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Impact of loneliness and social isolation on the cognition of healthy adults: a systematic review

Impacto de la soledad y el aislamiento social en la cognición de adultos sanos: una revisión sistemática

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ABSTRACT

Loneliness and social isolation are factors that increasingly affect many people around the world, and evidence suggests that they are related to cognitive processes deterioration. This article aims to review the available information on the effect of loneliness and social isolation on the cognition of middle-aged adults. A comprehensive structured search was conducted in PubMed, Scopus, Web of Science and EBSCO databases. In the first instance, the results of the databases were imported to the Mendeley reference manager, where duplicates were eliminated, to later extract articles relevant to the topic according to the title and abstract. The inclusion criteria included only articles published in English, conducted in humans, and published within the last ten years (2012-2022). Persistent loneliness was found to be associated with lower cognitive scores and reduced volumes in the temporal lobe and hippocampus, as well as enlarged lateral ventricles. However, when factors such as age, depressive symptoms, and the presence of the APOE ε4 allele were considered, the strength of these associations tended to diminish. A similar pattern was observed when loneliness and social isolation co-occurred, though this was not the case for social isolation alone. It is concluded that loneliness, more than social isolation, appears to be associated with poorer cognitive functioning, whether considered independently or in combination with social isolation, compared to individuals not exposed to these factors. Nonetheless, these findings should be interpreted with caution, as various intervening or moderating variables may influence this relationship. Further research focused specifically on middle-aged populations is needed to clarify the nature and mechanisms of these associations.

Keywords: loneliness; social isolation; cognition; executive profile; adults; middle-aged.

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RESUMEN

La soledad y el aislamiento social son factores que afectan cada vez más a muchas personas en todo el mundo, y la evidencia sugiere que están relacionados con el deterioro de los procesos cognitivos. El presente artículo tiene como objetivo revisar la información disponible sobre el efecto de la soledad y el aislamiento social en la cognición de adultos de mediana edad. Se realizó una búsqueda estructurada y exhaustiva en las bases de datos PubMed, Scopus, Web of Science y EBSCO. En primera instancia, los resultados fueron importados al gestor de referencias Mendeley, donde se eliminaron los duplicados, para posteriormente seleccionar los artículos relevantes al tema según el título y el resumen. Los criterios de inclusión fueron artículos publicados en inglés, realizados en humanos, con un período de publicación de 10 años (2012-2022). Se encontró que la soledad persistente se asoció con puntuaciones cognitivas más bajas y una reducción del volumen en el lóbulo temporal y el hipocampo, así como con una dilatación de los ventrículos laterales. Sin embargo, al considerar factores como la edad, los síntomas depresivos y la presencia del alelo APOE ε4, la fuerza de estas asociaciones tendió a disminuir. Se observó un patrón similar cuando la soledad y el aislamiento social coexistían, aunque no fue así en el caso del aislamiento social por sí solo. Se concluye que la soledad, más que el aislamiento social, parece estar asociada con un funcionamiento cognitivo más deficiente, tanto cuando se analiza de forma independiente como en combinación con el aislamiento social, en comparación con individuos no expuestos a estos factores. No obstante, estos hallazgos deben interpretarse con cautela, ya que diversas variables intervinientes o moderadoras pueden influir en esta relación. Se requiere mayor investigación enfocada específicamente en poblaciones de mediana edad para esclarecer la naturaleza y los mecanismos de estas asociaciones.

Palabras clave: soledad; aislamiento social; cognición; perfil ejecutivo; adultos; mediana edad.

INTRODUCTION

There is increasing evidence that people with loneliness or social isolation are highly vulnerable to a range of physical and mental problems; they have even been considered as risk factors for early mortality above obesity and comparable to other well-established factors such as smoking and alcoholism (1).

The concepts of loneliness and social isolation are closely related but conceptually distinct. Loneliness is understood as a subjective feeling of social isolation in which there are no meaningful relationships. It is often accompanied by sadness, dissatisfaction, or a sense of emptiness, even when surrounded by many people. In contrast, social isolation refers to an objective lack of social connections, such as living alone or having minimal contact with family, friends, or the broader community. While social isolation can sometimes lead to loneliness, it does not necessarily do so; some individuals may live in isolation and feel content, whereas others may have active social lives yet still experience profound loneliness (2).

Several societal trends have been contributing to the growing prevalence of loneliness worldwide. Increasing numbers of people living alone, lower marriage rates, fewer children, and declining religious affiliation are among the key factors that predispose individuals to reduced social connection and, consequently, greater feelings of loneliness (3). This emotional experience tends to rise temporarily between the ages of 30 and 60, and resurfaces again in later life (4). Recent data indicate that more than one-third of adults aged 45 and older report feeling lonely, while approximately one-quarter of those over 65 are socially isolated (5). The COVID-19 pandemic further exacerbated this issue: in several countries, the prevalence of severe loneliness rose from 6% to 21%, and around 21% of the population reported feeling isolated based on their usual social contacts (6).

Cognitive impairment is one of the major health problems to which adults experiencing prolonged loneliness and social isolation are exposed (7). This deterioration in cognition increases the risk of

developing dementia by up to 20% (8), representing a significant emotional, physical, and economic burden for the patients themselves, their caregivers, and society (9).

In light of the problems identified, this review aims to provide an analysis of the main findings in different studies regarding the effect of loneliness and social isolation on the cognitive processes of middle-aged adults, information that may be useful for further studies on this topic in this specific population group. Accordingly, the research question guiding this review is: What is the existing evidence on the association between loneliness and/or social isolation and cognitive functioning in middle-aged adults?

METHODOLOGY

Eligibility criteria

This systematic review was conducted in accordance with the updated 2020 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (10). The review question was structured using the PEO (Population: Middle-aged adults; Exposure: Loneliness and/or social isolation; Outcome: Changes in cognitive profile) framework to guide the eligibility criteria and literature search strategy. Observational studies were included if they assessed the impact of loneliness and/or social isolation on cognitive function in middle-aged adults. Only studies published between 2012 and 2022 were considered. Review articles, meta-analyses, editorials, letters to the editor, qualitative studies, and those unrelated to the topic, targeting other populations, or focusing on age groups outside the middle-aged range were excluded. Studies lacking specific measures for cognitive function or loneliness/social isolation were also excluded.

