

https://dspace.org/

Cumulative loneliness and subsequent memory function and rate of decline among adults aged 50 in the United States 1996 to 2016 Cumulative loneliness and memory aging in the US

X Yu; A C Westrick; Lindsay Kobayashi

https://hdl.handle.net/10539/39085
WOS

Downloaded from a DSpace repository. https://dspace.org/

Check for updates

Received: 5 April 2022 | Revised: 1 June 2022 | Accepted: 10 June 2022

DOI: 10.1002/alz.12734

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

FEATURED ARTICLE

Cumulative loneliness and subsequent memory function and rate of decline among adults aged ≥50 in the United States, 1996 to 2016

Cumulative loneliness and memory aging in the US

Xuexin Yu[1] | Ashly C. Westrick[1] | Lindsay C. Kobayashi[1,2,3]

[1]Center for Social Epidemiology and Population Health, Department of Epidemiology, University of Michigan School of Public Health, Ann Arbor, Michigan, USA

[2]Institute for Healthcare Policy and Innovation, University of Michigan, Ann Arbor, Michigan, USA

[3]MRC/Wits Rural Public Health and Health Transitions Research Unit (Agincourt), School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

Correspondence
Lindsay C. Kobayashi, Center for Social Epidemiology and Population Health, Department of Epidemiology, 2661 SPH I, 1415 Washington Heights, Ann Arbor, MI 48109, USA.
E-mail: lkob@umich.edu

Funding information
National Institute on Aging, NIH, Grant/Award Numbers: U01AG009740, P30AG012846, R01AG069128, R01AG070953

Abstract

Introduction: The study objective was to investigate the association between loneliness duration and memory function over a 20-year period.

Methods: Data were from 9032 adults aged ≥50 in the Health and Retirement Study. Loneliness status (yes vs. no) was assessed biennially from 1996 to 2004 and its duration was categorized as never, 1 time point, 2 time points, and ≥3 time points. Episodic memory was assessed from 2004 to 2016 as a composite of immediate and delayed recall trials combined with proxy-reported memory. Mixed-effects linear regression models were fitted.

Results: A longer duration of loneliness was associated with lower memory scores ($P < 0.001$) and a faster rate of decline ($P < 0.001$). The association was stronger among adults aged ≥65 than those aged <65 (three-way interaction $P = 0.013$) and was stronger among women than men (three-way interaction $P = 0.002$).

Discussion: Cumulative loneliness may be a salient risk factor for accelerated memory aging, especially among women aged ≥65.

KEYWORDS
loneliness trajectories, memory aging, middle aged, older adults, United States

Highlight

- A longer duration of loneliness was associated with accelerated memory aging.
- The association was stronger among women than men and among older adults than the younger.
- Reducing loneliness in mid- to late life may help maintain memory function.

1 | BACKGROUND

Loneliness is thought to be a modifiable psychosocial risk factor for poor cognitive health outcomes in later life, including increased risks of Alzheimer's disease and related dementias (ADRD).[1–8] As the subjective experience of social isolation, loneliness is theorized to be an adverse emotional state with the perception of unfulfilled personal and social needs.[9] The experience of loneliness could be persistent or

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.
© 2022 The Authors. *Alzheimer's & Dementia* published by Wiley Periodicals LLC on behalf of Alzheimer's Association.

time-varying, as it may be associated with individuals' personal coping strategies to stressful life events,[10] and its health effects may accumulate over time, leading to substantial heterogeneity in its putative effects on cognitive health.[11]

Although there exists rich evidence on the association between loneliness and cognitive health,[1–8] most prior studies have measured loneliness at a single time point.[6,12,13] Results using this approach may be subject to reverse causation: in addition to being a risk factor in its own right, loneliness could also be part of a preclinical syndrome of ADRD, whereby individuals may withdraw from their social networks due to early cognitive symptoms, and thus experience loneliness.[7,14–17] Although some studies have measured longitudinal loneliness trajectories over short periods of time[18] or simultaneously with cognitive outcome trajectories,[2,17,19] these short-term and synchronous measures of loneliness may not provide strong evidence regarding its temporality of association with cognitive outcomes. Finally, it remains unclear whether the cumulative effect of loneliness on cognitive aging varies across the life span and sex identity, although existing research has observed that the health effects of loneliness and subjective social support were more exaggerated in later life compared to earlier in life, and were stronger among women than men.[20,21]

RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed the literature using traditional (e.g., PubMed) sources. There were several relevant citations regarding loneliness, measured at single or two points in time, in relation to Alzheimer's disease and related dementias, which are appropriately cited. However, there were few studies that investigated the association between long-term duration of loneliness and memory aging as well as limited evidence on the effect modification by age and sex.
2. **Interpretation**: Long-term duration of loneliness may be a salient risk factor for accelerated memory aging, especially among women aged 65 and over in the United States.
3. **Future directions**: The mechanisms through which cumulative loneliness may affect memory function should be investigated.

1.1 | Study aims and hypotheses

This study aimed to investigate the association between the cumulative duration of loneliness over an 8-year exposure period and subsequent memory aging over a 12-year follow-up among adults aged ≥50 in the United States. We hypothesized that (1) a longer duration of loneliness would be associated with lower subsequent memory function and a faster rate of memory decline; (2) the association would be stronger among adults aged ≥65 than among those aged <65, and stronger among women than men, as older adults and women might require additional social support and social engagement to reduce or prevent feelings of loneliness.[22,23]

2 | METHODS AND MATERIALS

2.1 | Data sources and study design

Data were from biennial interviews in the US Health and Retirement Study (HRS) from 1996 to 2016. The HRS is a population-based longitudinal household survey of >20,000 adults aged >50 in the United States since 1992 and has been approved by the University of Michigan Institutional Review Board in the United States (IRB number: HUM0061128).[24] HRS has used a mixed mode of interview design since 2006. Half of the study sample aged <80 years is randomly assigned to face-to-face interview and the other half is assigned to telephone interview.[25] Written informed consent was obtained from all study participants. Patients and the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

The current study is a prospective cohort study with loneliness measured biennially from 1996 to 2004 (five waves) and the memory outcome assessed biennially from 2004 to 2016 (seven waves). Individuals aged ≥50 in 1996 with complete loneliness data from 1996 to 2004 and memory scores in at least 2004 were eligible for inclusion. A total of 9032 adults were included in the analyses, contributing 46,890 outcome observations from 2004 to 2016 (Figure S1 in supporting information).

2.2 | Measures

2.2.1 | Exposure: duration of loneliness from 1996 to 2004

At each biennial interview wave, individuals were asked to answer the question "Do you feel lonely?" (yes vs. no), which is an item from the eight-item Center for Epidemiologic Studies Depression (CES-D) scale.[26,27] We classified individuals according to duration of loneliness over the five HRS waves from 1996 to 2004: 0 time points, 1 time point, 2 time points, and ≥3 time points. We combined individuals experiencing loneliness at 3 time points ($n = 525$), 4 time points ($n = 344$), and 5 time points ($n = 200$) because of the limited number experiencing each of these durations.

