Journal of Alzheimer's Disease 91 (2023) 1243–1259
DOI 10.3233/JAD-220832
IOS Press

Systematic Review

Loneliness and Cognitive Function in Older Adults Without Dementia: A Systematic Review and Meta-Analysis

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Accepted 6 December 2022
Pre-press 3 January 2023

Abstract.
Background: Loneliness has been highlighted as a risk factor for dementia. However, the nature of the relationship between loneliness and cognitive function prior to onset of dementia is unclear.
Objective: The aim of this systematic review and meta-analysis was to examine the relationship between loneliness and cognitive function in samples screened for dementia at study commencement.
Methods: Five electronic databases (PubMed, PsycNET, Web of Science, EBSCOhost, Scopus) were searched from inception to August 31, 2021. A narrative review and random-effects meta-analysis were conducted on studies meeting search criteria. PROSPERO registration number: CRD42020155539.
Results: The sixteen studies that met inclusion criteria involved 30,267 individuals, with mean age ranging from 63.0 to 84.9 years. Studies varied in dementia screening criteria, measurement of loneliness and cognitive function, and statistical modeling approach. The narrative review indicated that loneliness was associated with poorer global cognition, episodic memory, working memory, visuospatial function, processing speed, and semantic verbal fluency. Results of the meta-analysis indicated that loneliness was negatively associated with global cognitive function (overall $r = –0.08$; 95% CI = –0.14, –0.02; $n = 6$). Due to lack of sufficient data and heterogeneity between studies, we were unable to explore associations with other cognitive domains or longitudinal associations.
Conclusion: Loneliness is associated with subtle impairment across multiple cognitive domains in older adults who were screened for dementia. Better characterization of this relationship will provide important information about how loneliness contributes to the clinical and pathological sequalae of AD and be informative for risk reduction and early detection strategies.

Keywords: Alzheimer disease, cognition, dementia, loneliness

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ISSN 1387-2877/$35.00

INTRODUCTION

With the global aging population, the number of people living with dementia is projected to almost triple in the coming decades, from an estimated 55 million currently to 139 million by 2050 [1]. Given the substantial social and economic costs associated with dementia [2], there is an urgent need for strategies to prevent or delay the onset of dementia. Loneliness has been highlighted as a significant risk factor for dementia that may provide a sensitive early indicator of emerging disease or a modifiable target for dementia risk reduction strategies [3]. Loneliness refers to a subjective unpleasant or distressing feeling that arises in response to a perceived discrepancy between an individual's desired and actual social relationships [4, 5]. Although the prevalence of loneliness follows a u-shaped trajectory across the lifespan, with the highest prevalence in younger adulthood [6], studies also report substantial variability in loneliness during late life [7, 8]. Among older adults (aged over 60 years), estimates of the prevalence of loneliness range between 3.9 and 44% worldwide [9, 10]. Findings from a recent meta-analysis indicated that loneliness is associated with a 26% increased risk of incident dementia over 10 years for adults aged over 50 years [11]. This is comparable to the effects of other well-established risk factors for dementia, such as late-life physical inactivity and smoking, and midlife hypertension and excessive alcohol consumption [12]. According to the precision health framework for loneliness and dementia, a critical step is to be able to predict pre-symptomatic changes in loneliness and brain health on an intra-individual level [13]. These models can then inform the timing and targeting of individualized preventative strategies for loneliness and dementia [13]. Thus, a key focus of this systematic review and meta-analysis is to characterize the relationship between loneliness and cognitive decline in older adults who do not have dementia to help inform prediction models for precision health.

While loneliness has been associated with dementia risk in general, there is growing evidence that it is more strongly related to Alzheimer's disease (AD) than other causes of dementia [14]. Evidence from cross-sectional neuroimaging studies indicate that greater severity of loneliness is associated with higher global cortical amyloid-β (Aβ) burden and accumulation of tau in the right entorhinal cortex in healthy older adults [15, 16]. This relationship persisted even after adjusting for age, sex, depression, anxiety, social isolation, and apolipoprotein E ε4 (APOE ε4) allele carriage. In the same study, individuals who were classified as having preclinical AD on the basis of Aβ neuroimaging were 7.5 (95%CI, 1.7–34.0) times more likely to be lonely than individuals who had normal Aβ levels. Among older adults with subjective cognitive decline and mild cognitive impairment (MCI), lonely individuals have been observed to have decreased grey matter volumes and increased cognitive decline relative to those who were not lonely [17]. These effects were not observed for individuals with dementia, suggesting that loneliness has a stronger relationship with brain structure and cognitive function prior to dementia onset. In contrast, loneliness is not related to postmortem indices of Aβ and tau, despite being associated with increased cognitive decline and dementia risk prior to death [18]. Although there is some inconsistency in the current evidence, overall these findings indicate the potential for loneliness to contribute to the etiology of AD, or be an early symptom of neurocognitive dysfunction, prior to progression to dementia.

An important precursor to the onset of dementia is cognitive decline, which begins decades prior to the emergence of the dementia syndrome [19]. Previous systematic reviews and meta-analyses have linked loneliness with lower cognitive function and increased risk for cognitive decline in older adults. A systematic review of ten studies by Boss et al. [20] reported that loneliness was significantly associated with poorer cognitive function across all of the included studies. When examining specific cognitive domains, they found that loneliness was most consistently associated with poorer global cognitive function, processing speed, as well as immediate and delayed episodic memory recall. Decline in each of these cognitive domains has been linked with preclinical AD previously [21–23] and in particular decline in episodic memory function is highlighted as one of the earliest cognitive changes to occur in the disease [19]. Further supporting the link between loneliness and cognitive function, the results of two meta-analyses [24, 25] indicated that poorer social relationships were associated with greater risk for cognitive decline. Specifically, these studies examined loneliness as part of a larger group of indicators of functional characteristics of social relationships (including social support and satisfaction with household members) that were associated with a 12–15% increased risk of cognitive impairment over 20 years. Taken together, the outcomes of these studies suggest that loneliness may be associated with cognitive decline prior to the onset of dementia.