Search strategy

An exhaustive literature search was conducted across four electronic databases: PubMed (n = 64), Scopus (n = 46), EBSCOhost (n = 6), and Web of Science (n = 2), with the aim of identifying relevant studies on the impact of social isolation and loneliness on cognitive and executive functioning in middle-aged adults. The search strategy involved the use of Boolean operators (AND, OR) and relevant synonyms. Key search terms included: "loneliness", "social isolation", "cognition", "executive functions", "middle-aged", and "adult." Detailed search strategies for each database are provided in Supplementary Table 1.

Selection of studies

Following the database search, all identified records were exported in RIS format and imported into the reference manager Mendeley for elimination of duplicates. The remaining records were independently screened by two reviewers based on titles and abstracts, applying the predefined eligibility criteria. Discrepancies were resolved through discussion until consensus was reached. Full-text articles were then retrieved and assessed independently by both reviewers to determine final inclusion.

The following filters were applied during the search: publication date between 2012 and 2022, English language, and studies involving human subjects. In PubMed, instead of using the MeSH term "middle-aged", the age filter "Middle Aged: 45-64 years" was applied to improve precision and avoid indexing inconsistencies.

The selection process is summarized in the PRISMA flow diagram (Figure 1).

After the search, selection of articles, and elimination of duplicates, 84 articles were obtained, of which 10 were selected after eliminating articles by title and abstract.

Quality assessment

To assess the methodological quality and risk of bias of the included studies, the Newcastle-Ottawa Scale (NOS) was employed. This tool is specifically designed to evaluate non-randomized observational studies, in this case, cohort studies, across three domains: selection of study groups, comparability between groups, and ascertainment of outcomes. Each domain is rated with stars, and the total score categorizes studies as being of good quality (8-9 stars), fair quality (5-7 stars), or poor quality (<5 stars), corresponding to a low, moderate, or high risk of bias, respectively (11). However, some studies, while using data from cohort populations, conducted only cross-sectional analyses without follow-up. These were therefore assessed using the modified version of the Newcastle-Ottawa Scale tailored for cross-sectional studies. This adaptation evaluates similar domains adjusted to the nature of cross-sectional design, and classifies studies as very good (9-10 points), good (7-8 points), satisfactory (5-6 points), or unsatisfactory (0-4 points) (12).

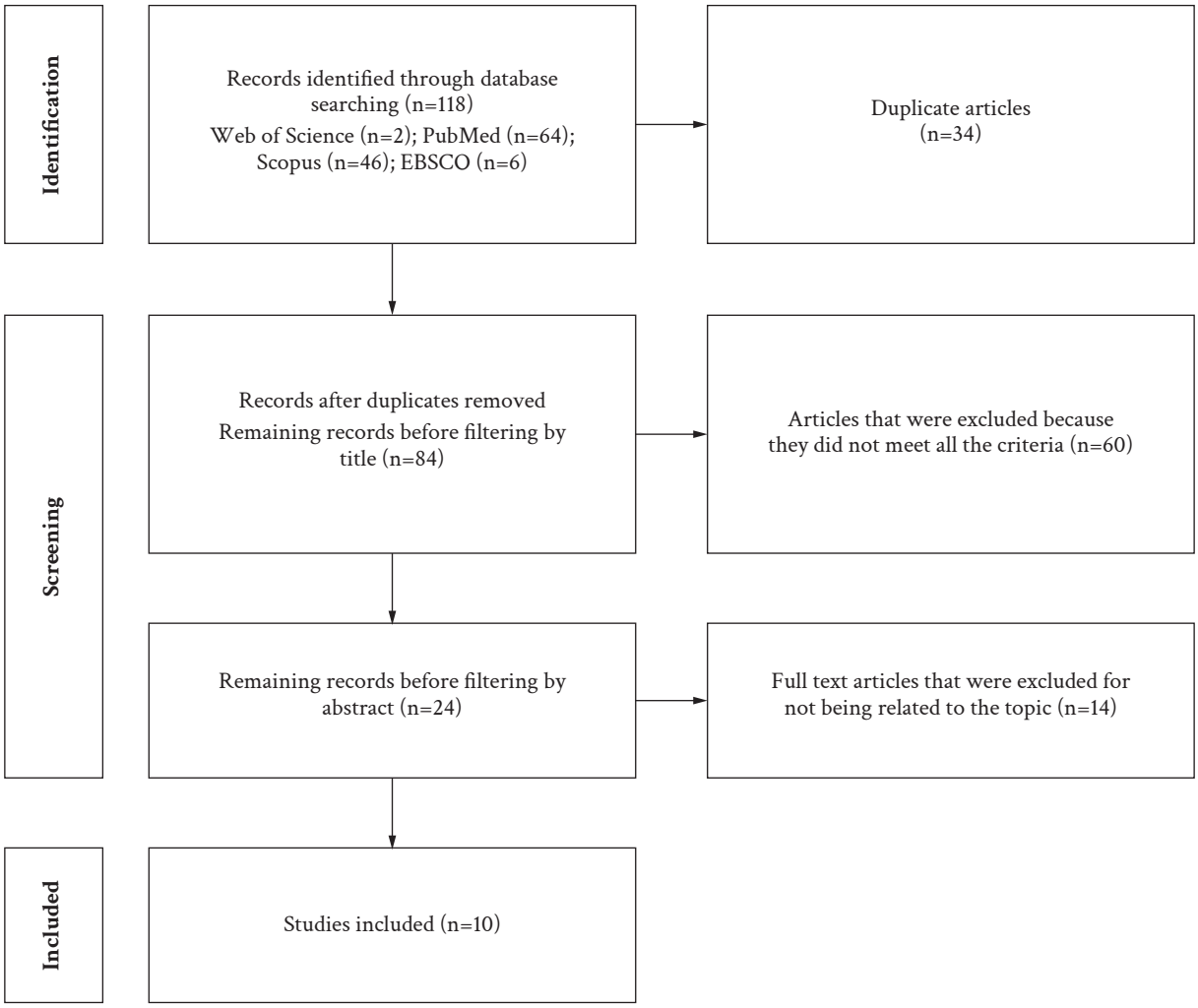

Figure 1. PRISMA flow diagram of article selection process.