2.2.2 | Outcome: composite memory z-scores from 2004 to 2016

At each biennial interview wave, episodic memory was assessed as immediate and delayed recall of a 10-word list read out loud by

15525279, 2023, 2, Downloaded from https://alz-journals.onlinelibrary.wiley.com/doi/10.1002/alz.12734 by South African Medical Research, Wiley Online Library on [05/02/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

the interviewer.[28] For HRS participants who were too impaired to directly participate in study interviews, memory was assessed in a proxy interview with a family member or friend to assess respondents' overall memory.[28] Proxy respondents were asked to answer the question "How would you rate the participant's memory at the present time?" (excellent, very good, good, fair, or poor).[28] We used an imputed composite memory score incorporating both the direct memory assessments and proxy memory assessments.[29] This imputed memory score has previously been validated and minimizes potential selection bias, as it allows for the retention of proxy participants in the analysis, who are the most cognitively impaired.[29,30] A total of 3.61% of the analytic sample (1693 observations) used proxy interviews from 2004 to 2016. We standardized imputed composite memory scores (range: −2.13 to 2.33) during the follow-up period from 2004 to 2016 according to its mean (0.94) and standard deviation (SD; 0.65) in 2004.

2.2.3 | Covariates in 1996

We included the following baseline covariates as potential confounders.[2,6,18] Sociodemographic characteristics included age (in years), sex (female vs. male), race (White; Black; other/unknown), marital status (partnered; separated/divorce; widowed; never married), education (less than high school; general education diploma; high school; some college; college and above), employment status (working for pay; not working for pay; unknown), and household wealth (in quintiles). We measured objective social isolation (range: 0 to 5) by assigning one point if the respondent answered "no", "never," or "zero" to each of the following questions: (a) "How many persons are living in the household?"; (b) "Do you have any good friends in your neighborhood?"; (c) "Do you have any relatives in your neighborhood?"; (d) "How often do you do volunteer work for religious or other charitable organizations?"; and (e) "How often do you get together with any of your neighbors just to chat or for a social visit?"[31,32] We assessed individuals' depressive symptoms using the CES-D scores (range: 0 to 7, excluding the loneliness item score).[12] Finally, physical disability was measured using Activities of Daily Living (ADL, range: 0 to 5) limitation scores by assessing difficulty with bathing, eating, dressing, walking across a room, and getting in or out of bed (yes/no for each).

2.3 | Statistical analysis

Descriptive analyses including analysis of variance, Pearson chi-square test, and Kruskal-Wallis rank-sum tests were conducted to compare baseline characteristics by the duration of loneliness. We fitted mixed-effects linear regression models with person-specific random intercepts and slopes to investigate the association of loneliness duration with subsequent composite memory z-scores in 2004 and rate of decline from 2004 to 2016 by including a statistical interaction term between duration of loneliness and years of follow-up (range: 0 to 12).[33] To test effect modification by age and sex, we repeated the analyses and included a three-way interaction term between loneliness duration, years of follow-up, and each of age (≥65; <65) and sex (female; male). We then conducted age- and sex-specific subgroup analyses to directly present the differences. Last, we tested the non-linear rate of decline in composite memory z-scores over time by including a squared term for years of follow-up, which was statistically significant ($P < 0.001$) and therefore was included in the analyses. Three sets of models were performed to sequentially control for (1) baseline age, sex, marital status, race, education, employment status, and household wealth; (2) objective social isolation index; and (3) CES-D scores and ADL scores.

We conducted five sensitivity analyses. First, we performed attrition-weighted modeling analyses by creating inverse probability weights of censoring and mortality to account for differential attrition.[34] Second, we repeated the modeling analyses restricting to individuals in the top 50th percentile of composite memory z-scores in 1996 to help rule out reverse causation between loneliness duration and memory function. Third, we additionally controlled for composite memory z-scores at baseline to help rule out reverse causation, although these model sets may be over-adjusted as baseline memory function could be affected by prior existing loneliness status and thus lie on the causal pathway. Fourth, we repeated the analyses restricting to participants without depression at baseline, defined as having a CES-D score lower than 3, to rule out any effect of pre-existing depression.[8,19] Last, we repeated the analyses with inverse probability treatment weights to account for time-varying confounders that may also be mediators of the relationship between loneliness and memory aging (details in eMethod in supporting information).[35,36]

This report followed the STROBE (Strengthening Reporting of Observational Studies in Epidemiology) reporting guideline for cohort studies. All analyses were performed with Stata/SE 17.0 (StataCorp).

3 | RESULTS

We included 9032 participants (mean [SD] age 63.99 [8.62]) with a 10-year median follow-up from 2004 to 2016 (Table 1). A total of 62.51% (5646/9032) of the study sample were women and 84.53% (7635/9032) were White. A total of 61.04% of participants (5514/9032) were never lonely from 1996 to 2004, 17.99% (1624/9032) experienced loneliness at one point in time, 9.13% (825/9032) experienced loneliness at two points in time, and 11.84% (1069/9032) experienced loneliness at three and over points in time (Table 1). Participants with a longer duration of loneliness had lower composite memory z-scores ($P < 0.001$), higher-level objective social isolation ($P < 0.001$), higher CES-D scores ($P < 0.001$), and higher ADL scores ($P < 0.001$) at baseline than non-lonely adults (Table 1). As shown in Table 1, they were also more likely to be older ($P < 0.001$), women ($P < 0.001$), Black ($P < 0.001$), and not working for pay ($P < 0.001$). The retention distribution of participants by duration of loneliness during the follow-up period from 2004 to 2016 is provided in Table S1 in supporting information. Baseline characteristics of included and excluded participants are provided in Table S2 in supporting information.

15525279, 2023, 2, Downloaded from https://alz-journals.onlinelibrary.wiley.com/doi/10.1002/alz.12734 by South African Medical Research, Wiley Online Library on [05/02/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE 1 Baseline characteristics by duration of loneliness among 9032 participants, the US Health and Retirement Study, 1996 to 2016

Characteristics	Total (*N* = 9032)	Duration of loneliness				
		Never (*n* = 5514)	1 time point (*n* = 1624)	2 time points (*n* = 825)	≥3 time points (*n* = 1069)	*P* value
Composite memory z-scores, mean (SD)	0.40 (0.52)	0.44 (0.47)	0.38 (0.56)	0.31 (0.60)	0.24 (0.64)	<0.001[a]
Age, mean (SD)	63.99 (8.62)	63.20 (8.11)	64.44 (8.81)	65.84 (9.56)	65.92 (9.52)	<0.001[a]
Age, median	62	61	62	63	63	
Age, range	50–95	50–94	50–91	50–90	50–95	
Men (vs. women), *n* (%)	3386 (37.49)	2350 (42.62)	528 (32.51)	241 (29.21)	267 (24.98)	<0.001[b]
Race, *n* (%)						<0.001[b]
White	7635 (84.53)	4839 (87.76)	1339 (82.45)	655 (79.39)	802 (75.02)	
Black	1155 (12.79)	548 (9.94)	238 (14.66)	144 (17.45)	225 (21.05)	
Other/Unknown	242 (2.68)	127 (2.30)	47 (2.89)	26 (3.15)	42 (3.93)	
Marital status, *n* (%)						<0.001[b]
Partnered	6606 (73.14)	4424 (80.23)	1132 (69.70)	521 (63.15)	529 (49.49)	
Separated/divorce	897 (9.93)	420 (7.62)	189 (11.64)	90 (10.91)	198 (18.52)	
Widowed	1287 (14.25)	533 (9.67)	255 (15.70)	191 (23.15)	308 (28.81)	
Never married	242 (2.68)	137 (2.48)	48 (2.96)	23 (2.79)	34 (3.18)	
Employment status, *n* (%)						<0.001[c]
Not working for pay	4797 (53.11)	2615 (47.42)	907 (55.85)	530 (64.24)	745 (69.69)	
Working for pay	4228 (46.81)	2897 (52.54)	715 (44.03)	295 (35.76)	321 (30.03)	
Unknown	7 (0.08)	2 (0.04)	2 (0.12)	-	3 (0.28)	
Education, *n* (%)						<0.001[c]
Less than high school	2116 (23.43)	995 (18.04)	403 (24.82)	266 (32.24)	452 (42.28)	
General education diploma	407 (4.51)	223 (4.04)	80 (4.93)	52 (6.30)	52 (4.86)	
High school	3047 (33.74)	1885 (34.19)	541 (33.31)	284 (34.42)	337 (31.52)	
Some college	1792 (19.84)	1182 (21.44)	328 (20.20)	128 (15.52)	154 (14.41)	
College and above	1670 (18.49)	1229 (22.29)	272 (16.75)	95 (11.52)	74 (6.92)	
Household wealth (in quintile), n (%)						<0.001[c]
1st (the poorest)	1369 (15.16)	557 (10.10)	286 (17.61)	184 (22.30)	342 (31.99)	
2nd	1738 (19.24)	945 (17.14)	342 (21.06)	182 (22.06)	269 (25.16)	
3rd	1876 (20.77)	1174 (21.29)	336 (20.69)	164 (19.88)	202 (18.90)	
4th	1987 (22.00)	1353 (24.54)	334 (20.57)	160 (19.39)	140 (13.10)	
5th (the richest)	2062 (22.83)	1485 (26.93)	326 (20.07)	135 (16.36)	116 (10.85)	
Objective social isolation index, mean (SD)	2.20 (1.07)	2.14 (1.06)	2.27 (1.11)	2.24 (1.03)	2.42 (1.06)	<0.001[a]
CES-D score, mean (SD)	1.02 (1.57)	0.55 (1.00)	1.16 (1.53)	1.69 (1.88)	2.74 (2.22)	<0.001[a]
ADL score, mean (SD)	0.17 (0.59)	0.09 (0.41)	0.21 (0.66)	0.27 (0.75)	0.44 (0.94)	<0.001[a]