The potential for reverse causality is a key limitation of the previous systematic review and meta-analyses that examined the association between loneliness and cognitive function, as they included studies that did not control or screen for dementia at baseline. Although the two meta-analyses included only studies that examined community-dwelling samples, they did not specifically consider whether these samples were screened for dementia. The systematic review by Boss et al. did not include any criteria related to the cognitive health of samples in the included studies, and indeed included at least one study where 19% of the sample had dementia. Given that worldwide approximately 5–8% of adults aged over 65 years have a dementia diagnosis [1], it is likely that some of the studies included in these prior systematic reviews and meta-analyses may have included some proportion of individuals with dementia in their samples. Additionally, one of the prior meta-analyses highlighted that 40–50% of the included studies did not adjust for relevant third variables (potential confounders or mediators), such as depression, alcohol use, and physical activity, in their analyses [24]. Consequently, the impact of loneliness on cognitive function independent of additional relevant factors and prior to dementia onset remains unclear.

The aim of the current systematic review and meta-analysis was to examine the nature and magnitude of the relationship between loneliness and cognitive function in samples that were screened for dementia diagnosis at study commencement. We expand on previous investigations in several key ways: 1) by considering the specific role of loneliness, rather than as part of a broader social relationship construct, 2) by examining the effects of loneliness on multiple cognitive domains rather than focusing on a single general indicator of cognition, and 3) by examining these relationships in samples that had been screened for dementia diagnosis at baseline to obtain estimates that were more representative of the effect of loneliness prior to the onset of dementia.

MATERIALS AND METHODS

The protocol of this study has been previously registered and any changes to the protocol documented at the International Prospective Register of Systematic Reviews (PROSPERO; registration number: CRD42020155539. This review and meta-analysis were conducted according to the Preferred Reporting Items for Systematic reviews and Meta-analyses guidelines [26] (see the Supplementary Material for the completed PRISMA checklist for this study).

Search strategy

A systematic search of five databases (PubMed, PsycNET, Web of Science, EBSCOhost, Scopus) from inception to August 31, 2021 was completed. The search strategy included the following subject terms across all databases:

1. Loneliness: Lonel* OR "social isolation" OR "subjective isolation" OR "social withdrawal" OR "feel isolated" OR "felt isolated" OR "feeling* of isolation" OR aloneness OR "felt alone" OR "feel* alone" OR "social alienation" OR "social exclusion"
2. Aging: aged OR elderly OR "older adult" OR aging OR geriatric OR ageing OR old
3. Cognition: Cogniti* OR memory OR executive OR speed OR visuospatial OR semantic OR attention OR psychomotor

Manual search of the reference lists of all included studies was also performed to identify any additional studies for inclusion. All records identified in the search were saved to a Zotero library.

Study selection

The study selection process is outlined in Fig. 1. Duplicate records were identified through electronic search and removed. Next, S.V. screened the title and abstract of all records to select potentially relevant studies according to the inclusion/exclusion criteria outlined below. Independent checking of the title and abstract screening was completed by K.D.H and J.K. and any discrepancies were reviewed and discussed. Full-texts of all potentially eligible studies were independently reviewed by two reviewers (K.D.H, S.V., or J.K.) for final selection and coded as either included or excluded with reason for exclusion noted. Any discrepancies were reviewed by a third reviewer (M.H.L, M.J.S, K.D.H, S.V., or J.K.) and discussed to reach consensus.

Studies were included if they met the following criteria: 1) loneliness (not objective social isolation) was one of the predictors or independent variables; 2) cognitive function was one of the primary outcomes or dependent variables; 3) the study included a sample of community-dwelling older adults with a sample