Based on these quality assessment criteria, two of the six cohort studies (13-18) were rated as fair quality, indicating a moderate risk of bias, while the remaining four were classified as good quality, reflecting a low risk of bias (Table 1). Among the cross-sectional studies (19-22), two were rated as very good quality and the other two as good quality (Table 2).

Table 1. Newcastle-Ottawa Scale (NOS) diagram for quality and risk of bias assessment in cohort studies.

Authors	Year	Selection (max 4)	Comparability (max 2)	Outcome (max 3)	Total Score	Risk of bias
Lara et al. (15)	2019	★★★	★	★★	6	Moderate risk
Luchetti et al. (14)	2020	★★★★	★	★★★	8	Low risk
Rafnsson et al. (17)	2020	★★★★	★	★★★	8	Low risk
Yu et al. (13)	2021	★★★	★	★★	6	Moderate risk
Akhter-Khan et al. (18)	2021	★★★	★★	★★★	8	Low risk
Tao et al. (16)	2022	★★★★	★★	★★	8	Low risk

Table 2. Newcastle-Ottawa Scale (NOS) diagram for quality and risk of bias assessment in cross sectional studies.

Authors	Year	Selection (max 5)	Comparability (max 1)	Outcome (max 3)	Total Score	Quality
Okruszek et al. (19)	2021	★★★★	-	★★★	7	Good
Spreng et al. (22)	2020	★★★★★	★	★★★	9	Very good
Beller & Wagner (21)	2017	★★★★	-	★★★	7	Good
Maharani et al. (20)	2019	★★★★★	★	★★★	9	Very good

Data extraction and synthesis

A qualitative approach based on narrative synthesis was used to analyze and summarize the findings of the included studies. Key information was extracted from each article, including characteristics of the study population, methods used to assess loneliness, social isolation, and cognitive function, as well as the main results. This information was first organized into a summary table to facilitate comparison and thematic analysis. The findings were then integrated to identify patterns, inconsistencies, and areas of consensus regarding the impact of loneliness and/or social isolation on the cognitive profile of middle-aged adults (Supplementary Table 2).

RESULTS

Loneliness as a risk factor for cognitive decline and dementia

Loneliness has been recognized as a significant risk factor for cognitive decline and dementia in longitudinal studies. A four-year follow-up found that loneliness was significantly associated with cognitive deterioration, even after adjusting for potential confounders such as age, sex, educational level, area of residence, chronic diseases, and disability (13). When loneliness was assessed using the UCLA Loneliness Scale as a continuous variable, each additional point was linked to a 31% increased risk of cognitive decline (14), along with lower scores in overall cognitive performance, immediate recall, and verbal fluency (15).

Persistent loneliness has been associated with a twofold increased risk of cognitive impairment compared to individuals who did not report feeling lonely, independent of clinical conditions, behavioral factors, social isolation, and depressive symptoms (14). This impact was observed across multiple cognitive domains, particularly in recall and retention tasks, though not consistently in the overall cognitive score (15, 16). While the strength of the association tends to attenuate by up to 50% after full adjustment for covariates, it remains statistically significant, especially among adults aged 65 and older (14).

Loneliness has also been linked to a heightened risk of developing dementia. Specifically, each additional point on the UCLA Loneliness Scale was associated with a 44% increased risk of future dementia, regardless of other covariates (17). In midlife, transient loneliness was associated with a reduced risk of developing dementia, whereas persistent loneliness emerged as a significant risk factor (18). An 18-year longitudinal study confirmed that both persistent and transient loneliness retained their respective risk patterns, even after adjusting for the presence of the APOE ε4 allele (16, 18).

In contrast, incidental and short-term loneliness did not significantly impact long-term cognitive performance in the same way as persistent loneliness, which was associated with declines in memory and executive function (16).

The impact of social isolation on cognitive function

Higher levels of social isolation have been associated with lower scores in global cognitive performance, verbal fluency, and forward digit span, although no significant effects were observed in other cognitive tests (15). Similarly, a four-year longitudinal study found that social isolation was linked to poorer performance in episodic memory and mental status, even after adjusting for multiple covariates, suggesting an independent relationship between isolation and decline in specific cognitive domains (13).

Individuals with a greater number of close social relationships showed a reduced risk of developing dementia (17). However, contrasting findings indicate

that socially isolated individuals did not exhibit a significantly faster cognitive decline compared to those who were less isolated (15), suggesting that social isolation may not be an independent predictor of dementia incidence (17) and that its effects may depend on the presence of moderating or mediating factors (15).

Only one study evaluated the relationship between social isolation and social cognition, defined as the set of processes that allow the course of important stimuli that help us understand other agents and their interactions. It found that lower-level social cue processing (integrating emotion recognition and social perception) was significantly associated with lower objective social isolation, while no effect was found for loneliness (19).

Effect of the association of loneliness and social isolation on cognition

Both loneliness and social isolation have been independently associated with cognitive decline; however, their simultaneous presence may have complex and heterogeneous effects on cognitive outcomes. Evidence from longitudinal studies suggests that while each factor alone may impair cognitive performance, their joint impact does not necessarily lead to a synergistic decline.

In one study conducted among middle-aged and older adults that excluded individuals with depressive symptoms, the negative associations between both loneliness and social isolation with cognitive performance remained consistent, indicating that their co-occurrence may contribute independently and additively to cognitive decline (16). Similarly, in a population of adults with hearing impairment, a group particularly vulnerable to social disconnection, both loneliness ($\beta = -0.08$; $p < 0.001$) and social isolation ($\beta = -0.09$; $p = 0.001$) were independently and significantly associated with lower episodic memory scores, further supporting the detrimental cognitive effects of these factors when they occur simultaneously (20).