Note:
[a]ANOVA.
[b]Pearson chi-square test.
[c]Kruskal-Wallis rank-sum tests.
Missing values on baseline marital status (*n* = 23) were filled with data from 1992–1994. A total of 4914 individuals (54.41%) had missing values on at least one of the five objective social isolation items, which were imputed with data from 1998–2004.
Abbreviations: ADL, Activities of Daily Living; ANOVA, analysis of variance; CES-D, Center for Epidemiologic Studies–Depression; SD, standard deviation.

Table 2 provides regression estimates and 95% confidence intervals (CIs) for the association between duration of loneliness and memory function and decline. A longer duration of loneliness over the period from 1996 to 2004 was associated with lower memory function in 2004 (Models 1–3 *P* trend $P < 0.001$) and a faster rate of subsequent decline from 2004 to 2016 (Models 1–3 *P* trend $p < 0.001$; Table 2). The average annual rate of decline in composite memory z-scores from 2004 to 2016 for those who never experienced loneliness was 0.087

15525279, 2023, 2, Downloaded from https://alz-journals.onlinelibrary.wiley.com/doi/10.1002/alz.12734 by South African Medical Research, Wiley Online Library on [05/02/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE 2 Multivariable mixed effects linear regression analyses of the association between duration of loneliness from 1996 to 2004 and memory function and rate of decline from 2004 to 2016, the US Health and Retirement Study, $N = 9{,}032$

	Model 1		Model 2		Model 3	
Characteristics	***β* (95% CI)**	***P***	***β* (95% CI)**	***P***	***β* (95% CI)**	***P***
Year	−0.063 (−0.067 to −0.059)	<0.001	−0.063 (−0.067 to −0.059)	<0.001	−0.063 (−0.067 to −0.059)	<0.001
Year^2	−0.002 (−0.002 to −0.002)	<0.001	−0.002 (−0.002 to −0.002)	<0.001	−0.002 (−0.002 to −0.002)	<0.001
Duration of loneliness						
Never	ref.		ref.		ref.	
One time point	−0.019 (−0.045 to 0.006)	0.131	−0.016 (−0.042 to 0.009)	0.204	−0.014 (−0.040 to 0.011)	0.278
Two time points	−0.049 (−0.082 to −0.015)	0.005	−0.044 (−0.078 to −0.010)	0.011	−0.040 (−0.075 to −0.005)	0.024
≥Three time points	−0.089 (−0.121 to −0.058)	<0.001	−0.083 (−0.114 to −0.051)	<0.001	−0.075 (−0.109 to −0.041)	<0.001
P trend		<0.001		<0.001		<0.001
Year × Duration of loneliness						
One time point	−0.014 (−0.020 to −0.008)	<0.001	−0.014 (−0.020 to −0.008)	<0.001	−0.014 (−0.020 to −0.008)	<0.001
Two time points	−0.028 (−0.036 to −0.020)	<0.001	−0.028 (−0.036 to −0.020)	<0.001	−0.028 (−0.036 to −0.020)	<0.001
≥Three time points	−0.035 (−0.042 to −0.028)	<0.001	−0.035 (−0.042 to −0.027)	<0.001	−0.035 (−0.042 to −0.027)	<0.001
P trend		<0.001		<0.001		<0.001

Note:
Model 1 adjusted for baseline age, sex, race, marital status, education, employment status, and household wealth.
Model 2 adjusted for baseline age, sex, race, marital status, education, employment status, household wealth, and objective social isolation index.
Model 3 adjusted for baseline age, sex, race, marital status, education, employment status, household wealth, objective social isolation index, CES-D scores, and ADL scores.
Abbreviations: ADL, Activities of Daily Living; CES-D, Center for Epidemiologic Studies–Depression; CI, confidence interval.

SD units per year (years of follow-up: $\beta = -0.063$, 95% CI: −0.067 to −0.059, $P < 0.001$; the squared term for years of follow-up: $\beta = -0.002$, 95% CI: −0.002 to −0.002). The experience of loneliness at 1 time point, 2 time points, and ≥3 time points were, respectively, associated with an additional 0.014 (95% CI: −0.020 to −0.008), 0.028 (95% CI: −0.036 to −0.020), and 0.035 (95% CI: −0.042 to −0.027) SD unit decline, indicating a dose-response relationship (Table 2; Figure 1).

Table 3 and Figure 2 provide age-specific estimates with 95% CIs for differences in composite memory z-scores in 2004 and annual rate of decline from 2004 to 2016 by duration of loneliness. A longer duration of loneliness was associated with worse memory function in 2004 among adults aged 50 to 64 (*P* trend $P = 0.042$) and those aged 65 and over (*P* trend $P < 0.001$; Model 3), while the association was stronger among adults aged ≥65 than those aged 50 to 64 (interaction between duration of loneliness and baseline age *P* trend $P < 0.001$). The average annual rate of memory decline for non-lonely older adults aged ≥65 during the 12-year follow-up period was 0.168 SD units (years of follow-up: $\beta = -0.120$, 95% CI: −0.130 to −0.110; the squared term for years of follow-up: $\beta = -0.004$, 95% CI: −0.004 to −0.003; Model 3). Those who experienced loneliness at 1 time point, 2 time points, and ≥3 time points had an additional 0.022 (95% CI: −0.036 to −0.008), 0.038 (95% CI: −0.056 to −0.021), and 0.036 (95% CI: −0.052 to −0.020) SD unit decline per year among older adults aged 65 and over, while the association was weaker among participants aged 50 to 64 (three-way interaction term *P* trend = 0.013, Model 3, Table 3, Figure 2).