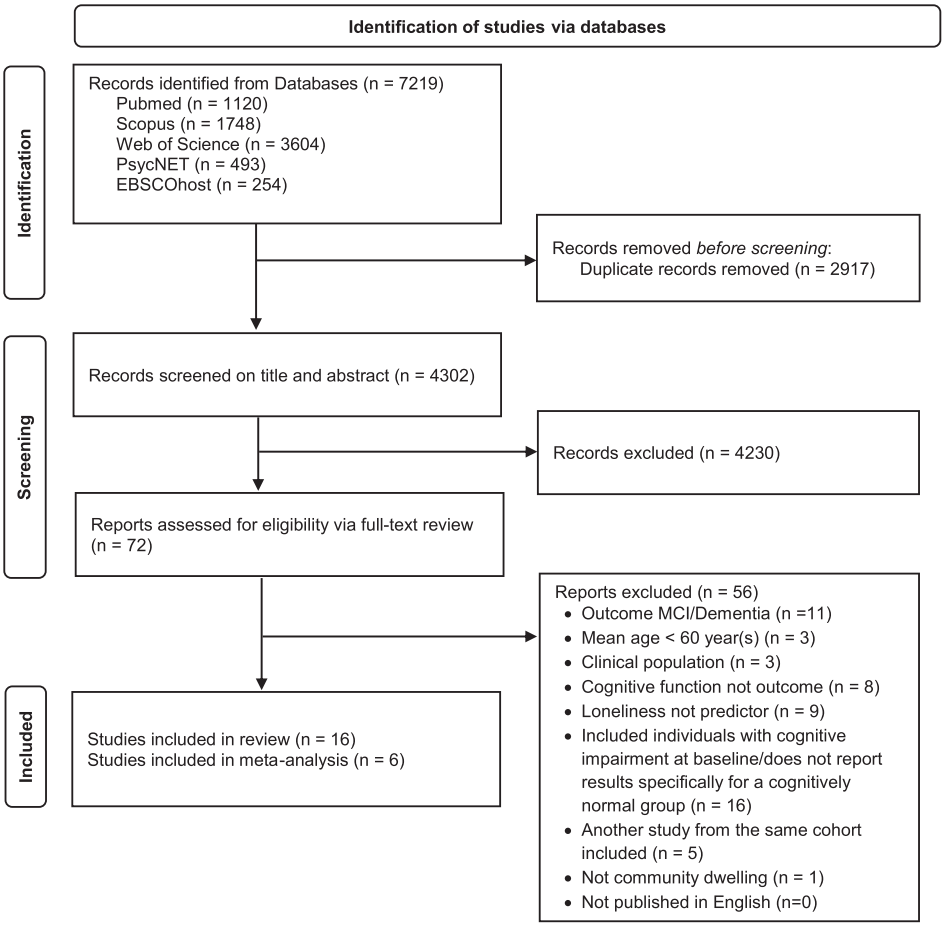

Fig. 1. PRISMA flowchart of study selection.

mean age over 60 years; 4) the study reported quantitative data for results; 5) was published in English; 6) and was a peer-reviewed journal article. Exclusion criteria for studies were: 1) cognitive function was included as a covariate only, or only considered in terms of diagnosis of mild cognitive impairment (MCI) or dementia; 2) findings were only reported for older adults with a dementia diagnosis, or results for a cognitively normal group were not reported; 3) the included sample was non-human or animal, a clinical population, or a younger-aged group. Additionally, review articles, conference abstracts, case studies, and experimental or quasi-experimental studies were not included. If multiple studies from the same cohort met the selection criteria, then the study with the largest sample size or that had the longest follow up was selected for inclusion to ensure that only one study from each cohort was included.

Data extraction

Data were extracted by K.D.H, S.V., and J.K. and saved in a shared online database. After the initial extraction, data for each study were independently cross-checked by a second reviewer. Any discrepancies were reviewed and discussed to reach consensus. From each study, demographics, study inclusion and exclusion criteria, recruitment and sampling processes, design, outcome measures, independent and dependent variables, standardized effect sizes, limitations, and implications were extracted. For longitudinal studies, duration of follow up and attrition rate were also extracted. Demographic data included author's name, year of publication, study design, study location, sample size, sex distribution (% female), mean age and standard deviation, age range, ethnicity, and level of education. For loneliness, the type of measure used and the effect size

for the relationship with cognition were extracted, as well as any adjustment for covariates. Loneliness measures could include psychometrically validated assessments or single-item measures. For cognition, the individual assessment measures used and cognitive domains that were assessed were extracted.

Classification of cognitive outcome measures

We included studies that characterized cognitive function using individual measures, including validated neuropsychological assessment measures and cognitive screening tools (e.g., Mini-Mental State Examination) [27], as well as composite cognitive measures derived from multiple tests. For each study, cognitive performance data were organized according to cognitive domain, with classification of domains made according to standard neuropsychological compendia [28, 29] and previous meta-analyses of cognition [21]. Table 1 provides a summary of the tests classified into each cognitive domain.

Quality assessment

The Joanna Briggs Institute (JBI) risk of bias checklist for cross-sectional studies and risk of bias checklist for cohort studies [30] were used to assess the risk of bias across studies. In line with PRISMA advice we did not calculate an overall quality score for individual studies, instead we examined quality across specific domains. The quality assessment was independently completed by K.D.H. and S.V., and any discrepancies were reviewed and discussed to reach consensus.

Statistical analysis

Meta-analysis for each cognitive domain was planned separately. Due to the complexities of pooling regression coefficients from models that include many covariates [31–35] and the heterogeneity of the models used in the longitudinal studies, we analyzed baseline correlation coefficients for the relationship between loneliness and cognitive function. Effect sizes were pooled for analysis if four or more studies reported effect sizes for equivalent cognitive outcome measures. Random effects meta-analysis with inverse variance method was performed due to the range of sampling methods, study settings, and outcomes being derived from different neuropsychological tests. The restricted maximum likelihood estimator was used to calculate the heterogeneity of variance and Knapp-Hartung adjustments to calculate the confidence interval around the pooled effect. The Cochran Q test and the I^2 statistic were used to assess heterogeneity between studies. Publication bias was assessed via visual inspection of contour-enhanced funnel plot where there were $\geq$10 studies with effect sizes for a given cognitive domain. Sensitivity analyses were conducted to test for outliers and influential studies, and to explore the robustness of the main findings.

RESULTS

Literature search

A total of 7,219 articles were retrieved based on the initial search strategy (Fig. 1). Following the removal of 2,917 duplicates, a total of 4,302 articles were screened on the basis of title and abstract. This resulted in the identification of 72 potentially relevant articles for full text screening. Fifty-six studies did not meet eligibility criteria and were excluded at this stage (see Fig. 1 for full exclusion details), leaving 16 studies meeting the full criteria. Of these, six were of cross-sectional design and ten were longitudinal (see Table 3 for summary of included studies).

