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Editor's choice

Original Research Report

Loneliness and Risk of Dementia

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Abstract

Objective: The present study tests whether loneliness is associated with risk of dementia in the largest sample to date and further examines whether the association is independent of social isolation, a related but independent component of social integration, and whether it varies by demographic factors and genetic vulnerability.

Method: Participants from the Health and Retirement Study (N = 12,030) reported on their loneliness, social isolation, and had information on clinical, behavioral, and genetic risk factors. Cognitive status was assessed at baseline and every 2 years over a 10-year follow-up with the modified Telephone Interview for Cognitive Status (TICSm). A TICSm score of 6 or less was indicative of dementia.

Results: Cox proportional hazards regression indicated that loneliness was associated with a 40% increased risk of dementia. This association held controlling for social isolation, and clinical, behavioral, and genetic risk factors. The association was similar across gender, race, ethnicity, education, and genetic risk.

Discussion: Loneliness is associated with increased risk of dementia. It is one modifiable factor that can be intervened on to reduce dementia risk.

Keywords: Dementia risk, Loneliness, Psychosocial risk factors, Social isolation

Social isolation has been recognized as a significant public health issue because it is associated with increased risk of poor health outcomes, including Alzheimer's disease and related dementias (Kuiper et al., 2015). The subjective experience of social isolation—loneliness—has been identified as a key factor in the relation with worse outcomes. Specifically, loneliness has been defined as "a distressing feeling that accompanies the perception that one's social needs are not being met by the quantity or especially the quality of one's social relationships" (p. 218; Hawkley & Cacioppo, 2010). Although loneliness overlaps with social isolation, it is distinct and has independent associations with health outcomes (Holt-Lunstad, Smith, Baker, Harris, & Stephenson, 2015; Holwerda et al., 2014). Despite the growing evidence that loneliness is associated with dementia risk, the published literature has been somewhat mixed. Out of seven published studies, for example, loneliness was found to be associated significantly with increased risk of dementia in four samples and not significant in the other three samples (Table 1). Among the studies that find an association, however, it is robust. The risk associated with loneliness, for example, is independent of number of social connections and social contact (Holwerda et al., 2014), which indicates that even among individuals who have relatively frequent social interactions and are otherwise socially connected, subjective feelings of isolation increase risk of developing incident dementia (Rafnsson, Orrell, d'Orsi, Hogervorst, & Steptoe, 2017; Wilson et al., 2007). This association is also

Table 1. Published Studies on Loneliness and Dementia

Study	Cohort	Country	Sample size	Loneliness measure	Dementia classification	Follow-up interval	Time-to-event analysis	Statistic
He et al., 2000	--	China	1,203	Unknown	Diagnosis	10 years	Yes	1.63 (0.93–2.86)
Wilson et al., 2007	Rush	United States	823	5 items	Diagnosis	4 years	Yes	1.51 (1.06–2.14)*,[a]
Holwerda et al., 2014	AMSTEL	The Netherlands	2,173	Single item	Structured interview	3 years	No	1.96 (1.33–2.89)*[a]
Rafnsson et al., 2017	ELSA	United Kingdom	6,677	3-item UCLA	Self, proxy, performance	6 years	Yes	1.44 (1.11–1.88)*[a]
Zhou et al., 2017	CLHLS	China	7,867	Single item	Self, proxy	3 years	No	1.22 (1.10–1.35)*,[a]
Poey et al., 2017	ADAMS	United States	663	Single item	Diagnosis	5 years	No	1.06 (0.44)
Rawtaer et al., 2017	SLAS	Singapore	1,601	Single item	Diagnosis (included MCI)	8 years	Yes	1.19 (0.78–1.81)

Note: The Table includes prospective cohort studies that measured loneliness among cognitively health participants at baseline who were subsequently tested or evaluated for dementia at a future follow-up assessment. PubMed and Web of Science databases were searched up to February 2018 with inclusion criteria: (1) longitudinal study of cognitively healthy participants at baseline, (2) loneliness assessed at baseline, (3) dementia assessed at follow-up, (4) report of the association (e.g., hazard ratio) associated with loneliness, and (5) written in English. All loneliness scales were included and cognitive status could be determined by a clinical diagnosis, self/proxy report, and/or a performance-based measure of cognition.

ADAMS = Aging, Demographics, and Memory Study; AMSTEL = Amsterdam Study of the Elderly; CLHLS = Chinese Longitudinal Healthy Longevity Survey; ELSA = English Longitudinal Study of Aging; MCI = Mild cognitive impairment; Rush = Rush Memory and Aging Project; SLAS = Singapore Longitudinal Ageing Study.