Table 4 and Figure 2 provide sex-specific estimates with 95% CIs for differences in composite memory z-scores in 2004 and annual rate of decline from 2004 to 2016 by duration of loneliness. The association between duration of loneliness and memory function in 2004 was similar among men and women (interaction between duration of loneliness and sex *P* trend $P = 0.189$ in Model 3). The magnitude of annual memory decline among non-lonely adults was also similar among women and men (*P* trend for interaction between year and sex = 0.486). The experience of loneliness at 1 time point, 2 time points, and ≥3 time points was associated with additional 0.017 (95% CI: −0.025 to −0.009), 0.034 (95% CI: −0.045 to −0.024), 0.040 (95% CI: −0.05 to −0.031) SD unit annual decline among women, while estimates for the additional rate of decline by duration of loneliness were comparatively lower among men (1 time point: −0.007 SD unit, 95% CI: −0.015 to 0.001; 2 time points: −0.011 SD unit, 95% CI: −0.023 to 0.001; ≥3 time points: −0.016 SD unit, 95% CI: −0.028 to −0.004; three-way interaction *P* trend $P = 0.002$, as shown in Model 3, Table 4 and Figure 2).

Results from the sensitivity analyses supported our main findings. Results from attrition-weighted modeling analyses yielded nearly identical estimates to the main analyses, although the 95% CIs for the three-way interaction term for duration of loneliness, years of follow-up, and baseline age were wider, likely due to the reduced statistical power imposed by attrition weights (Table S3 in supporting information). Results from the modeling analyses restricted to individuals in the upper 50th percentile of memory z-scores at baseline (Table S4 in supporting information, $n = 4{,}520$) and those additionally controlling

15525279, 2023, 2, Downloaded from https://alz-journals.onlinelibrary.wiley.com/doi/10.1002/alz.12734 by South African Medical Research, Wiley Online Library on [05/02/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

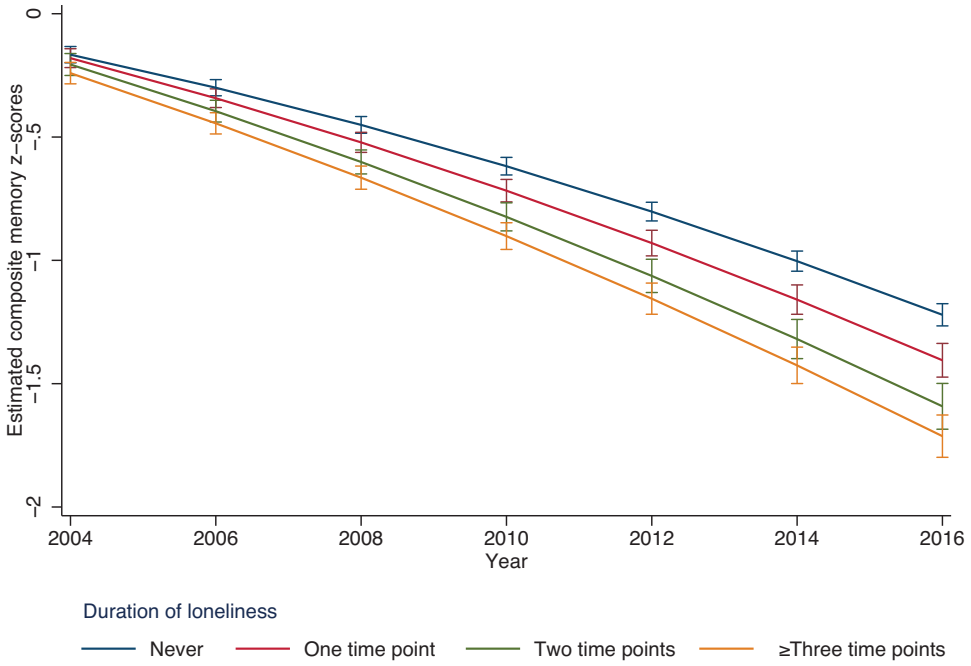


FIGURE 1 Predicted composite memory z-scores from 2004 to 2016 by duration of loneliness, the US Health and Retirement Study. Note: Composite memory z-scores (standard deviation units) are predicted by estimates in Model 3 in Table 2. Covariates in Model 3 were set to the following values: age 63 years, male, partnered, White, less than high school, second quintile of household wealth, objective social isolation index = 1, Center for Epidemiologic Studies–Depression score = 1, and Activities of Daily Living score = 1.

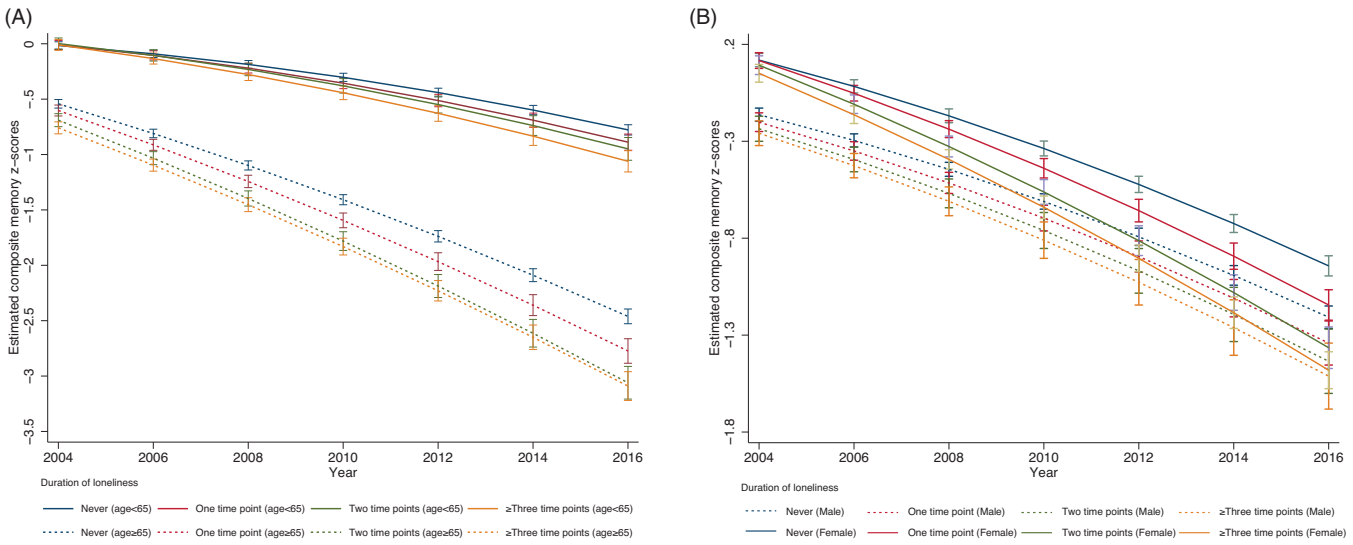


FIGURE 2 Predicted composite memory z-scores from 2004 to 2016 by duration of loneliness, sex and age, the US Health and Retirement Study. Note: Panel A: Predicted composite memory z-scores (standard deviation [SD] units) from 2004 to 2016 by duration of loneliness and baseline age. Composite memory z-scores are predicted using estimates from the fully adjusted pooled model with a three-way interaction term between duration of loneliness, year, and baseline age (50 to 64 vs. ≥65) in Table 3. Covariates were set to the following values: baseline age (60 for the age <65 group; 70 for the age ≥65 group), male, partnered, White, less than high school, second quintile household wealth, objective social isolation index = 1, Center for Epidemiologic Studies–Depression (CES-D) score = 1, and Activities of Daily Living (ADL) score = 1. Panel B: Predicted composite memory z-scores (SD units) from 2004 to 2016 by duration of loneliness and sex. Composite memory z-scores are predicted using estimates from the fully adjusted pooled model with a three-way interaction term between duration of loneliness, year, and sex in Table 4. Covariates were set to the following values: age 63 years, partnered, White, less than high school, 2nd quintile household wealth, objective social isolation index = 1, CES-D score = 1, and ADL score = 1.