Study and participant characteristics

Table 2 summarizes the study and participant characteristics for all included studies. The majority of the studies were conducted as part of larger aging research cohort projects [18, 36–46]. The studies were located across a diverse range of countries across Europe, North America, and Asia, with no country represented by more than three of the included studies. Eight of the studies were drawn from population-based samples that were originally designed to be nationally representative of their respective countries [38–45], five of the studies were community-based samples [18, 36, 46–48], one study used convenience sampling [49], and two studies did not report recruitment methodology [37, 50]. In order to exclude individuals with dementia, ten studies used cut off scores on cognitive or dementia screening tools [36–40, 42, 43, 45, 49, 50,]. Of these, one study additionally excluded individuals classified as having dementia based on the Automated Geriatric Examination Taxonomy (AGECAT) algorithm [43]. Of the remaining six studies, one excluded individuals who met criteria for dementia based on

Table 1
Summary of cognitive domains and neuropsychological tests in each of the included studies

Cognitive domain	Neuropsychological Test	Study
Episodic Memory	Word List Learning, Recall, Recognition (including CERAD, ADAS-COG, WMS-III versions)	[18, 36, 41, 42, 44, 50]
	Story Recall (including Logical Memory, East Boston Story, Rivermead Behavioral Memory Test)	[18, 49]
	Selective Reminding Test	[46]
	WMS-III Visual Reproduction	[36]
Global	Cambridge Cognitive Examination	[43]
	Composite Score	[18]
	Mini Mental State Examination (including English, Cantonese, Spanish, Chinese versions)	[36, 38, 40, 44, 45, 47, 49, 50]
	modified Telephone Interview for Cognitive Status	[39]
	Montreal Cognitive Assessment (including English and Hong Kong versions)	[47, 48]
Language	Boston Naming Test	[18]
Nonverbal Reasoning	Raven's Colored Progressive Matrices	[40]
Perceptual/Processing Speed	Number Comparison	[18]
	Symbol Digit Modalities Test (Oral Version)	[18]
	adapted version of the Coding Task	[40]
	modified Stroop Neuropsychological Screening Test	[18]
	Digit Symbol Substitution	[36]
Premorbid IQ	National Adult Reading Test	[18,36]
Verbal Fluency	Category Fluency	[18, 36, 37, 41, 42, 44, 45, 50]
	Phonological fluency	[18, 36, 45]
Visuospatial Function	Judgement of Line Orientation	[18]
	Standard Progressive Matrices	[18]
Working Memory & Executive Function	Digit Ordering	[18]
	Digit Span Forward and Backward	[18, 41]
	Letter-Number Sequencing	[36, 37, 49]
	Trail-Making Test (TMT A and B)	[49]

CERAD, Consortium to Establish a Registry for Alzheimer's Disease; WMS, Wechsler Memory Scale; WAIS, Wechsler Adult Intelligence Scale.

Table 2
Characteristics of included studies

First author (year)	Cohort	Location	Recruitment Method	Sample size (% of women)	Education	Mean age (SD)	Follow-up duration	Loneliness measurement	Statistical Model	Adjustment for covariates
Cross-sectional Studies										
Fung (2019) [50]	N/A	Hong Kong	Not reported	497 (54.7%)	10.01 (4.68) M (SD) years	68.7 (6.4)	–	6-item DJGLS (Chinese Version)	Linear regression	Education, marital status, living situation, physical burdens, mental health, neuroticism, depression, social network, and social network X loneliness
O'Luanaigh (2012) [36]	Dublin Healthy Aging Study	Ireland	Community	466 (56.6%)	Not reported	75.5 (6.1)	–	Single-item CESD	Linear regression	Age, gender, age left school, social network, social class, marital status, depression, and premorbid IQ
Simpson (2019) [45]	ELES	Spain	Population	962 (52.2%)	Not reported	64.3	–	6-item DJGLS	Linear regression	
Lam (2017) [48]	N/A	Hong Kong	Community	100 (77%)	59% Secondary School or higher	70.2 (6.4)	–	20-item UCLA-LS (Chinese Version)	Bootstrapped modera-tion analysis	Age, non-verbal intelligence, marital status, depression, and depression X loneliness
Montoliu (2019) [49]	N/A	Spain	Convenience	86 (52.3%)	59.7% Secondary School or higher	67.4 (4.4)	–	20-item UCLA-LS (Spanish Version)	Linear regression	Age, sex, marital status, education, and depression
Sol (2021) [46]	WHICAP	United States	Community	425 (63.4)	14.73 (3.18) M (SD) years	74.2 (6.2)	–	NIH Toolbox Emotion Module Loneliness Short Form	Linear regression	Age, sex, race, education, reading ability, and reading ability X loneliness

(*Continued*)

Table 2
(*Continued*)

First author (year)	Cohort	Location	Recruitment Method	Sample size (% of women)	Education	Mean age (SD)	Follow-up duration	Loneliness measurement	Statistical Model	Adjustment for covariates
Longitudinal Studies										
McHugh Power (2019) [44]	TILDA	Ireland	Population	7433 (53.4%)	69.3% Secondary School or higher	64 (9.8)	2 years	5-item UCLA-LS	Structural equation modelling	Age, sex, education, number of cardiovascular conditions, depression, and anxiety
Lara (2019) [41]	Edad con Salud	Spain	Population	1691 (52.8%)	10.5 (6.4) M (SD) years	64.5 (9.8)	3 years	3-item Loneliness Scale	Generalized estimating equation models	Age, sex, education, level of physical activity, alcohol consumption, disability with ADLs, depression, history of stroke, diabetes, and social isolation
Duan (2017) [47]	N/A	China	Community	219 (50.7%)	8.98 (4.18) M (SD) years	69.9 (5.5)	5.2 years	20-item UCLA-LS (Chinese Version)	Linear regression	Age, sex, education, smoking, alcohol consumption, body mass index, history of hypertension, use of antihypertensive agents, history of diabetes mellitus, use of hypoglycemic agents, blood pressure, and fasting blood lipid levels, fasting blood glucose levels, baseline total white matter hyperintensities, and depression
Wilson (2007) [18]	Rush Memory and Aging Project	United States	Community	791 (75.7%)	14.5 (3.0) M (SD) years	80.7 (7.1)	4 years	modified DJGLS (5 items for emotional loneliness only)	Mixed-effects modeling	Age, sex, and education
Yin (2019) [42]	ELSA	England	Population	5885 (55.4%)	72.9% Secondary School or higher	65.3 (10)	10 years	3-item Loneliness Scale	Bivariate dual-change model	Age, sex, education, wealth, limiting long-standing illness, and depressive symptoms
Zhong (2016) [38]	Chinese Longitudinal Healthy Longevity Survey	China	Population	2995 (50.6%)	48.5% No schooling	75.6 (8.3)	6 years	Single-item	Linear regression	Age, sex, education, marital status, living situation, physical exercise habits, current smoking, interviewer-rated physical health, and emotional well-being