[a]Remains significant when social isolation is included as a covariate.

*Significant association.

independent of depression (Wilson et al., 2007) and other clinical risk factors (Rafnsson et al., 2017).

Models of loneliness and health specify several pathways through which loneliness may increase risk of poor health outcomes (Cacioppo & Cacioppo, 2014; Cacioppo, Cacioppo, Capitanio, & Cole, 2015; Ong, Uchino, & Wethington, 2016). In particular, three pathways are frequently highlighted in models of loneliness and morbidity and mortality: health-risk behaviors, physiological dysregulation, and psychological distress. These three pathways are also relevant for cognition. In the behavioral pathway, for example, individuals who experience loneliness are more likely to smoke (Dyal & Valente, 2015) and less likely to exercise (Hawkley, Thisted, & Cacioppo, 2009); both of these behaviors have likewise been implicated in dementia risk (Norton, Matthews, Barnes, Yaffe, & Brayne, 2014). In the physiological pathway, loneliness has been associated with clinical risk factors that increase risk of cognitive impairment, including hypertension (Momtaz et al., 2012), obesity (Petitte et al., 2015), and diabetes (Christiansen, Larsen, & Lasgaard, 2016). Loneliness is also associated with greater physiological dysregulation in response to stress (Brown, Gallagher, & Creaven, 2018), such as a greater inflammatory response to acute stressors (Jaremka et al., 2013b), which has been related to dementia risk (Sundelöf et al., 2009). In the psychological pathway, depressive symptoms and negative affect are implicated in the relation between loneliness and poor health, mechanisms that likely extend to cognition. For example, negative affect has been found to mediate the longitudinal relation between loneliness and worse health over time (Böger & Huxhold, 2018), and negative affect is a risk factor for incident dementia (Korthauer et al., 2018). As such, theoretical models of loneliness and health outcomes are also likely to apply to cognitive outcomes.

The association between loneliness and dementia risk may not be the same across all sociodemographic groups. There is some evidence, for example, that gender moderates this association, with the relation between loneliness and dementia risk stronger among men than women (Zhou, Wang, & Fang, 2017). Research on other health outcomes also points to potential differences. A meta-analysis of loneliness and mortality indicated that loneliness was a stronger predictor of mortality at relatively younger ages than relatively older ages (Holt-Lunstad et al., 2015). A similar difference may emerge for cognitive impairment. In addition, there are racial and ethnic differences in dementia risk, as well as differences by educational attainment (Alzheimer's Association, 2017). There may be a synergistic risk of having two risk factors that increases vulnerability to cognitive impairment. When identifying risk factors for dementia, it is critical to determine whether the risk is similar across groups with more and less vulnerability.

Despite the consistency of the association between loneliness and dementia risk across some studies, three studies did not find a significant association (He, Zhang, & Zhang, 2000;

Poey, Burr, & Roberts, 2017; Rawtaer et al., 2017). Studies with longer follow-up intervals tend not to find an association, which suggests that the relation between loneliness and dementia risk may be due to reverse causality—loneliness may be a clinical manifestation of the disease process rather than a risk factor. Alternatively, one study may have been underpowered to detect an effect (N = 663; Poey et al., 2017), another included mild cognitive impairment in the classification of dementia (Rawtaer et al., 2017), which may dilute the predictive power to detect severe cognitive impairment, and the third did not specify how dementia was assessed (He et al., 2000). The purpose of the present research is to add to the current literature on loneliness and risk of dementia using the largest sample to date with one of the longest follow-up intervals. We also address whether this association is independent of social isolation, behavioral and clinical risk factors, depressive symptoms, and genetic risk. Finally, with a large sample that is relatively demographically diverse, we address whether the association varies by age, gender, race, ethnicity, education, and genetic risk status.

Method

Participants and Procedure

The current study makes use of the Health and Retirement Study (HRS), a longitudinal study of Americans aged 50 years and older and their spouses (Sonnega et al., 2014). Data are available for public download at http://hrsonline.isr.umich.edu/. A random half of HRS participants completed the leave-behind questionnaire that included the loneliness measure in 2006; the other half completed it in 2008. These two subsamples were combined as baseline. Participants were administered a cognitive battery during the regular HRS assessments that occur every 2 years. Participants were selected into the analytic sample if they completed the loneliness measure in 2006 or 2008, did not have dementia (see below) at baseline, and had at least one follow-up cognitive assessment through the 2016 assessment. A total of 13,020 participants had baseline data. Of these participants, 990 participants were excluded because they did not have follow-up data. Of these 990 participants, 710 participants died before a follow-up assessment. The remaining 280 participants were older and had fewer years of education than the 12,030 participants who had the necessary follow-up data to be included in the analysis. There were no differences in gender, Hispanic ethnicity, or loneliness scores between those included in the analyses and those who did not have follow-up data. The analyses are based on the 12,030 participants who had complete baseline measures and a follow-up cognitive assessment.

