their gender specificity of the impact of social isolation and loneliness on Alzheimer's disease. Evidence from multiple cohort studies is first cited to clarify the association between social isolation and loneliness and the risk of developing AD. Next, the complex intricate ways that loneliness and social isolation impact AD progression are analyzed from multiple perspectives, including neurobiology, psychology, and inflammatory response. Finally, this review will focus on disparities between genders in how social isolation and loneliness affect AD, analyzing the differences and possible causes of cognitive decline and psychological problems between females and males, as well as providing insights into the underlying gender-specific mechanisms. By systematically sorting out and analyzing these aspects, this review aims to provide an expanded comprehension of AD prevention and intervention strategies, and to shed light on future research directions.

2. Cohort studies

In recent years, several large-scale cohort studies have provided strong epidemiologic evidence for the association between social isolation and loneliness and the risk of Alzheimer's disease (AD) and its associated cognitive disorder. These studies have revealed the independent or synergistic effects of these two psychosocial factors on cognitive functioning and dementia incidence through long-term follow-up.

Sutin et al. (2018) followed 12,030 participants in the Health and Retirement Study (HRS) cohort for 10 years and showed that a 40% higher risk of dementia was linked to loneliness [4]. This research study makes it clear that the correlation between the two factors continued to exist even after adjustments for issues like social isolation and other relevant factors such as medical conditions, behaviors, and genetic predispositions. Additionally, it was observed that this link remained just as robust across various demographic and risk-based categories, including gender, racial or ethnic backgrounds, educational attainments, and genetic susceptibility levels. This implies that loneliness is an independent and intervenable factor in dementia risk.

Another larger prospective study by Sutin et al. (2023) based on the UK Biobank (N=492,322) further extends this finding by revealing that loneliness not only elevates the likelihood of dementia across the board by nearly 60 percent, but it also exacerbates the risks associated with vascular dementia (VD) and frontotemporal dementia (FTD) to a far greater extent than Alzheimer's Disease itself [5]. Specifically, loneliness increased the risk of VD by 82%, FTD by 64%, and AD by 40%.

However, not all studies agree that loneliness is a major independent risk factor. Shen et al. (2022) utilized the UK Biobanking cohort of 462,619 participants followed for 11.7 years on average and showed that a 1.26-fold increased risk of dementia was linked to social isolation, and this association held true regardless of other risk factors like depression and loneliness [6]. In contrast, the association between loneliness and dementia had a fully adjusted risk ratio of 1.04, with 75% of the association attributable to depressive symptoms. This suggests that objective social isolation may contribute more to dementia risk than subjective loneliness in some large cohorts, or that the effects of loneliness are mediated more through psychological factors such as depression. This is supported by the UK Biobank cohort study by Elovainio et al. (2022), who found that social isolation (risk ratio 1.62) was associated with an increased risk of dementia, whereas loneliness was not significant [7]. The study also noted that socially isolated individuals had an increased risk of dementia at all levels of genetic risk and that genetic risk did not interact with loneliness or social isolation.

In summary, despite the fact that social isolation and loneliness have slightly different independent contributions across studies, the overall trend suggests that both psychosocial states, whether objective lack of social connectedness or subjective feelings of isolation, are closely linked to a higher chance of developing dementia, including AD. These cohort studies provide a solid foundation for sub-

sequent in-depth exploration of the mechanisms behind them.

3. Mechanisms of Influence

3.1 Neurobiological Mechanisms

At the neurobiological level, social isolation and loneliness may increase AD susceptibility by affecting brain structure and function through multiple pathways.

First, several researches have demonstrated a strong correlation between social isolation and loneliness and changes in the brain's gray matter volume (GMV). The UK Biobank study by Shen et al. (2022) further found that people who were socially isolated showed reduced gray matter volume in important brain areas like the hippocampus, frontal lobe, and temporal lobe [6]. Mediation analyses showed that differences in gray matter volume in these brain regions partially mediated the relationship between follow-up cognitive functioning and baseline social isolation. A longitudinal neuroimaging study by Lammer et al. (2023) provided similar evidence, finding that social isolation, both baseline and its fluctuations, have been linked to a decrease in hippocampal volume and cortical thickness, which in turn correlates with a decline in cognitive abilities like memory, processing speed, and executive function [8]. All of these studies suggest that social isolation may lead to structural atrophy of key cognitive regions of the brain, thereby impairing cognitive function.