Evans (2019) [43]	CFAS-Wales	Wales	Population	1498 (50.6%)	12.07 (2.90) M (SD) years	73.5 (6.2)	2 years	6-item DJGLS	Linear regression	Age, gender, education, marital status, social isolation, social activity, impairment in activities of daily living, living situation, and baseline cognitive performance
Ellwardt (2013) [40]	LASA	Netherlands	Population	2255 (54%)	Not reported	63 (6.7)	6 years	11-item DJGLS	Latent growth mediation models	Age, sex, education, self-reported physical functioning, and emotional support
Griffin (2020) [39]	Health and Retirement Study	United States	Population	4448 (57.5%)	78.26% Secondary School or higher	74.3 (7.1)	6 years	3-item Loneliness Scale	Multi-level modeling	Age, sex, education, race, socioeconomic status, marital status, objective social isolation, cynical hostility, self-reported health, and functional limitations
Windsor (2020) [37]	Berlin Aging Study	Germany	Not reported	516 (50%)	10.75 (2.26) M (SD) years	84.9 (8.7)	13 years	8-items selected from the 20-item UCLA-LS	Multi-level modeling	Age, sex, education, number of physician-observed diagnoses of moderate to severe chronic conditions, depressive symptoms, probable dementia, social network size, and support for others

ELES, Longitudinal Study Aging in Spain; WHICAP, Washington Heights/Inwood Columbia Aging Project; TILDA, The Irish Longitudinal Study on Ageing; ELSA, The English Longitudinal Study of Ageing; CFAS, Cognitive Function and Ageing Studies; LASA, Longitudinal Aging Study Amsterdam; DJGLS, De Jong Gierveld Loneliness Scale; CESD, Center for Epidemiologic Studies Depression Scale; UCLA-LS, University of California Los Angeles Loneliness Scale.

clinician assessment [18], one based on participant self-report of dementia diagnosis [44], one based on inability of the individual to participate in the study assessments due to cognitive impairment [41], and three studies [46–48] reported that dementia diagnosis was an exclusion criteria but did not state how this was assessed. One study [48] additionally excluded individuals who reported taking anti-dementia medication.

The mean age across all included studies was 71.0 years (SD = 7.2, range of mean sample age 63.0–84.9) and the majority of studies included close to equal proportions of females and males (mean 56.7% female across all studies). Most studies [36–38, 40–45, 47, 49, 50] did not report race or ethnicity of their samples. Level of education varied across studies. Five studies reported that >50% of the sample had completed secondary school or higher [39, 42, 44, 48, 49], while one study reported that 48.5% of the sample did not receive any schooling [38]. Seven studies reported years of education [18, 37, 41, 43, 46, 48, 50], the mean of which ranged from 8.98 to 14.73 years across the studies. For the ten longitudinal studies the duration of follow up ranged from 2 to 13 years. While the cross-sectional studies primarily conducted multiple linear regression analyses, the longitudinal studies utilized a range of modelling techniques including structural equation modelling [44], generalized estimating equation models [41], mixed-effects or multilevel models [18, 39], latent growth mediation models [40], and bivariate dual-change models [42].

Loneliness measure

Twelve of the studies used established loneliness measures including the 6-item [43, 45, 50] and 11-item versions [40] of the De Jong Gierveld Loneliness Scale, 5-item [44] and 20-item [47–49] versions of the UCLA Loneliness Scale, NIH Toolbox Emotion Module – Loneliness Short Form [46], and the 3-item Loneliness Scale [39, 41, 42]. Two studies used modified versions of the scales mentioned above. One study [37] used a modified version of the 20-item UCLA Loneliness Scale that retained 8-items, and one other study [18] used a modified version of the 11-item De Jong Gierveld Loneliness Scale that retained 5-items that measured emotional loneliness. Two studies [36, 38] used single-item measures of loneliness, one of which was an item from the Center for Epidemiological Studies Depression (CES-D) scale [51].

Cognitive measures

All studies, except three [37, 42, 46], included a measure of global cognition. Of these, two studies [18, 41] used a composite score derived from a larger neuropsychological battery as an indicator of global cognition, while all other studies used a cognitive screening tool (e.g., MMSE, TICS-M). Six studies [18, 36, 41, 42, 46, 49] included measures of episodic memory, six studies [18, 36, 37, 41, 42, 45] included semantic memory/verbal fluency, four studies [18, 36, 41, 49] included working memory and/or executive function, four studies [18, 36, 37, 49] included processing/perceptual speed, and one study [18] included visuospatial ability. The individual test measures that were categorized into each domain are summarized in Table 1.