In contrast, another study among Chinese adults aged 50 years and older found that only social isolation remained significantly associated with cognitive impairment after adjusting for covariates, while the association between loneliness and cognitive decline became non-significant. Similarly, another investigation reported trends toward lower cognitive performance among individuals experiencing loneliness; however, the only statistically significant negative effect was observed among those living alone, reinforcing the unique impact of objective social disconnection (21). This suggests that in certain populations or contexts, social isolation may pose a greater independent risk than loneliness alone (13).

Neurobiological and structural brain correlates of loneliness and social isolation

Loneliness and social isolation have been associated with distinct neurobiological patterns involving regions of the so-called "social brain," such as the medial prefrontal cortex, medial temporal lobes, temporoparietal junction, and posteromedial cortex. These structures are crucial for social cognition, emotional regulation, and self-referential processing. Individuals experiencing loneliness show heightened vigilance to negative social cues, increased self-focused and imaginative thinking about social interactions, and even behaviors like anthropomorphizing pets. These psychological features are paralleled by functional alterations in the visual cortex, limbic system, and prefrontal areas, as well as increased microstructural integrity in the fornix, a white matter tract linked to emotional memory and internal simulation of social experiences (22).

Beyond functional correlates, structural brain differences have also been reported. Persistent loneliness has been linked to reduced volumes in the temporal lobe and hippocampus, and enlargement of the lateral ventricles, particularly among women. These associations were more pronounced in carriers of the APOE ε4 allele, who also showed greater volume loss in the parietal lobe. Interestingly, in men, only incidental loneliness was associated with greater hippocampal volume (16). Despite these findings, the evidence remains inconclusive. For instance, another study did not find significant associations between loneliness and global or regional brain volumes, highlighting the need for further research using harmonized methods and longitudinal designs (18).

Moderating factors in the relationship between social isolation, loneliness, and cognitive function

Several sociodemographic and health-related factors appear to modulate the relationship between social isolation, loneliness, and cognitive function in middle-aged adults. Greater age, female sex, lower educational attainment, rural residence, alcohol use, functional impairment, and depressive symptoms have been consistently associated with increased levels of both

social isolation and loneliness (13). Individuals who developed dementia over a 6.25-year follow-up were more likely to be older, less educated, economically disadvantaged, and to present with a greater burden of chronic diseases, despite having lower cognitive performance at baseline (17).

Persistent loneliness has been linked to specific characteristics such as female sex, depressive symptoms, smoking, higher body mass index, single or unemployed status, and lower scores on social relationship indices. Notably, although loneliness was more prevalent among women, only men with persistent loneliness exhibited significant cognitive decline after adjusting for relevant covariates (16). Furthermore, the presence of the APOE ε4 allele, along with widowhood, older age, and functional limitations, emerged as an independent predictor of dementia. When APOE ε4 status was taken into account, the association between persistent loneliness and risk of dementia weakened and lost statistical significance, suggesting a potential genetic moderation effect (18).

Depressive symptoms as a mediating factor between loneliness and cognitive function

The association between loneliness and dementia risk, particularly Alzheimer's disease, in middle-aged adults appears to be influenced by the presence of depressive symptoms. Among individuals without depression (CES-D score <16), persistent loneliness was associated with an increased risk of developing dementia. Notably, 43.9% of those reporting persistent loneliness did not exhibit depressive symptoms, suggesting that loneliness may serve as an independent risk factor for Alzheimer's disease in this age group (18).

However, when adjusting for depressive symptoms, the association between loneliness and dementia risk was no longer statistically significant (13). Persistent loneliness was linked to alterations in memory and executive function, but only in participants without depression. Among those experiencing depressive symptoms, no significant relationship was observed between different types of loneliness and cognitive performance (16).

DISCUSSION

This review aimed to elucidate the effect of loneliness and social isolation on the cognitive profile of middle-aged adults. To achieve this, we analyzed 10 observational studies published in the last 10 years, including longitudinal and cohort designs with follow-up periods ranging from 3 to 18 years. Overall, the findings highlight the role of both loneliness and social isolation as factors that may negatively influence cognitive function in this age group. Some studies reported a stronger association between loneliness and cognitive decline (14, 16-18, 22), while others identified social isolation as the more relevant factor, though its impact varied depending on the cognitive domains assessed and the sociocultural contexts involved (13, 19, 21). In addition, several investigations observed a synergistic effect, where the co-occurrence of both loneliness and social isolation was associated with greater cognitive deterioration (15, 20).

Loneliness was found to predict more negative cognitive outcomes, particularly at moderate to severe levels (15). These findings contrast with those from a study conducted in an East Asian population, which concluded that social isolation, rather than loneliness, was more strongly associated with cognitive decline (13). Such inconsistencies may be partially explained by the use of different instruments to assess loneliness. In the study among Chinese adults, loneliness was measured using a single item from the Center for Epidemiologic Studies Depression Scale (CES-D), the same item used in another study where the association between loneliness and cognitive function was significantly reduced. However, when this item was replaced with a more comprehensive measure (UCLA Loneliness Scale 3), the association regained significance in over 50% of the models tested (14).

In the absence of depression, persistent loneliness has been associated with an increased risk of developing dementia, particularly through its impact on memory and executive functioning (13). However, when depression is taken into account, the association between different types of loneliness and cognitive performance loses statistical significance (16).

Various sociodemographic and health-related factors must also be considered, as they influence the relationship between loneliness, social isolation, and cognitive function. Being female, older in age, having a low level of education, living in rural areas, experiencing alcoholism, functional disabilities, and depressive symptoms have all been associated with higher levels of social isolation and loneliness (13). Individuals who developed dementia during follow-up often shared some of these characteristics; however, some already exhibited lower cognitive profiles at baseline (17). Persistent loneliness was more prevalent

among women, yet it was only in men that it was associated with progressive cognitive decline (16).