The effects of loneliness on specific brain regions have also been shown in the initial phases of the disease. Zhang et al. (2022) studied 176 elderly patients with memory problems, involving individuals with subjective cognitive decline(SCD),mild cognitive impairment (MCI), and Alzheimer's disease (AD) ,and found that loneliness was linked to a reduction in regional gray matter volume in the thalamus of both sides of the brain in the patients with SCD, and with a decrease in gray matter volume in the left midoccipital gyrus and regional gray matter volume reductions in the I-V lobules of the cerebellum [9]. These findings suggest that patients with SCD or MCI may have comorbid symptoms of perceived social isolation or loneliness, which increases their vulnerability to the neuropathology of future AD progression.

In addition, neurotransmitters and hormonal systems may also play a role.Takahashi et al. (2023) noted the function of oxytocin (OXT), a hormone primarily involved in social bonding, in AD and its close relationship with social interactions [10]. Neuronal activation linked to OXT can be altered by social enrichment or social isolation. Their recent study showed that OXT reversed learning and memory deficits in animal models of AD, suggesting that OXT might be an AD treatment target and providing mechanistic clues as to how social interactions may affect AD through neuroendocrine pathways.

3.2 Psychological mechanisms

Psychological factors play a key role in the association of social isolation and loneliness with AD, with depressive symptoms and lack of cognitive stimulation being particularly prominent.

Depressive symptoms are thought to be an important mediator linking loneliness and dementia risk. A study by Shen et al. (2022) found that 75% of the association between loneliness and dementia was attributable to depressive symptoms [6]. This suggests that loneliness may indirectly increase the risk of dementia by inducing or exacerbating depressive mood, which in turn may indirectly increase the risk of dementia. This is corroborated by a longitudinal study by Dabiri et al. (2024) who found that the association between loneliness and cognitive decline was partially mediated by gray matter volume and depressive symptoms [11]. Individuals who are chronically lonely are more likely to experience negative moods like depression and anxiety, which are themselves known factors of risk for cognitive decline and dementia. Depression may accelerate brain aging and neurodegenerative pathologies by affecting mechanisms such as neuroplasticity, neuroinflammation, and stress responses.

Lack of cognitive stimulation is another important psychological mechanism. Karska et al. (2024) noted that loneliness itself may lead to depletion of sensory and cognitive stimulation, thereby reducing neural reserve [12]. The brain's capacity to sustain cognitive function in the face of pathological damage is known as neural reserve. Prolonged lack of social interaction and cognitive stimulation may lead to decreased brain activity and reduced synaptic density, thereby reducing the brain's resistance to pathological changes in AD and accelerating the process of cognitive decline. In addition, sensory loss (including hearing and visual impairments) may mediate the relationship between loneliness and dementia, as sensory impairments can limit social participation, exacerbate feelings of isolation, and may directly impact cognitive function.

3.3 Inflammatory responses and molecular mechanisms

In addition to macroscopic neurobiological and psychological mechanisms, the impact of social isolation and loneliness on AD reach down to the molecular and genetic level, particularly through inflammatory responses and altered gene expression.

The inflammatory response is considered to be an im-

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portant link in the pathophysiology of AD. Santiago et al. (2023) recognized molecular "on-off" genes in the nucleus ambiguous of the brain of individuals known to be lonely that lead to significant transcriptional changes through co-expression network analysis [13]. These loneliness-associated on/off genes were rich in pathways linked to infection, innate immunity, and cancer. More importantly, these loneliness-associated on/off genes significantly overlap with gene expression in 82% of human AD studies and 68% of Parkinson's disease (PD) studies, and a number of on/off genes have been identified as genetic risk factors for AD. This provides direct molecular evidence that loneliness affects AD, suggesting that it may promote neurodegeneration by affecting cell survival, metabolism, and inflammation-related pathways.