Measures

Dementia

The modified Telephone Interview for Cognitive Status (TICSm) was administered every 2 years to HRS participants. Three tasks from the TICSm were used to assess dementia status: immediate and delayed recall of 10 words (range 0–20 points), serial 7 subtraction (range 0–5 points), and backward counting (range 0–2 points). The composite immediate and delayed recall is a marker of episodic memory, serial 7s is a marker of working memory, and backward counting is one marker of overall mental status (Fisher, McArdle, McCammon, Sonnega, & Weir, 2013), which are all implicated in dementia (Crimmins, Kim, Langa, & Weir, 2011). Partial correlations at baseline indicated that loneliness was correlated negatively with the composite immediate and delayed recall (r = –.08, p < .001) and serial 7s (r = –.05, p < .001) but not backward counting (r = .02, p = .07), controlling for age, gender, race, ethnicity, and education.

Participants were classified into either dementia (TICSm ≤ 6) or not dementia (TICSm ≥ 7), a cutoff validated previously against a comprehensive neuropsychological assessment and clinical diagnosis of dementia (Crimmins et al., 2011; Langa et al., 2005). The TICSm in the HRS has been used to track national trends in dementia (Langa et al., 2017). In supplemental analyses, participants at baseline were further differentiated into normal function (TICSm ≥ 12) and cognitive impairment not dementia (CIND; TICSm between 7 and 11).

Loneliness

Loneliness was assessed with a three-item version of the UCLA Loneliness Scale that was developed for use in large-scale epidemiological studies (Hughes, Waite, Hawkley, & Cacioppo, 2004). Specifically, participants were asked, "How much of the time do you feel…" and rated each item ("You lack companionship?", "left out?", and "isolated from others?") on a scale from 1 (*often*) to 3 (*hardly ever or never*). Items were reverse scored in the direction of greater loneliness and the mean taken across items (alpha = .88).

Social isolation

Social isolation was the index of contact with four types of relationships (Ertel, Glymour, & Berkman, 2008): spouse, children, other family, and friends. First, participants were asked whether they lived with their spouse or partner. Participants who did not live with a partner or spouse were scored as 1 and participants who did live with a spouse or partner were scored as zero. Participants were also asked whether they had children, other immediate family (e.g., brothers or sisters, parents, cousins or grandchildren), and friends. For each relationship, participants were asked about the frequency with which they met them in person, spoke over the phone, and wrote or e-mailed. Responses for each relationship were dichotomized into having contact (met, phone, wrote/e-mail) once or more a month (0) or less than once a month (1). The sum was then taken across the four relationships, with an index that ranged from 0 (social integration) to 4 (social isolation). The correlation between loneliness and social isolation was .25 (p < .01).

Covariates

In addition to basic demographic covariates (age, sex, race, ethnicity, and education), several additional covariates were considered because of their association with risk of cognitive impairment. Clinical covariates were BMI (kg/m^2) and reported physician diagnosis of hypertension (yes/no) and diabetes (yes/no). Depressive symptoms were measured as the sum of seven items from the Center for Epidemiologic Studies Depression scale (CESD); the HRS measure of the CESD included an eighth item on loneliness ("Much of the time during the past week you felt lonely" rated yes/no) that was excluded from the depressive symptoms scale. Behavioral covariates were frequency of moderate physical activity (ranging from 1 = hardly ever or never to 4 = more than once a week) and smoking status (yes/no). All covariates were measured at the same assessment as the baseline loneliness measure. A subset of participants (n = 9,775) had genetic information on *APOE* risk status; carriers of the ε4 risk variant (ε2/ε4, ε3/ε4, ε4/ε4) were contrasted against noncarriers.