Loneliness and social isolation have been associated with heightened exposure to daily stress, which can lead to increased levels of cortisol and proinflammatory cytokines. This neuroendocrine response disrupts the activity of the hypothalamic-pituitary-adrenal (HPA) axis, resulting in neuronal damage in brain regions such as the frontal lobe and limbic system, which ultimately contributes to cognitive decline (15, 17, 18). Structurally, persistent loneliness has been linked to reduced temporal lobe volume. Moreover, in women, particularly those carrying the APOE ε4 allele, higher loneliness scores have been associated with smaller volumes in the temporal lobe and hippocampus, as well as enlargement of the lateral ventricles (16). These findings suggest a biological vulnerability that may be more pronounced in certain subgroups.

From a broader neurobiological perspective, social cognitive functions engage key regions of the so-called "social brain," including the medial prefrontal cortex, medial temporal lobes, temporoparietal junction, and posteromedial cortex (22). Loneliness and social isolation have been shown to affect these regions, leading to alterations in gray matter volume, functional connectivity, and white matter tract integrity. Such changes are also reflected in altered brain-behavior dynamics, with individuals exhibiting increased self-focused attention, greater self-referential thinking, and a tendency to imagine desired social interactions (22). Furthermore, lonely or socially isolated individuals have been found to carry a higher risk of mortality from cancer and circulatory diseases, potentially driven by unhealthy lifestyle behaviors such as smoking, alcohol consumption, and obesity (23).

Another relevant point is that, although one study considered apolipoprotein E ε4, the most important genetic risk factor for developing Alzheimer's disease (24), loneliness remained an independent factor in the risk of cognitive impairment and development of Alzheimer's disease. Even in this study, it was observed that people with transient loneliness have a lower risk of dementia, which may suggest that resilience to this situation may promote various activities that improve physical and social integration (18).

Loneliness and social isolation have been identified as risk factors for both physical and mental health problems (23). However, their specific association with cognitive function and the mechanisms underlying this relationship require further investigation in middle-aged adults, excluding older populations, to better understand their impact and inform early intervention strategies. Although this review focused on middle-aged individuals, several included studies involved older adults, which may have influenced the findings due to age-related cognitive decline. Nonetheless, many of these studies accounted for age as a covariate or confounder, and those providing stratified or interpretable results for middle-aged groups still offer valuable insights into this at-risk population.

Notably, a more specific link has been reported between loneliness, social isolation, and social cognitive capacity, suggesting that individuals who do not feel lonely are more likely to sustain meaningful social relationships, preserve stronger social cognitive skills, and thus maintain better overall cognitive function (19). This highlights the significance of meaningful social networks in promoting cognitive health through enhanced social cognition.

CONCLUSION

Recent research has linked both social isolation and loneliness to the development of cognitive decline in middle-aged adults. Findings from various longitudinal studies indicate a stronger association between persistent loneliness and impairments in memory and executive functions compared to social isolation. However, these associations are not consistent across all populations, as some studies reported a stronger link between social isolation and cognitive impairment than with loneliness. The simultaneous presence of both factors appears to have a synergistic effect, particularly on memory decline over time. Nonetheless, when potential moderating variables, such as older age, depressive symptoms, and genetic predisposition to Alzheimer's disease, are considered, the strength of the association tends to diminish or even become nonsignificant.

Persistent loneliness has also been associated with structural brain changes, including reduced volume in the temporal lobe and hippocampus, and enlarged lateral ventricles, especially in women carrying the APOE ε4 allele. These alterations may reflect the impact of chronic stress linked to loneliness, which can elevate cortisol and inflammatory cytokine levels, disrupt the hypothalamic-pituitary-adrenal axis, and damage key brain regions such as the limbic system and frontal lobes, contributing to cognitive decline. Although several theories have been proposed to

explain these associations, more research is needed to elucidate the neural mechanisms underlying the effects of social isolation and loneliness.

Most of the reviewed studies included both middle-aged and older adults, potentially limiting the representativeness of findings specific to the middle-aged population. Therefore, future research should focus exclusively on middle-aged adults to determine whether social isolation and loneliness significantly impact cognitive functioning in otherwise healthy individuals. Given the growing prevalence of these psychosocial factors, addressing them should be considered a public health priority.

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HAAN, CPM: searched the data, conducted the systematic review, read and approved the final manuscript.
MJMS: writing – original draft, read and approved the final manuscript.
SCS: writing – original draft, read and approved the final manuscript.
JAZV: conceived and designed the study, drafted the study, read and approved the final manuscript.