A study by Shen et al. (2022) also found that lower gray matter volume associated with social isolation was associated with lower expression of genes down-regulated in AD as well as genes involved in mitochondrial dysfunction and oxidative phosphorylation [6]. This suggests that social isolation may contribute to neuronal damage and cognitive decline by affecting key cellular processes such as cellular energy metabolism and oxidative stress. The connection between loneliness and cognitive decline and the function of pro-inflammatory cytokines and brain-derived neurotrophic factor (BDNF) expression was also explored in research by Dabiri et al. (2024) [11]. They found that semantic memory and visuospatial skills declined more slowly in those with higher BDNF expression, suggesting that BDNF may play a protective role in cognitive impairment due to loneliness, whereas imbalances in inflammatory factors may accelerate this process.

In conclusion, the effect of social isolation and loneliness on AD is a complex process with multiple levels and dimensions. It not only affects the accumulation of core pathological markers of AD by altering brain structure and function, but also contributes to the onset and progression of AD by inducing or exacerbating depressive symptoms, weakening cognitive reserve, as well as regulating molecular mechanisms such as inflammatory responses and gene expression. These mechanisms are interrelated and form a complex network that together explain the important role of psychosocial factors in the pathophysiology of AD.

4. Gender differences

Gender differences are a longstanding but not yet fully clarified key issue in Alzheimer's disease (AD) research. Women are way more susceptible to AD and face a heavier load of diseases related to it than men, which has led scientists to dive headfirst into understanding the connection between gender and the development of AD. They're also examining how gender affects the impact of social isolation and loneliness on the progression of AD.

4.1 Gender differences in AD prevalence and experience of loneliness

First, epidemiologic data on AD show that women dominate the number of people with AD. Kolahchi et al. (2024) noted that two-thirds of people with AD in the United States are women, suggesting that there are significant differences between the genders in terms of the age and intensity of disease manifestations, cognitive deficits, neuroinflammatory factors, structural and functional brain changes, and psychosocial and cultural environments [14]. Significant gender differences also exist in the experience of social isolation and loneliness. A study by Plaska et al. (2024) noted that women experience greater loneliness than men, despite the fact that men report more physical isolation and smaller social networks [15]. It appears that the experience of objective social isolation and subjective loneliness can vary greatly between the genders. A study conducted in China revealed that older women tend to have lower levels of social loneliness, while men might be more susceptible to social isolation, and although this study did not directly explore the association with AD, it provides clues to understanding gender differences in different cultural contexts [3].

4.2 Gender specificity of the mechanisms of influence

4.2.1 Gender specificity of genetic and molecular mechanisms

The co-expression network analysis of Santiago et al. (2023) identified 'on-off' genes specific to chronically lonely males that were more abundant in pathways linked to infection, innate immunity, and cancer, when stratified by sex [13]. This provides direct molecular-level evidence that loneliness in men may influence neurodegenerative diseases through immune- and inflammation-related pathways. Although this study did not directly identify similar specific switch genes in females, this does not rule out the existence of other unique molecular mechanisms in females. Kolahchi et al. (2024) also emphasized the presence of gender dimorphism in AD, including genetic, hormonal, and inflammatory influences, which provides a macroscopic framework for understanding how loneliness may differentially impact the sexes through these pathways [14]. For example, the APOEε4 gene is the largest genetic factor of risk for AD, and Sutin et al. (2023) found that the association of loneliness with all-cause dementia and AD risk was stronger in non-APOEε4 carriers, which

may be related to sex-specificity, as the effect of APOEε4 on AD risk may be more pronounced in women [5].

4.2.2 Gender Specificity of Hormonal and Inflammatory Responses

Sex hormones, particularly estrogen, play an important role in female brain health and AD pathology. Estrogen levels decline dramatically in women after menopause, which is thought to be an important factor in the increased risk of AD in women. A review by Warren (2024) discusses gender differences between dietary habits, neuroinflammation, and AD, with a particular emphasis on interactions between diet, hormones, and inflammation [16]. Loneliness and chronic stress may have differential effects between the sexes by affecting hormonal balance (e.g., cortisol levels) and neuroinflammatory pathways. For example, women's physiological responses to stress may differ from men's, which may lead to a greater likelihood of developing chronic inflammation in a state of chronic loneliness, which in turn accelerates the progression of AD pathology.