15525279, 2023, 2, Downloaded from https://alz-journals.onlinelibrary.wiley.com/doi/10.1002/alz.12734 by South African Medical Research, Wiley Online Library on [05/02/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE 3 Age-specific multivariable-adjusted mixed-effects linear regression analyses of the association between duration of loneliness from 1996 to 2004 and memory function and rate of decline from 2004 to 2016, the US Health and Retirement Study

	Model 1		Model 2		Model 3	
Characteristics	***β* (95% CI)**	***P***	***β* (95% CI)**	***P***	***β* (95% CI)**	***P***
Baseline age 50–64 (*n* = 5761)						
Year	−0.036 (−0.039 to −0.032)	<0.001	−0.035 (−0.039 to −0.032)	<0.001	−0.036 (−0.039 to −0.032)	<0.001
Year^2	−0.002 (−0.003 to −0.002)	<0.001	−0.002 (−0.003 to −0.002)	<0.001	−0.002 (−0.003 to −0.002)	<0.001
Duration of loneliness						
Never	ref.		ref.		ref.	
One time point	−0.018 (−0.036 to 0.001)	0.051	−0.017 (−0.035 to −0.001)	0.071	−0.012 (−0.030 to 0.007)	0.207
Two time points	−0.015 (−0.041 to 0.010)	0.236	−0.014 (−0.039 to 0.012)	0.290	−0.005 (−0.031 to 0.022)	0.736
≥Three time points	−0.051 (−0.075 to −0.027)	<0.001	−0.048 (−0.073 to −0.024)	<0.001	−0.030 (−0.057 to −0.004)	0.026
P trend		<0.001		<0.001		0.042
Year × Duration of loneliness						
One time point	−0.010 (−0.015 to −0.005)	<0.001	−0.010 (−0.015 to −0.005)	<0.001	−0.010 (−0.015 to −0.005)	<0.001
Two time points	−0.016 (−0.023 to −0.009)	<0.001	−0.016 (−0.023 to −0.009)	<0.001	−0.016 (−0.023 to −0.009)	<0.001
≥Three time points	−0.024 (−0.031 to −0.017)	<0.001	−0.024 (−0.031 to −0.017)	<0.001	−0.024 (−0.031 to −0.017)	<0.001
P trend		<0.001		<0.001		<0.001
Baseline age ≥65 (n = 3,271)						
Year	−0.120 (−0.131 to −0.110)	<0.001	−0.120 (−0.130 to −0.110)	<0.001	−0.120 (−0.130 to −0.110)	<0.001
Year^2	−0.004 (−0.004 to −0.003)	<0.001	−0.004 (−0.004 to −0.003)	<0.001	−0.004 (−0.004 to −0.003)	<0.001
Duration of loneliness						
Never	ref.		ref.		ref.	
One time point	−0.029 (−0.087 to 0.029)	0.327	−0.027 (−0.084 to 0.031)	0.366	−0.024 (−0.083 to 0.034)	0.410
Two time points	−0.083 (−0.155 to −0.011)	0.024	−0.079 (−0.151 to −0.007)	0.031	−0.075 (−0.148 to −0.002)	0.044
≥Three time points	−0.159 (−0.225 to −0.094)	<0.001	−0.155 (−0.221 to −0.089)	<0.001	−0.146 (−0.217 to −0.076)	<0.001
P trend		<0.001		<0.001		<0.001
Year × Duration of loneliness						
One time point	−0.022 (−0.036 to −0.009)	0.002	−0.022 (−0.036 to −0.008)	0.002	−0.022 (−0.036 to −0.008)	0.002
Two time points	−0.038 (−0.056 to −0.020)	<0.001	−0.038 (−0.056 to −0.020)	<0.001	−0.038 (−0.056 to −0.021)	<0.001
≥Three time points	−0.036 (−0.052 to −0.020)	<0.001	−0.036 (−0.052 to −0.020)	<0.001	−0.036 (−0.052 to −0.020)	<0.001
P trend		<0.001		<0.001		<0.001
P trend (Year × Baseline age)*		<0.001		<0.001		<0.001
P trend (Duration of loneliness × Baseline age)*		<0.001		<0.001		<0.001
P trend (Year × Duration of loneliness × Baseline age)*		0.015		0.014		0.013

Note: * *P* values were derived from pooled models.
Model 1 adjusted for baseline age (in years), sex, race, marital status, education, employment status, and household wealth.
Model 2 adjusted for baseline age (in years), sex, race, marital status, education, employment status, household wealth, and objective social isolation index.
Model 3 adjusted for baseline age (in years), sex, race, marital status, education, employment status, household wealth, objective social isolation index, CES-D scores, and ADL scores.
Abbreviations: ADL, Activities of Daily Living; CES-D, Center for Epidemiologic Studies–Depression; CI, confidence interval.

for baseline composite memory z-scores (Table S5 in supporting information) were negligibly different from the main findings, suggesting that reverse causation is unlikely. Results from analyses restricted to individuals with CES-D scores <3 (*n* = 7,702) were similar to our main findings (Table S6 in supporting information), suggesting that our measure of loneliness does not simply reflect depressive symptoms. Finally, models with inverse probability treatment weights generated similar results with main findings (Table S7 in supporting information). Estimates for the three-way interaction term between age, duration of loneliness, and years of follow-up from these models were in the same direction but imprecise, likely due to the increased variance imposed by weighting (Table S7).

15525279, 2023, 2, Downloaded from https://alz-journals.onlinelibrary.wiley.com/doi/10.1002/alz.12734 by South African Medical Research, Wiley Online Library on [05/02/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE 4 Sex-specific multivariable-adjusted mixed-effects linear regression analyses of the association between duration of loneliness from 1996 to 2004 and memory function and rate of decline from 2004 to 2016, the US Health and Retirement Study