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REFERENCES

1. Holt-Lunstad J, Smith TB, Baker M, Harris T, Stephenson D. Loneliness and social isolation as risk factors for mortality: a meta-analytic review. Perspect Psychol Sci [Internet]. 2015; 10(2): 227-237. Available from: https://doi.org/10.1177/1745691614568352
2. Russo F. Loneliness can be toxic. Sci Am [Internet]. 2018; 318(1): 64-69. Available from: https://doi.org/10.1038/scientificamerican0118-64
3. Holt-Lunstad J. The potential public health relevance of social isolation and loneliness: prevalence, epidemiology, and risk factors. Public Policy Aging Rep [Internet]. 2017; 27(4): 127-130. Available from: https://doi.org/10.1093/ppar/prx030
4. Luhmann M, Hawkley LC. Age differences in loneliness from late adolescence to oldest old age. Dev Psychol [Internet]. 2016; 52(6): 943-959. Available from: https://doi.org/10.1037/dev0000117
5. National Academies of Sciences, Engineering, and Medicine; Division of Behavioral and Social Sciences and Education; Health and Medicine Division; Board on Behavioral, Cognitive, and Sensory Sciences; Board on Health Sciences Policy; Committee on the Health and Medical Dimensions of Social Isolation and Loneliness in Older Adults. Social Isolation and Loneliness in Older Adults: Opportunities for the Health Care System [Internet]. Washington DC: National Academies Press; 2020. Available from: https://www.ncbi.nlm.nih.gov/books/NBK557974/
6. O'Sullivan R, Burns A, Leavey G, Leroi I, Burholt V, Lubben J, et al. Impact of the COVID-19 pandemic on loneliness and social isolation: a multi-country study. Int J Environ Res Public Health [Internet]. 2021; 18(19): 9982. Available from: https://doi.org/10.3390/ijerph18199982
7. Zhou Z, Mao F, Zhang W, Towne SD, Wang P, Fang Y. The association between loneliness and cognitive impairment among older men and women in China: a nationwide longitudinal study. Int J Environ Res Public Health [Internet]. 2019; 16(16): 2877. Available from: https://doi.org/10.3390/ijerph16162877
8. Center for Healthy Aging. The loneliness of social isolation can affect your brain and raise dementia risk in older adults [Internet]. 2020; August 4. Available from: https://healthyaging.psu.edu/news-events/news/loneliness-social-isolation-can-affect-your-brain-and-raise-dementia-risk-older
9. Duong S, Patel T, Chang F. Dementia: what pharmacists need to know. Can Pharm J [Internet]. 2017; 150(2): 118-129. Available from: https://doi.org/10.1177/1715163517690745
10. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ [Internet]. 2021; 372: n71. Available from: http://doi.org/10.1136/bmj.n71
11. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa

Scale (NOS) for assessing the quality of non-randomized studies in meta-analysis [Internet]. Ottawa: Ottawa Hospital Research Institute; 2000. Available from: https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp?utm_source=chatgpt.com
12. Blanchard L, Ray S, Law C, Vega-Salas MJ, Bidonde J, Bridge G, et al. The effectiveness, cost-effectiveness and policy processes of regulatory, voluntary and partnership policies to improve food environments: an evidence synthesis. National Institute for Health and Care Research. Public Health Res [Internet]. 2024; 12(8). Available from: https://www.ncbi.nlm.nih.gov/books/NBK607540/
13. Yu B, Steptoe A, Chen Y, Jia X. Social isolation, rather than loneliness, is associated with cognitive decline in older adults: the China Health and Retirement Longitudinal Study. Psychol Med [Internet]. 2021; 51(14): 2414-2421. Available from: https://doi.org/10.1017/s0033291720001014
14. Luchetti M, Terracciano A, Aschwanden D, Lee JH, Stephan Y, Sutin AR. Loneliness is associated with risk of cognitive impairment in the Survey of Health, Ageing and Retirement in Europe. Int J Geriatr Psychiatry [Internet]. 2020; 35(7): 794-801. Available from: https://doi.org/10.1002/gps.5304
15. Lara E, Caballero FF, Rico-Uribe LA, Olaya B, Haro JM, Ayuso-Mateos JL, et al. Are loneliness and social isolation associated with cognitive decline? Int J Geriatr Psychiatry [Internet]. 2019; 34(11): 1613-1622. Available from: https://doi.org/10.1002/gps.5174
16. Tao Q, Akhter-Khan SC, Ang TF, DeCarli C, Alosco ML, Mez J, et al. Different loneliness types, cognitive function, and brain structure in midlife: findings from the Framingham Heart Study. EClinicalMedicine [Internet]. 2022; 53: 101643. Available from: https://doi.org/10.1016/j.eclinm.2022.101643
17. Rafnsson SB, Orrell M, D'Orsi E, Hogervorst E, Steptoe A. Loneliness, social integration, and incident dementia over 6 years: prospective findings from the English Longitudinal Study of Ageing. J Gerontol B Psychol Sci Soc Sci [Internet]. 2020; 75(1): 114-124. Available from: https://doi.org/10.1093/geronb/gbx087
18. Akhter-Khan SC, Tao Q, Ang TF, Itchapurapu IS, Alosco ML, Mez J, et al. Associations of loneliness with risk of Alzheimer's disease dementia in the Framingham Heart Study. Alzheimers Dement [Internet]. 2021; 17(10): 1619-1627. Available from: https://doi.org/10.1002/alz.12327
19. Okruszek Ł, Piejka A, Krawczyk M, Schudy A, Wiśniewska M, Żurek K, et al. Owner of a lonely mind? Social cognitive capacity is associated with objective, but not perceived social isolation in healthy individuals. J Res Pers [Internet]. 2021; 93: 104103. Available from: https://doi.org/10.1016/j.jrp.2021.104103
20. Maharani A, Pendleton N, Leroi I. Hearing impairment, loneliness, social isolation, and cognitive function: longitudinal analysis using English Longitudinal Study on Ageing. Am J Geriatr Psychiatry [Internet]. 2019; 27(12): 1348-1356. Available from: https://doi.org/10.1016/j.jagp.2019.07.010
21. Beller J, Wagner A. Disentangling loneliness: differential effects of subjective loneliness, network quality, network size, and living alone on physical, mental, and cognitive health. J Aging Health [Internet]. 2018; 30(4): 521-539. Available from: https://doi.org/10.1177/0898264316685843
22. Spreng RN, Dimas E, Mwilambwe-Tshilobo L, Dagher A, Koellinger P, Nave G, et al. The default network of the human brain is associated with perceived social isolation. Nat Commun [Internet]. 2020; 11(1): 6393. Available from: https://doi.org/10.1038/s41467-020-20039-w
23. Elovainio M, Hakulinen C, Pulkki-Råback L, Virtanen M, Josefsson K, Jokela M, et al. Contribution of risk factors to excess mortality in isolated and lonely individuals: an analysis of data from the UK Biobank cohort study. Lancet Public Health [Internet]. 2017; 2(6): e260-e266. Available from: https://doi.org/10.1016/s2468-2667(17)30075-0
24. Kim J, Basak JM, Holtzman DM. The role of apolipoprotein E in Alzheimer's disease. Neuron [Internet]. 2009; 63(3): 287-303. Available from: https://doi.org/10.1016/j.neuron.2009.06.026

SUPPLEMENTARY MATERIAL

Supplementary Table 1. Detailed search strategy used in the review, including databases, keywords, and Boolean operators.