Narrative review

Cross-sectional relationship between loneliness and cognitive function

Three cross-sectional studies [36, 45, 50] and all ten longitudinal studies [18, 37–44, 47] reported a significant negative relationship between loneliness and cognitive function at baseline. Each of these studies noted that loneliness was associated with poorer global cognitive function, even after adjusting for covariates such as age, sex, education, social network size, physical health conditions, and depression. In addition to global cognition, loneliness predicted poorer episodic memory [18, 36, 41, 42], working memory [18, 41], visuospatial function [18], processing speed [18, 36, 37], and was specifically associated with poorer semantic [18, 37, 41, 42, 45], but not phonologic [45], verbal fluency. Of the three cross-sectional studies [46, 48, 49] that did not find a significant relationship, two found that the relationship was altered when taking covariates into account. One study [49] reported that loneliness was associated with poorer working memory performance, but this was not significant after adjusting for age, sex, marital status, education, and depressive symptoms. While in the other study [48], the association between loneliness and poorer global cognition was only significant among depressed individuals. Notably, these two studies had the smallest samples ($n \leq 100$) of all the studies included in this review. Consequently, they may not have had sufficient power to reliably detect associations between loneliness and cognitive function.

Longitudinal relationship between loneliness and cognitive function

Six of the longitudinal studies [18, 38, 41, 42, 44, 47] reported that baseline loneliness significantly predicted decline in cognitive function over time. Three of these studies [18, 41, 42] measured specific cognitive domains beyond global cognition, and reported that greater baseline loneliness predicted more rapid decline in episodic memory, working memory, semantic verbal fluency. One study [18] additionally reported that loneliness was associated with more rapid decline in processing speed and visuospatial ability. Of the four studies that did not find a significant longitudinal relationship between loneliness and cognitive function, three studies [39, 40, 43] assessed only global cognition while one study [37] assessed processing speed and semantic fluency. Only three studies [38, 41, 47] reported results for models that were not adjusted for covariates in addition to the fully adjusted models. Notably, the model outcomes were largely unchanged after adjusting for covariates in these studies. One study [37] examined social and emotional aspects of loneliness separately and did not find any differences the relationship between each of these components of loneliness and the cognitive outcomes. Another study [38] examined effects of transient and chronic loneliness on global cognitive function and found that while both were associated with faster decline in cognition, the effect size was greater for chronic loneliness (i.e., loneliness that persisted across multiple timepoints). Additionally, one study [42] examined the bi-directional relationships between loneliness and cognition over time. This study reported that in addition to baseline loneliness predicting decline in memory and verbal fluency, higher baseline memory function predicted a slower increase in loneliness over time, and that declining memory over time was associated with acceleration in worsening of loneliness over time.

Quality assessment

The results of the quality assessment of included studies according to the JBI tools are summarized in Table 3. Methodological issues were found for use of valid and reliable tools for exposure assessment (4/16 included studies) [18, 36–38], description of the study participants and setting (1/16) [50], and that participants were free of the outcome (dementia/cognitive impairment) at the start of the study (1/16) [39]. Additionally, for the longitudinal studies methodological issues were identified for lack of complete follow up (2/10) [37, 40] and use of strategies to address incomplete follow up (1/10) [40].

Meta-analysis

Six studies [37, 40, 43, 45, 46, 48] reported correlation coefficient effect sizes in the main text or supplementary materials. The remaining ten studies were contacted to request these details, only two [39, 41] of which responded. Global cognition was the only cognitive domain for which more than four studies reported an effect size, therefore we conducted the meta-analysis only for this domain.

Loneliness and global cognitive function

Pooled estimates for the association between loneliness and global cognitive function are displayed in Fig. 2. Data from six independent studies ($n = 10{,}954$) were included in the meta-analysis. Greater loneliness was associated with poorer global cognitive function (overall $r = -0.08$; 95% CI = –0.14, –0.02). There was substantial heterogeneity between the studies ($I^2 = 84.2\%$, 95% CI = 67.3%, 92.4%) and the Cochran Q test was significant (χ^2 (5) = 31.69, $p < 0.0001$).

Publication bias

Due to the limited number of included studies ($n = 6$) we did not conduct statistical testing for asymmetry or visual examination of a contour-enhanced funnel plot.

Sensitivity analyses

Influence analyses indicated that Griffin et al. [39] and Evans et al. [43] were potential influential outliers that contributed to the substantial heterogeneity between studies. We conducted sensitivity analyses leaving out each of these studies in turn. When Griffin et al. [39] was not included in the meta-analysis the pooled estimated decreased to $r = -0.06$ (95% CI = –0.12, 0.00), and I^2 decreased to 70%. When Evans et al. [43] was not included in the meta-analysis the pooled estimate increased to $r = -0.11$ (95% CI = –0.15, –0.06), and I^2 decreased to 60%. Notably, the 95% CI for each of these estimates overlapped with the results of the main analysis and with each other, indicating that removal of either of these studies did not significantly alter the effect estimate.

We additionally conducted subgroup analyses and meta-regression to examine the potential for the meta-analysis outcomes to vary with study design, mean age of sample, proportion of females included in the

Table 3
Results of the quality assessment using the Joanna Briggs Institute (JBI) risk of bias checklist for cross- sectional studies and risk of bias checklist for cohort studies