Analytic Strategy

The association between loneliness and risk of incident dementia was tested with Cox proportional hazard models. Loneliness was entered as a predictor of incident dementia over the up to 10-year follow-up period. Time was measured in years from baseline and coded as time-to-incidence. For participants who did not develop dementia, cases were censored at the last available cognitive assessment. The proportional hazards assumption was not violated. We first tested whether loneliness was associated with risk of dementia controlling for the basic sociodemographic covariates (Model 1). To test whether this association was independent of other common risk factors, we repeated this analysis including the clinical and behavioral risk factors (Model 2), social isolation (Model 3), and depressive symptoms (Model 4) as additional covariates. We also tested whether this association was independent of genetic risk with the subsample with information on *APOE* risk status. In the full sample, we tested whether the association held when using a single item on loneliness from the CESD instead of the three-item UCLA scale to assess whether the association was dependent on the scale used. We did two sensitivity analyses to address whether the association was due solely to reverse causation. First, we restricted the sample to participants who had at least 6 years of follow-up data. Second, we excluded participants who scored in the CIND range at baseline. We also tested whether loneliness was associated with conversion from CIND to dementia among participants with CIND at baseline. We also did an additional sensitivity analysis for social isolation. Specifically, we selected participants who scored low in social isolation and tested whether loneliness was associated with dementia risk in this socially integrated group. Finally, we tested whether the association was moderated by age, sex, race, ethnicity, education, or genetic risk. Interactions were tested separately for each potential moderator, and all demographic covariates were included in the model (e.g., when the interaction between loneliness and age was tested, sex, race, ethnicity, and education were included as covariates). The exception was genetic risk: Because of the reduced sample size, genetic risk was not included as a covariate for testing the sociodemographic factors as moderators. For the analysis of genetic risk as a moderator, the sociodemographic factors were included as covariates.

Results

Over the up to 10-year follow-up period (88,824 person years), 1,104 participants (9%) developed dementia. Descriptive statistics for study variables for the total sample and by dementia status are in Table 2; correlations among all study variables are shown in Supplementary Table 1. Table 3 shows the results of the survival analysis. For every 1-point increase in loneliness, there was a 40% increased risk of developing dementia over the follow-up, controlling for age, sex, race, ethnicity, and education. The association was independent of clinical and behavioral risk factors (Model 2), social isolation (Model 3), and depressive symptoms (Model 4). The association was also independent of genetic risk (hazard ratio [HR] = 1.30, 95% confidence interval [CI] = 1.16–1.46). Finally, the relation between loneliness and dementia risk was similar if the loneliness item (yes/no) from the CESD was used instead of the three-item UCLA loneliness scale (HR = 1.40, 95% CI = 1.21–1.63).

Sensitivity analyses that restricted the sample to participants who had at least 6 years of follow-up data (n = 9,132; 514 cases with incident dementia) showed a similar effect of loneliness on dementia risk (HR = 1.35; 95% CI = 1.16–1.58). Loneliness likewise remained a significant predictor of dementia when participants with CIND at baseline were excluded from the model (HR = 1.44, 95% CI = 1.23–1.69, n = 10,272; 489 cases with incident dementia). Among participants with CIND at baseline (n = 1,755), loneliness was associated with conversion to dementia over the follow-up (HR = 1.19, 95% CI = 1.03–1.37). It was, however, reduced to nonsignificance in the fully-adjusted model due to overlap with depressive symptoms (HR = 1.11, 95% CI = 0.95–1.29). The final sensitivity analysis focused on participants with the greatest social integration (i.e., a score of 0 on the index of social isolation), which indicated at least monthly contact with all four relationships. Among this highly connected group (n = 5,128), loneliness was associated with an over 50% increased risk of dementia (HR = 1.55, 95% CI = 1.26–1.90), controlling for demographic, clinical, and behavioral risk factors.

There was little evidence that the association between loneliness and dementia risk varied across demographic groups. The only significant interaction emerged for age: The association between loneliness and dementia risk was slightly stronger among relatively younger than relatively

Table 2. Descriptive Statistics for the Total Sample and by Cognitive Status at Follow-up

Variable	Full sample	Cognitive status at follow-up	
		Nondementia	Dementia
Age (years)	67.30 (10.45)	66.68 (9.87)	73.36 (9.79)
Gender (female)	60%	60%	60%
Race (African American)	12%	11%	25%
Race (Other)	4%	4%	6%
Race (white)	84%	85%	69%
Ethnicity (Hispanic)	8%	7%	13%
Education (years)	12.84 (2.93)	13.05 (2.77)	10.76 (3.56)
Body Mass Index	29.05 (6.05)	29.09 (6.09)	28.70 (5.67)
Hypertension (yes)	57%	56%	66%
Social Isolation	0.81 (0.84)	0.79 (0.84)	1.01 (0.91)
Diabetes (yes)	19%	19%	28%
Depressive Symptoms	1.17 (1.68)	1.12 (1.64)	1.66 (1.90)
Smoking (yes)	13%	13%	13%
Physical Activity	3.14 (1.17)	3.16 (1.15)	2.78 (1.30)
APOE ε4[a]	21%	20%	28%
Loneliness	1.47 (0.54)	1.46 (0.53)	1.59 (0.57)