PubMed
Publication year: 2012-2022 **Filters applied:** • English • Humans • Middle Aged: 45-64 years **Search strategy:** (((Loneliness OR homesickness) AND ("social isolation" OR "isolation, social" OR "social exclusion" OR "exclusion, social" OR "social exclusions")) AND (cognition OR cognitions OR "cognitive function" OR "cognitive functions" OR "function, cognitive" OR "functions, cognitive" OR "executive function" OR "executive functions" OR "function, executive" OR "functions, executive" OR "executive control" OR "executive controls"))
Scopus
Publication year: 2012-2022 **Filters applied:** • **Document type:** Article **Search strategy** TITLE-ABS-KEY ("social isolation" OR "isolation, social" OR "social exclusion" OR "exclusion, social" OR "social exclusions") AND TITLE-ABS-KEY (loneliness OR homesickness) AND TITLE-ABS-KEY ("middle aged" OR "middle age") AND TITLE-ABS-KEY (cognition OR cognitions OR "cognitive function" OR "cognitive functions" OR "function, cognitive" OR "functions, cognitive" OR "executive function" OR "executive functions" OR "function, executive" OR "functions, executive" OR "executive control" OR "executive controls") AND PUBYEAR > 2011 AND PUBYEAR < 2023 AND (LIMIT-TO (DOCTYPE, "ar"))
EBSCO
Publication year: 2012-2022 **Search strategy** (Loneliness OR homesickness) AND ("social isolation" OR "isolation, social" OR "social exclusion" OR "exclusion, social" OR "social exclusions") AND (cognition OR cognitions OR "cognitive function" OR "cognitive functions" OR "function, cognitive" OR "functions, cognitive" OR "executive function" OR "executive functions" OR "function, executive" OR "functions, executive" OR "executive control" OR "executive controls") AND ("middle aged" OR "middle age")
Web of Science
Search strategy (TS = "loneliness" OR TS = "homesickness") AND (TS = "social isolation" OR TS = "isolation, social" OR TS = "social exclusion" OR TS = "exclusion, social" OR TS = "social exclusions") AND (TS = "cognition" OR TS = "cognitions" OR TS = " cognitive function" OR TS = "cognitive functions" OR TS = "function, cognitive" OR TS = "functions, cognitive" OR TS = "executive function" OR TS = "executive functions" OR TS = "function, executive" OR TS = "functions, executive" OR TS = "executive control" OR TS = "executive controls") AND (TS = "middle aged" OR TS = "middle age")

Supplementary Table 2. Findings related to the effect of loneliness and/or social isolation on cognition.

Publication	Year	Country/ region	Type	Sample size (n) - age	Variables	Covariates	Instruments	Results	Conclusions
Lara et al. (15)	2019	Spain	Longitudinal 3 years	n = 1,691 (≥50 years)	Loneliness Social isolation Cognitive function	Age Sex Educational level Physical activity Alcohol consumption Disability Depression Stroke Diabetes	Loneliness 3-item UCLA Loneliness Scale Social isolation 5-item Social Isolation Index Cognitive function Immediate verbal recall Delayed verbal recall Digit span forward and backwards Animal naming task	After adjusting for covariates, loneliness was associated with a lower composite cognitive score (β = -3.16; 95% CI: -4.95 to -1.37), as well as lower scores on each of the cognitive assessments. Social isolation was also associated with a lower composite cognitive score (β = -0.85; 95% CI: -1.55 to -0.1); however, no effects of social isolation were observed on the immediate and delayed recall tests.	Both loneliness and social isolation are associated with a decline in cognitive function over a 3-year follow-up period.
Akhter-Khan et al. (18)	2021	USA	Longitudinal 18 years	n = 2,880 (>45 years)	Loneliness Dementia Alzheimer's disease	Age Sex Education Widowhood Index of social networks Living situation Activities of daily living Cardiovascular diseases Apolipoprotein ε4	Loneliness 20 items from the Center for Epidemiological Studies Depression Scale *Dementia and AD were diagnosed by experts.	After adjusting the results for covariates, compared with those with no loneliness, persistent loneliness was found to be associated with an increased risk of the onset of dementia and AD (HR 1.91, 95 % CI: 1.25-2.90; P < 0.01), whereas transient loneliness with a lower risk (HR, 0.34; 95 % CI: 0.14-0.84; P < 0.05).	The presence of persistent loneliness in middle-aged adults constitutes an independent risk factor for dementia and Alzheimer's disease; on the other hand, recovery from transient loneliness suggests resilience to dementia risk.

Luchetti et al. (14)	2020	Europe	Longitudinal 11 years (evaluations every 2-3 years)	n = 14,114 (≥50 years)	Loneliness Social isolation Cognitive function	Age Sex Educational level BMI Hypertension Diabetes Physical activity Smoking status Health-related limitations Depression Widowhood	Loneliness 3-item UCLA Loneliness Scale One item from the Center for Epidemiological Studies Depression Social isolation 5-item Social Isolation Index Cognitive function Memory recall task Animal fluency task	Loneliness was associated with an increased risk of cognitive impairment (HR = 1.31; 95% CI: 1.19-1.44); this association decreased after taking into consideration all covariates, however, it remained significant.	Loneliness is a modifiable factor that can be intervened upon before the development of severe disability or dementia.
Yu et al. (13)	2020	China	Longitudinal 4 years	n = 7,761 (≥50 years)	Loneliness Social isolation Cognitive function	Age Genre Education Place of residence (rural/urban) Alcoholism Smoking Functional limitations Hypertension Diabetes Cardiac diseases Depression	Loneliness One item from the Center for Epidemiological Studies Depression Social isolation 3-item Social Isolation Index Cognitive assessment Episodic memory: immediate recall of words Mental status integrity: questions from the "Cognitive status telephone interview". Visuospatial ability: accurately redrawing a previously displayed image	After adjusting for covariates, the association of loneliness with cognitive impairment became insignificant; however, social isolation maintained its significant association with cognitive impairment during follow-up (episodic memory: $\beta = -0.05$; $p < 0.001$; mental status: $\beta = -0.03$; $p < 0.01$) even after controlling for loneliness and all confounding variables.	Social isolation is associated with cognitive decline in Chinese adults, and these relationships are independent of loneliness.