	Model 1		Model 2		Model 3	
Characteristics	***β* (95% CI)**	***P***	***β* (95% CI)**	***P***	***β* (95% CI)**	***P***
Women ($n = 5,646$)						
Year	−0.060 (−0.066 to −0.055)	<0.001	−0.060 (−0.066 to −0.054)	<0.001	−0.060 (−0.066 to −0.054)	<0.001
Year^2	−0.003 (−0.003 to −0.002)	<0.001	−0.003 (−0.003 to −0.002)	<0.001	−0.003 (−0.003 to −0.002)	<0.001
Duration of loneliness						
Never	ref.		ref.		ref.	
One time point	−0.010 (−0.044 to 0.023)	0.534	−0.008 (−0.041 to 0.025)	0.629	−0.006 (−0.039 to 0.028)	0.733
Two time points	−0.040 (−0.084 to 0.003)	0.068	−0.037 (−0.080 to 0.007)	0.097	−0.032 (−0.077 to 0.012)	0.150
≥Three time points	−0.091 (−0.130 to −0.051)	<0.001	−0.085 (−0.125 to −0.046)	<0.001	−0.077 (−0.120 to −0.034)	<0.001
P trend		<0.001		<0.001		0.001
Year × Duration of loneliness						
One time point	−0.017 (−0.025 to −0.010)	<0.001	−0.017 (−0.025 to −0.009)	<0.001	−0.017 (−0.025 to −0.009)	<0.001
Two time points	−0.035 (−0.045 to −0.024)	<0.001	−0.034 (−0.045 to −0.024)	<0.001	−0.034 (−0.045 to −0.024)	<0.001
≥Three time points	−0.040 (−0.050 to −0.031)	<0.001	−0.040 (−0.050 to −0.031)	<0.001	−0.040 (−0.050 to −0.031)	<0.001
P trend		<0.001		<0.001		<0.001
Men (n = 3,386)						
Year	−0.069 (−0.075 to −0.063)	<0.001	−0.069 (−0.074 to −0.063)	<0.001	−0.069 (−0.074 to −0.063)	<0.001
Year^2	−0.001 (−0.002 to −0.001)	<0.001	−0.001(−0.002 to −0.001)	<0.001	−0.001(−0.002 to −0.001)	<0.001
Duration of loneliness						
Never	ref.		ref.		ref.	
One time point	−0.041 (−0.080 to −0.003)	0.036	−0.037 (−0.075 to 0.002)	0.063	−0.034 (−0.073 to 0.005)	0.092
Two time points	−0.073 (−0.127 to −0.018)	0.009	−0.066 (−0.121 to −0.012)	0.017	−0.061 (−0.116 to −0.005)	0.032
≥Three time points	−0.098 (−0.152 to −0.044)	<0.001	−0.090 (−0.144 to −0.035)	0.001	−0.079 (−0.137 to −0.020)	0.008
P trend		<0.001		<0.001		0.001
Year × Duration of loneliness						
One time point	−0.007 (−0.015 to 0.001)	0.089	−0.007 (−0.015 to 0.001)	0.089	−0.007 (−0.015 to 0.001)	0.089
Two time points	−0.012 (−0.023 to −0.001)	0.047	−0.011 (−0.023 to 0.001)	0.051	−0.011 (−0.023 to 0.001)	0.051
≥Three time points	−0.016 (−0.028 to −0.004)	0.008	−0.016 (−0.028 to −0.004)	0.008	−0.016 (−0.028 to −0.004)	0.008
P trend		0.001		0.001		0.001
P trend (Year × Sex)*		0.475		0.486		0.486
P trend (Duration of loneliness × Sex)*		0.182		0.200		0.189
P trend (Year × Duration of loneliness × Sex)*		0.002		0.002		0.002

Note: * *P* values were derived from pooled models.
Model 1 adjusted for baseline age, race, marital status, education, employment status, and household wealth.
Model 2 adjusted for baseline age, race, marital status, education, employment status, household wealth, and objective social isolation index.
Model 3 adjusted for baseline age, race, marital status, education, employment status, household wealth, objective social isolation index, CES-D scores, and ADL scores.
Abbreviations: ADL, Activities of Daily Living; CES-D, Center for Epidemiologic Studies–Depression; CI, confidence interval.

4 | DISCUSSION

In this population-based, prospective cohort of 9032 middle-aged and older adults in the United States, cumulative loneliness over an 8-year exposure period was associated with accelerated memory aging during the subsequent 12-year follow-up, indicating a dose–response relationship. The observed association was modified by age and sex, suggesting that ameliorating loneliness status in mid- to late life may help delay memory aging, especially among women aged 65 and over.

4.1 | Comparison to existing studies

Our findings are consistent with existing studies demonstrating the role of loneliness as a potential risk factor for cognitive aging.[4,17–19]

15525279, 2023, 2, Downloaded from https://alz-journals.onlinelibrary.wiley.com/doi/10.1002/alz.12734 by South African Medical Research, Wiley Online Library on [05/02/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

This study contributes to the existing literature by measuring the duration of loneliness over a sustained mid- to late life period, thus providing additional support for a causal relationship. Biological plausibility for the observed association is strong: the sustained experience of loneliness may induce emotional stress, anger, and anxiety,[37] resulting in unhealthy coping behaviors such as alcohol consumption,[38] physical inactivity,[39] smoking,[40] and sleep fragmentation,[41] thus leading to increased risks of hypertension,[42] stroke,[43] heart disease,[43] depressive symptoms,[44] and amyloid beta (Aβ) deposition.[45,46] These are all important predictors of risks for dementias and accelerated cognitive aging among older adults.[47,48]

Consistent with our second hypothesis, we found that the association of loneliness with memory aging was stronger among adults aged 65 and over than among those aged under 65. This finding is in line with existing studies indicating that loneliness exacerbates age-related differences in evaluated systolic blood pressure and cardiovascular risk.[49,50] Notably, our findings are contradictory to existing research indicating that the association between loneliness and dementia risk becomes weaker in magnitude with older age.[12] One potential explanation for this heterogeneity is that our study applied validated composite memory z-scores that ensured the inclusion of the most cognitively impaired older adults to minimize potential selection bias in our findings.[29] However, these inconsistent findings may also indicate a domain-specific association between loneliness and cognitive function, which requires further investigation.

Our observed effect modification by sex is consistent with several studies demonstrating the effects of loneliness on mental health are greater among women than men.[51,52] Gender roles and social norms, such as the expectations and demands of social relationships where women tend to have larger and more multifaceted social networks than men, may make women less likely to feel lonely than men, but more vulnerable once experiencing cumulative loneliness.[21,23,51,52] However, existing studies focusing on the sex-specific association between loneliness and cognitive function have yielded inconsistent findings.[12,53] One prior population-based study in China found that the experience of loneliness was associated with a greater risk of dementia among men than women,[53] while another study in the United States suggested no sex-specific effects of loneliness on global cognitive performance.[12] The inconsistency between these findings and ours could be attributable to population differences in the effects of loneliness on cognitive aging, but could also be due to the use of different measures of loneliness exposure or systematic measurement error that may vary across populations whereby men may be more reluctant to admit loneliness than women due to fear of social stigma.[54] Further research is warranted from diverse populations in which the cultural meaning and experience of loneliness and its subsequent effects on cognitive aging may vary.

4.2 | Limitations and strengths

This study has limitations. First, as we did not employ the three-item University of California Los Angeles loneliness scale because of limitations in its use in the 1992 to 2000 HRS datasets,[55] our use of a single item to assess loneliness may result in measurement error. However, this item has been validated as part of a larger depression scale and our use of repeated measures of loneliness over an 8-year period helps to minimize within-person variance in loneliness exposure. Second, selection bias may exist as we required participants to survive and to have been retained in the HRS from 1996 through 2004 to have complete five-wave data on loneliness. This may have led to our results underestimating the true magnitude of association, as older adults with a longer duration of loneliness and with lower memory function could be more likely to have died or dropped out of the study during the exposure period. Third, there could be residual confounding by objective social isolation, as there is no single well-accepted measure of objective social isolation. We incorporated multiple measures capturing different forms of social connections to measure and adjust for objective social isolation as best as possible. Moreover, just over half of participants (54%) had missing values on at least one objective social isolation item and these values were imputed in later waves (1998 to 2004), possibly leading to over-adjustment and attenuation of estimates in Models 2 and 3.

To the best of our knowledge, this is one of the first studies to measure cumulative duration of loneliness over an 8-year period in mid- to late life in relation to memory aging. We investigated this association overall and by age and sex. The observed dose–response association between loneliness duration and memory aging indicates the potential for a biological link between the psychological experience of loneliness and memory function, which should be further investigated. Our sensitivity analyses restricted to cognitively healthy individuals at baseline help to rule out reverse causation, adding support for a potential causal relationship to the literature on this topic.

4.3 | Conclusion

In this population-based cohort study of middle-aged and older adults in the United States, cumulative duration of loneliness in mid- to late life may be a salient risk factor for accelerated memory aging, especially among women aged 65 and over. Further research from diverse populations to investigate underlying biological mechanisms is warranted.