4.2.3 Gender specificity of psychosocial factors and cognitive resilience

The study by Plaska et al. (2024) aimed to explore whether gender and loneliness influence plasma AD biomarkers, suggesting that researchers are exploring gender-specific links between psychosocial factors and biomarkers [15]. Women may differ from men in their social interactions and emotional expression, which may lead them to adopt different strategies in coping with loneliness or to bear different psychological burdens. For example, women may be more inclined to internalize loneliness, which can up the ante on their chances of dealing with depression and anxiety. These conditions have been pinpointed as key players in the connection between loneliness and the gradual loss cognition [6, 11]. The study by Dabiri et al. (2024) also aimed to ascertain if the association between loneliness and cognitive impairment varies by gender among the elderly, and although the abstract does not give specific results, but this line of research itself emphasizes the importance of gender as a moderating variable [11]. In addition, there may also be differences in the structure and functioning of social support networks between the sexes, which may affect an individual's ability to cope with social isolation and loneliness, and thus cognitive resilience.
Understanding how social isolation and loneliness exacerbate cognitive decline and AD, with attention to gender differences, will help to unravel the underlying mechanisms of their role as risk factors for AD and to create efficient preventative or therapeutic strategies. Therefore, future research needs to more systematically integrate multi-dimensional information from biology, psychology and sociology, use gender-stratified analyses, and even develop gender-specific animal models to comprehensively reveal the gender-specific mechanisms of the effects of social isolation and loneliness on AD, in order to offer a scientific foundation for precision medicine and personalized interventions.

5.Conclusion

This review systematically examines the available evidence, potential mechanisms, and their gender specificity of the effects of social isolation and loneliness on Alzheimer's disease (AD). A large number of cohort studies have confirmed that both significantly elevate an individual's risk of developing AD and all-cause dementia. In terms of mechanisms of action, social isolation and loneliness affect AD through multiple complex pathways involving neurobiological (e.g., leading to reduced gray matter volume and cortical thinning in key brain regions), psychological (e.g., inducing depressive symptoms and decreasing cognitive stimulation), as well as inflammatory and molecular (e.g., activating immune-inflammatory pathways shared with AD and triggering gene expression abnormalities). Of interest, there are significant gender differences in these effects: women not only have a higher burden of AD and are more likely to perceive intense loneliness, whereas men may be at higher risk of objective social isolation. These gender-specific effects have implications at the molecular level, at the hormonal level, and at the psychosocial level.
Despite significant progress in existing research, several research gaps and future directions remain. First, a precise definition of the causal relationship between social isolation and loneliness and AD still needs to be validated by more rigorous longitudinal and intervention studies. Second, although multiple potential mechanisms have been identified, the interactions and relative contributions of these mechanisms remain incompletely understood. Future studies should utilize multimodal data and advanced statistical methods, among others, to more fully elucidate the complex network of social isolation and loneliness influencing AD. In addition, in-depth studies addressing gender differences are an important future direction, and more research is needed to compare AD pathologic progression, cognitive trajectories, and responses to interventions across genders in response to social isolation/loneliness exposure. This includes more detailed analyses of gender-specific genetic susceptibility, hormonal environment, and psychosocial factors to reveal their specific roles in AD pathogenesis.
Finally, based on the available evidence, there is an urgent public health need to develop and evaluate interventions targeting social isolation and loneliness with a view to

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delaying or preventing the development of AD. These interventions should take into account the characteristics and needs of different groups of older adults in order to achieve individualized and precise prevention strategies. Through multidisciplinary collaboration and innovative research, we aim for an enriched insight into the pivotal importance of social support networks in maintaining cognitive health in older adults and ultimately contribute to reducing the global burden of AD.

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