First author (year)	Was the exposure measured in a valid and reliable way?	Were confounding factors identified?	Were strategies to deal with confounding factors stated?	Were the outcomes measured in a valid and reliable way?	Was appropriate statistical analysis used?	Were the criteria for inclusion in the sample clearly defined?	Were the study subjects and the setting described in detail?	Were objective, standard criteria used for measurement of the condition?			
Cross-sectional studies											
Simpson (2019) [45]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	–	–	–
Fung (2019) [50]	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	NA	–	–	–
Lam (2017) [48]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	–	–	–
Montoliu (2019) [49]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	–	–	–
O'Luanaigh (2012) [36]	No	Yes	Yes	Yes	Yes	Yes	Yes	NA	–	–	–
Sol (2021) [46]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	–	–	–
	Was the exposure measured in a valid and reliable way?	Were confounding factors identified?	Were strategies to deal with confounding factors stated?	Were the outcomes measured in a valid and reliable way?	Was appropriate statistical analysis used?	Were the two groups similar and recruited from the same population?	Were the exposures measured similarly to assign people to both exposed and unexposed groups?	Were the participants free of the outcome at the start of the study (or at the moment of exposure)?	Was the follow up time reported and sufficient to be long enough for outcomes to occur?	Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	Were strategies to address incomplete follow up utilized?
Longitudinal studies											
Duan (2017) [47]	Yes	Yes	Yes	Yes	Yes	NA	NA	Yes	Yes	Yes	NA
Ellwardt (2013) [40]	Yes	Yes	Yes	Yes	Yes	NA	NA	Yes	Yes	Unclear	No
Evans (2019) [43]	Yes	Yes	Yes	Yes	Yes	NA	NA	Yes	Yes	Yes	Yes
Griffin (2020) [39]	Yes	Yes	Yes	Yes	Yes	NA	NA	No	Yes	Yes	Yes
Lara (2019) [41]	Yes	Yes	Yes	Yes	Yes	NA	NA	Yes	Yes	Yes	NA
McHugh (2019) [44]	Yes	Yes	Yes	Yes	Yes	NA	NA	Yes	Yes	Yes	Yes
Wilson (2007) [18]	No	Yes	Yes	Yes	Yes	NA	NA	Yes	Yes	Yes	NA
Windsor (2020) [37]	No	Yes	Yes	Yes	Yes	NA	NA	Yes	Yes	No	Yes
Yin (2019) [42]	Yes	Yes	Yes	Yes	Yes	NA	NA	Yes	Yes	Yes	NA
Zhong (2016) [38]	No	Yes	Yes	Yes	Yes	NA	NA	Yes	Yes	Yes	NA

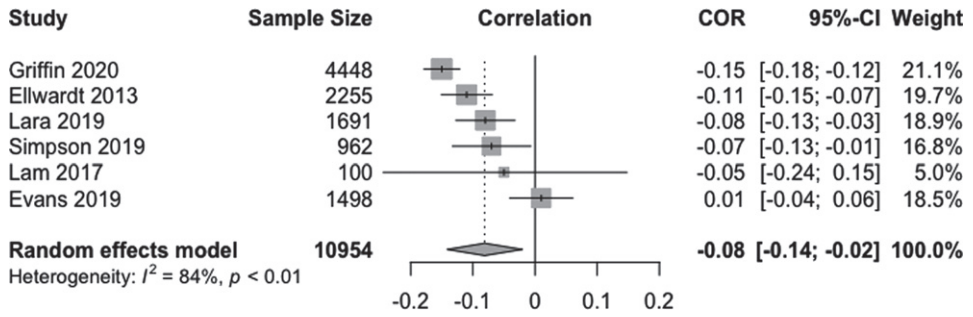

Fig. 2. Forest plot for the effect of loneliness on global cognition. An inverse-variance weighted random-effect meta-analysis is displayed. Effect size corresponds to baseline correlation. COR, correlation; CI, confidence interval.

sample, and type of dementia exclusion criteria. We did not find any significant effects of any of these factors on the meta-analysis results.

DISCUSSION

This systematic review and meta-analysis identified 16 studies that explored the association between loneliness and cognitive function in older adults that were community dwelling and did not have dementia at study commencement. The narrative review of these studies indicated that loneliness had a significant negative relationship with multiple cognitive abilities, both cross-sectionally and longitudinally. However, this was not observed in all studies and in a small number of studies was differed when controlling for demographic and psychological factors, such as depression. Importantly, among the cross-sectional studies those with the smallest samples were the studies that failed to find a significant association between loneliness and cognitive function. This suggests that these studies may not have been adequately powered to detect the relationship of interest. Furthermore, results of the meta-analysis confirmed that loneliness was associated with lower global cognitive function cross-sectionally. A large degree of heterogeneity between studies was identified in the meta-analysis, which may account for some of the inconsistencies in outcomes noted in the narrative review. Sensitivity analyses indicated that the outcome of the meta-analysis was not altered by study design, mean age of sample, proportion of females included in the sample, or type of dementia exclusion criteria. Furthermore, these results closely align with previous systematic reviews and meta-analyses that identified that loneliness was associated with poorer function across multiple cognitive domains despite a large degree of heterogeneity between studies [20, 24, 25]. The present study extends on these previous findings to demonstrate that the relationship between loneliness and cognitive function persists in samples of older adults that were screened for dementia diagnosis at study enrollment.

Although we were not able to conduct meta-analysis across multiple cognitive domains, our narrative review and the results of previous meta-analyses indicate that loneliness is associated with poorer episodic memory, working memory, visuospatial function, processing speed, and semantic verbal fluency. However, the most commonly measured cognitive domain across studies was global cognition. Of the 13 studies that assessed global cognition, all but two studies used a cognitive screening tool to assess this domain. This is important to note because these types of screening measures have been demonstrated to not be sensitive to variation in cognitive function among unimpaired individuals [52, 53]. Additionally, each of the other cognitive domains were assessed in less than half of the studies included in the review and the measures included across studies varied widely. As a consequence, the reliability of results across studies and cognitive domains is unclear. Thus, it is essential for future studies to use measures of cognitive function that are sensitive to detect variation in performance among healthy individuals, to include measures of multiple cognitive domains, and to provide outcomes in standardized metrics that allow for comparison across studies. This would enable greater precision in the characterization of cognitive performance and the association with loneliness.