ACKNOWLEDGMENTS

The authors thank Dr. Lindsay Pool and Brendan O'Shea for providing methodology support in the creation of inverse probability treatment weights. The authors thank Dr. Fan Xia for modifying Figures 1–2.

The Health and Retirement Study is funded by the National Institute on Aging (U01AG009740) and performed at the Institute for Social Research, University of Michigan. Dr. Kobayashi was supported by National Institute on Aging at the National Institutes of Health grants P30AG012846, R01AG069128, and R01AG070953.

The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data;

15525279, 2023, 2, Downloaded from https://alz-journals.onlinelibrary.wiley.com/doi/10.1002/alz.12734 by South African Medical Research, Wiley Online Library on [05/02/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

CONFLICTS OF INTEREST

The authors report no conflicts of interest. Author disclosures are available in the supporting information.

ORCID

Xuexin Yu https://orcid.org/0000-0002-6484-6035

REFERENCES

1. Evans IEM, Llewellyn DJ, Matthews FE, et al. Living alone and cognitive function in later life. *Arch Gerontol Geriatr*. 2019;81:222-233. doi:10.1016/j.archger.2018.12.014
2. Wilson RS, Krueger KR, Arnold SE, et al. Loneliness and risk of Alzheimer disease. *Arch Gen Psychiatry*. 2007;64(2):234-240. doi:10.1001/archpsyc.64.2.234
3. 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 Sco Sci*. 2017;75(1):114-124. doi:10.1093/geronb/gbx087
4. Shankar A, Hamer M, McMunn A, Steptoe A. Social isolation and loneliness: relationships with cognitive function during 4 years of follow-up in the English longitudinal study of ageing. *Psychosom Med*. 2013;75(2):161-170. doi:10.1097/PSY.0b013e31827f09cd
5. Holwerda TJ, Deeg DJ, Beekman AT, et al. Feelings of loneliness, but not social isolation, predict dementia onset: results from the Amsterdam Study of the Elderly (AMSTEL). *J Neurol Neurosurg Psychiatry*. 2014;85(2):135-142. doi:10.1136/jnnp-2012-302755
6. Poey JL, Burr JA, Roberts JS. Social connectedness, perceived isolation, and dementia: does the social environment moderate the relationship between genetic risk and cognitive well-being? *Gerontologist*. 2017;57(6):1031-1040. doi:10.1093/geront/gnw154
7. Boss L, Kang DH, Branson S. Loneliness and cognitive function in the older adult: a systematic review. *Int Psychogeriatr*. 2015;27(4):541-553. doi:10.1017/s1041610214002749
8. Donovan NJ, Wu Q, Rentz DM, Sperling RA, Marshall GA, Glymour MM. Loneliness, depression and cognitive function in older U.S. adults. *Int J Geriatr Psychiatry*. 2017;32(5):564-573. doi:10.1002/gps.4495
9. Smoyak SA. Loneliness: a sourcebook of current theory, research and therapy. *J Psychosoc Nurs Ment Health Ser*. 1984;22(6):40-41. doi:10.3928/0279-3695-19840601-09
10. Mund M, Freuding MM, Möbius K, Horn N, Neyer FJ. The stability and change of loneliness across the life span: a meta-analysis of longitudinal studies. *Pers Soc Psychol Rev*. 2020;24(1):24-52. doi:10.1177/1088868319850738
11. Saczynski JS, Pfeifer LA, Masaki K, et al. The effect of social engagement on incident dementia: the Honolulu-Asia Aging Study. *Am J Epidemiol*. 2006;163(5):433-440. doi:10.1093/aje/kwj061
12. Sutin AR, Stephan Y, Luchetti M, Terracciano A. Loneliness and risk of dementia. *J Gerontol B Psychol Sci Sco Sci*. 2018;75(7):1414-1422. doi:10.1093/geronb/gby112
13. Rawtaer I, Gao Q, Nyunt MSZ, et al. Psychosocial risk and protective factors and incident mild cognitive impairment and dementia in community dwelling elderly: findings from the Singapore Longitudinal Ageing Study. *J Alzheimers Dis*. 2017;57:603-611. doi:10.3233/JAD-160862
14. Okely JA, Deary IJ. Longitudinal associations between loneliness and cognitive ability in the Lothian Birth Cohort 1936. *J Gerontol B Psychol Sci Soc Sci*. 2019;74(8):1376-1386. doi:10.1093/geronb/gby086
15. Kaup AR, Byers AL, Falvey C, et al. Trajectories of depressive symptoms in older adults and risk of dementia. *JAMA Psychiatry*. 2016;73(5):525-531. doi:10.1001/jamapsychiatry.2016.0004
16. Li G, Wang LY, Shofer JB, et al. Temporal relationship between depression and dementia: findings from a large community-based 15-year follow-up study. *Arch Gen Psychiatry*. 2011;68(9):970-977. doi:10.1001/archgenpsychiatry.2011.86
17. Zhong BL, Chen SL, Tu X, Conwell Y. Loneliness and cognitive function in older adults: findings from the Chinese Longitudinal Healthy Longevity Survey. *J Gerontol B Psychol Sci Sco Sci*. 2017;72(1):120-128. doi:10.1093/geronb/gbw037
18. Akhter-Khan SC, Tao Q, Ang TFA, et al. Associations of loneliness with risk of Alzheimer's disease dementia in the Framingham Heart Study. *Alzheimers Dement*. 2021;17(10):1619-1627. doi:10.1002/alz.12327
19. Lara E, Caballero FF, Rico-Uribe LA, et al. Are loneliness and social isolation associated with cognitive decline? *Int J Geriatr Psychiatry*. 2019;34(11):1613-1622. doi:10.1002/gps.5174
20. Hawkley LC, Masi CM, Berry JD, Cacioppo JT. Loneliness is a unique predictor of age-related differences in systolic blood pressure. *Psychol Aging*. 2006;21(1):152-164. doi:10.1037/0882-7974.21.1.152
21. Yu B, Steptoe A, Niu K, Jia X. Social isolation and loneliness as risk factors for grip strength decline among older women and men in China. *J Am Med Dir Assoc*. 2020;21(12):1926-1930. doi:10.1016/j.jamda.2020.06.029
22. Weiner MR, Monin JK, Mota N, Pietrzak RH. Age differences in the association of social support and mental health in male US veterans: results from the National Health and Resilience in Veterans Study. *Am J Geriatr Psychiatry*. 2016;24(4):327-336. doi:10.1016/j.jagp.2015.11.007
23. Antonucci TC, Akiyama H. An examination of sex differences in social support among older men and women. *Sex Roles*. 1987;17(11):737-749. doi:10.1007/BF00287685
24. Sonnega A, Faul JD, Ofstedal MB, Langa KM, Phillips JW, Weir DR. Cohort profile: the health and retirement study (HRS). *Int J Epidemiol*. 2014;43(2):576-585. doi:10.1093/ije/dyu067
25. Langa KM, Ryan LH, McCammon RJ, et al. The health and retirement study harmonized cognitive assessment protocol project: study design and methods. *Neuroepidemiology*. 2020;54(1):64-74. doi:10.1159/000503004
26. Steffick DE. *Documentation of affective functioning measures in the Health and Retirement Study*. Ann Arbor, Michigan: Institute for Social Research, University of Michigan; 2020.
27. Lewinsohn PM, Seeley JR, Roberts RE, Allen NB. Center for epidemiologic studies depression scale (CES-D) as a screening instrument for depression among community-residing older adults. *Psychol Aging*. 1997;12(2):277-287. doi:10.1037//0882-7974.12.2.277
28. Mary Beth O, Gwenith GF, Herzog AR. *Documentation of cognitive functioning measures in the Health and Retirement Study*. Ann Arbor, Michigan: Institute for Social Research, University of Michigan; 2005.
29. Wu Q, Tchetgen EJ, Osypuk TL, White K, Mujahid M, Maria Glymour M. Combining direct and proxy assessments to reduce attrition bias in a longitudinal study. *Alzheimer Dis Assoc Disord*. 2013;27(3):207-212. doi:10.1097/WAD.0b013e31826cfe90
30. Whitlock EL, Diaz-Ramirez LG, Smith AK, et al. Association of coronary artery bypass grafting vs percutaneous coronary intervention with memory decline in older adults undergoing coronary revascularization. *JAMA*. 2021;325(19):1955-1964. doi:10.1001/jama.2021.5150
31. Shaw JG, Farid M, Noel-Miller C, et al. Social isolation and medicare spending: among older adults, objective social isolation increases expenditures while loneliness does not. *J Aging Health*. 2017;29(7):1119-1143. doi:10.1177/0898264317703559
32. Peng S, Roth AR. Social isolation and loneliness before and during the covid-19 pandemic: a longitudinal study of US adults older than 50.