Note: N = 12,030; n = 10,926 without dementia and n = 1,104 with incident dementia. Depressive symptoms are measured as the sum of seven symptoms (range 0–7) and physical activity is measured on a scale from 1= hardly ever or never to 4 = more than once a week.
[a]N = 9,808 for APOE risk status due to missing genetic information on some participants.

Table 3. Cox Regression Predicting Dementia Risk from Loneliness

Variable	Model 1	Model 2	Model 3	Model 4
Age (years)	1.09 (1.09–1.10)**	1.09 (1.08–1.10)**	1.08 (1.08–1.09)**	1.09 (1.08–1.09)**
Gender (female)	0.95 (0.8401.08)	0.95 (0.84–1.07)	0.94 (0.83–1.07)	0.93 (0.82–1.06)
Race (African American)	2.70 (2.34–3.12)**	2.58 (2.23–2.90)**	2.57 (2.22–2.98)**	2.59 (2.24–3.00)**
Race (Other)	1.56 (1.19–2.06)**	1.55 (1.18–2.05)**	1.55 (1.18–2.05)**	1.59 (1.21–2.10)**
Ethnicity (Hispanic)	1.14 (0.92–1.41)	1.09 (0.87–1.35)	1.10 (0.88–1.36)	1.08 (0.87–1.35)
Education (years)	0.85 (0.83–0.86)**	0.85 (0.84–0.86)**	0.85 (0.84–0.87)**	0.86 (0.84–0.87)**
Hypertension	--	1.02 (0.90–1.17)	1.02 (0.90–1.17)	1.01 (0.88–1.15)
Diabetes	--	1.36 (1.18–1.56)**	1.36 (1.18–1.56)**	1.36 (1.18–1.56)**
Smoking	--	1.34 (1.11–1.61)**	1.31 (1.08–1.58)**	1.30 (1.07–1.56)**
Physical activity	--	0.90 (0.85–0.94)**	0.90 (0.86–0.94)**	0.91 (0.87–0.96)**
Body mass index	--	0.98 (0.97–0.99)**	0.98 (0.98–0.99)**	0.98 (0.97–0.99)**
Social isolation	--	--	1.12 (1.05–1.20)**	1.12 (1.04–1.20)**
Depressive symptoms	--	--	--	1.08 (1.05–1.12)**
Loneliness	1.40 (1.26–1.56)**	1.35 (1.22–1.50)**	1.30 (1.17–1.45)**	1.19 (1.05–1.33)**

Note: N = 12,030; n = 12,029 for Model 3 due to missing data on social isolation; n = 11,965 for Model 4 due to missing data on depressive symptoms.
**$p < .01$.

older participants ($HR_{loneliness \times age}$ = 0.98; 95% CI = 0.98–0.99). The association between loneliness and dementia risk was not moderated by gender ($HR_{loneliness \times gender}$ = 0.85, 95% CI = 0.69–1.06), race ($HR_{loneliness \times race}$ =1.00, 95% CI = 0.77–2.01), ethnicity ($HR_{loneliness \times ethnicity}$ = 0.93, 95% CI = 0.69–1.26), education ($HR_{loneliness \times education}$ = 1.03, 95% CI = 0.99–1.05), or genetic risk status ($HR_{loneliness \times genetic\ risk}$ = 0.84, 95% CI = 0.66–1.08).

Discussion

With the largest sample to date, the present research indicates that loneliness is associated with increased risk of incident dementia. This association is independent of social isolation, behavioral, clinical, and genetic risk factors for dementia, and depressive symptoms. The present research also indicates that this association is similar across demographic groups and supports the view that it is unlikely to be due to reverse causality.

Loneliness has previously been associated with numerous health challenges and health-risk behaviors (Hawkley & Cacioppo, 2010) that are also implicated in dementia risk (Alzheimer's Association, 2017). Individuals who experience feelings of loneliness, for example, tend to have worse cardio-metabolic health (Valtorta, Kanaan, Gilbody, Ronzi, & Hanratty, 2016), report more symptoms of depression (Jaremka et al., 2013a), and engage in more health-risk behaviors, such as physical inactivity

(Hawkley et al., 2009). It is of note then that the relation between loneliness and dementia risk held when controlling for these risk factors. The relation did decrease by about 12% when these covariates were included, which suggests that these factors are one, but not the sole, pathway through which loneliness increases risk of dementia.