An important caveat is that much of this evidence is based on cross-sectional observations or from studies where either loneliness or cognitive function were measured at only one time point. For example, only two of the ten longitudinal studies included

in the narrative review evaluated patterns of loneliness across multiple measurement occasions. These studies highlighted the importance of chronicity [38] and changes in loneliness severity over time [42] as predictors of cognitive dysfunction, over and above transient loneliness or baseline levels of loneliness. More recent studies have further underscored the importance of characterizing loneliness trajectories. For example, among middle-aged and older adults, greater duration of loneliness across 8 years was associated with lower baseline memory performance and more rapid memory decline over the following 12 years [54]. Persistent loneliness (loneliness reported across two consecutive 4-year assessments) in middle age has also been associated with increased risk for dementia onset over up to 18 years, relative to not experiencing loneliness [55]. In contrast, transient loneliness (loneliness at the first but not the second assessment) was observed to be associated with decreased risk for dementia onset relative to not experiencing loneliness, suggesting that recovery from loneliness may confer some resilience to dementia [55]. In studies where loneliness is measured only once, it is not possible to identify these types of patterns to identify those at greatest risk for cognitive dysfunction. Furthermore, on the basis of the current evidence it is not clear that loneliness precedes cognitive dysfunction and is exerting a causal influence. For example, greater self-reported memory difficulties are associated with less social participation [56, 57] and elevated Aβ is associated with increased likelihood to experience loneliness among cognitively normal older adults [15]. This suggests that loneliness may arise in response to accumulating neuropathology or cognitive deficits, functioning as an indicator of emerging disease and dysfunction rather than a causal factor. Prospective assessment of both loneliness and cognitive function would help to move beyond simple confirmation of an association by enabling greater understanding of the timing and directionality of the relationship, which can be informative for precision health models of loneliness and dementia.

A further issue is the large degree of heterogeneity between studies in the existing literature on the relationship between loneliness and cognitive function in older adults. As highlighted in this and previous systematic reviews and meta-analyses [20, 24, 25], studies vary widely in terms of the samples included, the measures of loneliness and cognitive function, and statistical modeling approaches. For example, across the 16 studies identified in this systematic review there were 12 different measures of loneliness and almost every study had a different approach to measuring cognition (particularly when measuring multiple cognitive domains). Furthermore, the number and type of covariates included in analyses also varied across studies, with up to 20 covariates included in models. This heterogeneity substantially limits the ability to compare results across studies or to aggregate outcomes for meta-analysis. Thus, while there is growing evidence to indicate that loneliness is associated with poorer cognitive function in older adults, there is much opportunity to further clarify the nature and magnitude of this association prior to dementia onset. Standardization of measures and methods across studies, careful consideration of inclusion of covariates, and more comprehensive assessment of cognitive function with measures that are suitable to detect impairment in cognitively normal older adults [52, 53, 58], is essential to this endeavor.

Limitations

Our research was limited in several ways that are important to note. Although the studies identified in our review included samples from nine countries across Europe, North America, and Asia, our results may not generalize to other populations. In particular we note that our search did not identify any studies from low- and middle-income countries (LMIC), which have greater numbers of individuals living with dementia than high income countries [59]. Although one of our selection criteria were that studies be published in English, we did not exclude any studies on this basis. As such, it is unlikely that the lack of studies from LMIC populations is due to our search criteria, and instead highlights the need for studies focusing on associations between loneliness and cognitive function in these regions. Additionally, our results are limited by the small number of included studies, which meant that we were unable to evaluate effects across multiple domains of cognitive function and were not able to statistically test for publication bias across studies. Furthermore, the results of our meta-regression analyses should be interpreted with caution given the small number of studies, which will have limited our power to detect differences between studies. Nevertheless, our findings point to the need for greater consistency in approaches across studies. This would then enable more robust evaluation of findings across multiple cognitive domains and studies, as well as evaluation of sources of heterogeneity

in study findings such as study design and sample characteristics. Despite these limitations, our systematic review and meta-analysis addressed an important gap by only including studies that evaluated participants for the presence of dementia prior to enrollment or at study commencement. While this does not completely overcome issues of reverse causality, it does provide support for the hypothesis that loneliness is associated with lower cognitive function in older adults who do not have dementia. Furthermore, our findings underscore the importance for preventative strategies from precision heath frameworks to address social and cognitive health among older adults.

Conclusions

There is clear evidence that loneliness is associated with increased risk for dementia [11] and is prevalent among older adults [9, 10]. The results of this systematic review and meta-analysis indicate that prior to dementia onset, loneliness is associated with worse cognitive function across multiple domains. However, the reliance on cross-sectional observations, screening tools to assess cognitive function, and the heterogeneity between studies in terms of sampling, measurement, and analytical methods limits the interpretability of findings across studies. Future studies examining associations between loneliness and cognitive function should ensure that they use standardized, age invariant, and psychometrically-validated measures and carefully select covariate and analytic approaches that allow for comparison of outcomes across studies. Furthermore, prospective designs, with adequate sample size and power for detecting effects, and that measure loneliness and cognitive function across time are needed to clarify the timing and directionality of the relationship. We need to better understand the dynamic relationships between loneliness and cognitive function, above and beyond known correlates of loneliness, such as social isolation, poor physical and mental health, and other social determinants of health factors [60]. This is especially so because loneliness has the potential to be an early indicator of cognitive dysfunction, supporting AD identification and prevention strategies, as well as to be a modifiable target to impede cognitive decline in older adults and delay dementia onset.

ACKNOWLEDGMENTS

The authors have no acknowledgements to report.

FUNDING

This work was supported by Iverson Health Innovation Research Institute Funding to Dr. Michelle H. Lim and National Institute on Aging Grant T32 AG049676 to The Pennsylvania State University.

CONFLICT OF INTEREST

Dr Michelle H. Lim is the Chairperson and Scientific Chair of Ending Loneliness Together and co-director of the Global Initiative on Loneliness and Connection.

All other authors have no conflict of interest to report.

DATA AVAILABILITY

The data supporting the findings of this study are available within the article.

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: https://dx.doi.org/10.3233/JAD-220832.

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