15525279, 2023, 2, Downloaded from https://alz-journals.onlinelibrary.wiley.com/doi/10.1002/alz.12734 by South African Medical Research, Wiley Online Library on [05/02/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

J Gerontol B Psychol Sci Sco Sci. 2022;77(7):e185-e190. doi:10.1093/geronb/gbab068
33. Van Dongen HPA, Olofsen E, Dinges DF, Maislin G. Mixed-model regression analysis and dealing with interindividual differences. *Methods in Enzymology*. Academic Press; 2004;384:139-171.
34. Weuve J, Tchetgen EJ, Glymour MM, et al. Accounting for bias due to selective attrition: the example of smoking and cognitive decline. *Epidemiology*. 2012;23(1):119-128. doi:10.1097/EDE.0b013e318230e861
35. Robins JM, Hernán MA, Brumback B. Marginal structural models and causal inference in epidemiology. *Epidemiology*. 2000;11(5):550-560. doi:10.1097/00001648-200009000-00011
36. Pool LR, Burgard SA, Needham BL, Elliott MR, Langa KM, Mendes de Leon CF. Association of a negative wealth shock with all-cause mortality in middle-aged and older adults in the United States. *JAMA*. 2018;319(13):1341-1350. doi:10.1001/jama.2018.2055
37. Cacioppo JT, Hawkley LC, Ernst JM, et al. Loneliness within a nomological net: an evolutionary perspective. *J Res Pers*. 2006;40(6):1054-1085. doi:10.1016/j.jrp.2005.11.007
38. Akerlind I, Hörnquist JO. Loneliness and alcohol abuse: a review of evidences of an interplay. *Soc Sci Med*. 1992;34(4):405-414. doi:10.1016/0277-9536(92)90300-f
39. Hawkley LC, Thisted RA, Cacioppo JT. Loneliness predicts reduced physical activity: cross-sectional & longitudinal analyses. *Health Psychol*. 2009;28(3):354-363. doi:10.1037/a0014400
40. Dyal SR, Valente TW. A systematic review of loneliness and smoking: small effects, big implications. *Subst Use Misuse*. 2015;50(13):1697-1716. doi:10.3109/10826084.2015.1027933
41. Kurina LM, Knutson KL, Hawkley LC, Cacioppo JT, Lauderdale DS, Ober C. Loneliness is associated with sleep fragmentation in a communal society. *Sleep*. 2011;34(11):1519-1526. doi:10.5665/sleep.1390
42. Hawkley LC, Thisted RA, Masi CM, Cacioppo JT. Loneliness predicts increased blood pressure: 5-year cross-lagged analyses in middle-aged and older adults. *Psychol Aging*. 2010;25(1):132-141. doi:10.1037/a0017805
43. Valtorta NK, Kanaan M, Gilbody S, Ronzi S, Hanratty B. Loneliness and social isolation as risk factors for coronary heart disease and stroke: systematic review and meta-analysis of longitudinal observational studies. *Heart*. 2016;102(13):1009-1016. doi:10.1136/heartjnl-2015-308790
44. Lee SL, Pearce E, Ajnakina O, et al. The association between loneliness and depressive symptoms among adults aged 50 years and older: a 12-year population-based cohort study. *Lancet Psychiatry*. 2021;8(1):48-57. doi:10.1016/S2215-0366(20)30383-7
45. Ju YS, Ooms SJ, Sutphen C, et al. Slow wave sleep disruption increases cerebrospinal fluid amyloid-β levels. *Brain*. 2017;140(8):2104-2111. doi:10.1093/brain/awx148
46. Spira AP, Chen-Edinboro LP, Wu MN, Yaffe K. Impact of sleep on the risk of cognitive decline and dementia. *Curr Opin Psychiatry*. 2014;27(6):478-483. doi:10.1097/YCO.0000000000000106
47. Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *Lancet*. 2020;396(10248):413-446. doi:10.1016/S0140-6736(20)30367-6
48. Zeki Al Hazzouri A, Caunca MR, Nobrega JC, et al. Greater depressive symptoms, cognition, and markers of brain aging. Northern Manhattan Study. *Neurology*. 2018;90(23):e2077-e2085. doi:10.1212/wnl.0000000000005639
49. Ong AD, Rothstein JD, Uchino BN. Loneliness accentuates age differences in cardiovascular responses to social evaluative threat. *Psychol Aging*. 2012;27(1):190-198. doi:10.1037/a0025570
50. Hawkley LC, Masi CM, Berry JD, Cacioppo JT. Loneliness is a unique predictor of age-related differences in systolic blood pressure. *Psychol Aging*. 2006;21(1):152-164. doi:10.1037/0882-7974.21.1.152
51. Boehlen FH, Maatouk I, Friederich H-C, Schoettker B, Brenner H, Wild B. Loneliness as a gender-specific predictor of physical and mental health-related quality of life in older adults. *Qual Life Res*. 2021;31(7):2023-2033. doi:10.1007/s11136-021-03055-1
52. Liu H, Zhang M, Yang Q, Yu B. Gender differences in the influence of social isolation and loneliness on depressive symptoms in college students: a longitudinal study. *Soc Psychiatry Psychiatr Epidemiol*. 2020;55(2):251-257. doi:10.1007/s00127-019-01726-6
53. Zhou Z, Wang P, Fang Y. Loneliness and the risk of dementia among older Chinese adults: gender differences. *Aging Ment Health*. 2018;22(4):519-525. doi:10.1080/13607863.2016.1277976
54. Borys S, Perlman D. Gender differences in loneliness. *Pers Soc Psychol Bull*. 1985;11(1):63-74. doi:10.1177/0146167285111006
55. Russell DW. UCLA Loneliness Scale (Version 3): reliability, validity, and factor structure. *J Pers Assess*. 1996;66(1):20-40. doi:10.1207/s15327752jpa6601_2

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Yu X, Westrick AC, Kobayashi LC. Cumulative loneliness and subsequent memory function and rate of decline among adults aged ≥50 in the United States, 1996 to 2016. *Alzheimer's Dement*. 2023;19:578–588. https://doi.org/10.1002/alz.12734

15525279, 2023, 2, Downloaded from https://alz-journals.onlinelibrary.wiley.com/doi/10.1002/alz.12734 by South African Medical Research, Wiley Online Library on [05/02/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License