Okruszek et al. (19)	2021	Poland	Cross-sectional	n = 252 (18-50 years)	Loneliness Social isolation Social cognitive ability	Cardiovascular diseases Psychiatric disorders Neurological disorders	<u>Loneliness</u> UCLA Scale <u>Social isolation</u> Lubben SNS Social isolation based on indicators of social isolation <u>Social Cognition</u> Study of Psychometric Assessment of Social Cognition (SCOPE)	Poorer lower-level processing of social cues predicted a higher level of objective social isolation, but not perceived social isolation (loneliness)	Objective social cognitive ability can predict objective, but not perceived, levels of social functioning. At the same time, social cognitive biases can affect both objective and perceived social isolation in healthy individuals.
Rafnsson et al. (17)	2020	London	Longitudinal 6 years (evaluations every 2 years)	n = 6,677 (≥52 years)	Loneliness Social Isolation Cognitive function	Age Sex Socioeconomic level Educational level Marital status Initial cognition level Previous illnesses Depression	<u>Loneliness</u> 3-item UCLA Loneliness Scale <u>Social isolation</u> 5-item Social Isolation Index <u>Cognitive function</u> Immediate and delayed recall 3 tasks of the Mini-Mental State Examination <u>Dementia evaluation</u> Medical diagnosis based on the short version of the "IQCODE questionnaire."	Of the 6,677 study participants, 220 (3.3%) were diagnosed with dementia (n = 172) during the mean follow-up period of 6 years and 3 months. They had a relatively poorer cognitive function at baseline ($p < 0.001$) and were more likely to have mobility problems ($p < 0.001$).	Dementia risk is associated with loneliness and having fewer close relationships in adulthood. The underlying mechanisms remain to be elucidated, but efforts to improve the quality of older people's relationships may be relevant to dementia risk.

Spreng et al. (22)	2020	UK	Cross-sectional	n = 40,000 (40-69 years)	Loneliness Perceived social isolation Default network	Age Sex BMI Education level Depression Anxiety Alcohol consumption	<u>Loneliness</u> UCLA scale. <u>Neuroimaging studies on loneliness</u> Structural, functional, and diffusion brain scanning (divergent magnetic resonance imaging). Brain imaging of gray matter morphology, white matter microstructure, and neuronal activity fluctuations.	Volume variation in the default network dominated the relationship with loneliness, with most of the variance explained. The greatest significance of the collection of default network regions in loneliness was followed by general associations of the limbic network, dorsal attention network, somatomotor network, visual network, frontoparietal control network, and the least explanatory salience network.	Solitary individuals may demonstrate stronger communication in the default network and greater microstructural integrity of their fornix pathway. Thus, there is a possibility that positive regulation of these neural circuits supports mentalization, reminiscence, and imagination to fill the social void.
Beller & Wagner (21)	2017	Germany	Cross-sectional	n = 4,184 (>40 years)	Loneliness Network size Living alone Physical health Mental health Cognitive health	-	<u>Loneliness</u> Six-item De Jong Gierveld Loneliness Scale <u>Network size</u> Number of members Connectedness towards every member on a scale from 1 to 5 <u>Living alone</u> Dichotomized household size: 1 (living alone), 2 (with at least one other person) <u>Cognitive health</u> Digit Symbol Substitution Test (from WAIS)	Among all indicators of social disconnectedness, only living alone was significantly associated with lower cognitive performance (β = –1.27; p = .005). Subjective loneliness showed a non-significant trend in the same direction (β = –0.63; p = .067), while network quality (β = –0.19; p = .596) and network size (β = 0.09; p = .132) were not significantly associated.	Living alone emerged as the only significant predictor of poorer cognitive performance, highlighting the relevance of objective social disconnectedness.

Tao et al. (16)	2022	US	11 years	n = 2,609 (>45 years)	Loneliness Social isolation Memory	Age Sex Education Province Area of residence Annual household income Functional capacity Alcohol use Smoking Chronic diseases	Loneliness One item from the Center for Epidemiological Studies Depression Social isolation 5-item Social Isolation Index Memory Rey Auditory Verbal Learning Test (RAVLT)	Experiencing both loneliness and social isolation had the strongest negative association with memory (β = –0.80; 95% CI: –1.22, –0.39), followed by loneliness alone (β = –0.73; 95% CI: –1.13, –0.34), social isolation alone (β = –0.69; 95% CI: –1.09, –0.29), and neither condition (β = –0.65; 95% CI: –1.05, –0.25).	Co-occurring loneliness and social isolation are associated with a greater risk of memory decline.
Maharani et al. (20)	2019	UK	Cross-sectional	n = 8,199 (≥50 years)	Hearing Loneliness Social isolation	Age Sex Education Wealth Marital status Depression	Hearing impairment Single question related to the quality of hearing Cognitive Function Episodic memory scores Loneliness 3-item UCLA Loneliness Scale Social isolation 5-item Social Isolation Index	After adjusting for age, sex, education, and wealth, hearing impairment was significantly associated with lower episodic memory scores over 10 years (b = –0.41; p < 0.001). This relationship was partially mediated by loneliness (b = –0.08; p < 0.001) and social isolation (b = –0.09; p = 0.001), with hearing impairment linked to higher levels of both (b = 0.10 and b = 0.04, respectively; both p < 0.001). The direct association between hearing impairment and memory remained significant (b = –0.29; p < 0.001). Depression also mediated the association (b = –0.10; p = 0.001).	Loneliness and social isolation partially explained the association between hearing impairment and episodic memory. Strengthening social networks in older adults with hearing impairment may help prevent cognitive decline.