Accounting for depressive symptoms did more to reduce the association between dementia risk than accounting for the clinical and behavioral covariates. Loneliness is frequently included on measures of depressive symptoms (Radloff, 1977) and even when measures distinguish loneliness from depression, the two are highly correlated (Beutel et al., 2017). Thus, it is not a surprise that controlling for depressive symptoms would reduce the size of the association. Even accounting for the overlap with depressive symptoms, however, the association persisted, which indicates that loneliness is capturing a specific aspect of depressive symptomatology associated with dementia risk that is distinct from its other aspects (e.g., negative emotionality). Loneliness, in fact, is associated with greater increases in symptoms of depression over time rather than depressive symptoms increasing risk of loneliness (Cacioppo, Hawkley, & Thisted, 2010). There is likely a distinct interpersonal component that contributes to risk. Meaningful social engagement can be cognitively stimulating, increase feelings of purpose in life, and build reciprocal mechanisms of support with other people. Over time, this greater stimulation (Wang, Karp, Winblad, & Fratiglioni, 2002), purpose (Sutin, Stephan, & Terracciano, 2018), and supportive interpersonal relationships (Fratiglioni, Paillard-Borg, & Winblad, 2004) may help support brain health and lower risk of severe cognitive impairment.

There are other pathways not considered in the present study that may explain the association between loneliness and dementia risk. It is likely that the relation is mediated, in part, through stress-related biomarkers. Individuals with loneliness have more systemic inflammation (Jaremka et al., 2013b) and greater cortisol reactivity to stress (Brown et al., 2018). These biomarkers have likewise been implicated in the etiology of dementia (Ennis et al., 2017; Schmidt et al., 2002). Loneliness may also be intertwined with other risk factors for dementia. For example, hearing loss increases risk of incident dementia (Lin et al., 2011) and individuals tend to become lonely when their hearing declines to a point that it leaves them socially isolated (Mick, Parfyonov, Wittich, Phillips, & Kathleen Pichora-Fuller, 2018). Finally, results from neuroscience further suggest that loneliness has an impact on brain structure and function (Cacioppo, Capitanio, & Cacioppo, 2014), particularly neural structures implicated in dementia. It is theorized, for example, that the orbitofrontal cortex and medial prefrontal cortex are sensitive to loneliness and stimulate the hypothalamic-pituitary-adrenocortical (HPA) axis (Cacioppo et al., 2014), which contributes to the greater cortisol reactivity observed in response to stress among individuals high in loneliness (Brown et al., 2018). Dysregulation of the HPA axis, in turn, is thought to damage the hippocampus, which is one of the most vulnerable neural structures in Alzheimer's disease (Maloney, 2015).

A distinction can be made between social connection/isolation and subjective feelings of loneliness. That is, individuals who have frequent social interactions can still have feelings of loneliness, and, likewise, individuals who are physically isolated may nonetheless feel close to others (Cacioppo & Cacioppo, 2014). Although related, loneliness and social isolation have independent associations with health outcomes (Holt-Lunstad et al., 2015). Previous research has found that both loneliness and social isolation are independent predictors of risk of dementia (Rafnsson et al., 2017; Wilson et al., 2007). Our findings are consistent with this literature. Of greater note, however, is the sensitivity analysis that focused specifically on participants who were the most socially integrated. Among this group of participants, loneliness had a stronger association with dementia risk than in the overall sample. This association points to the importance of evaluating the subjective experience of social connection, in addition to amount of social contact, to identify individuals most at risk. This pattern suggests that the subjective evaluation of one's social connection is as important as frequency of contact with other people.

There was little evidence that the association between loneliness and dementia varied by sociodemographic factors. Some previous research has found that the association is stronger among men than women (Zhou et al., 2017), but no such difference emerged in HRS. Rather, in HRS, the only significant interaction was for age: relatively younger participants with loneliness were slightly more vulnerable to dementia than relatively older participants. This pattern suggests that age may overwhelm the harmful effect of loneliness, and thus loneliness may be a more potent risk factor at relatively younger ages. Interestingly, this same pattern has emerged previously for mortality: The association between loneliness and mortality is stronger among relatively younger than older individuals (Holt-Lunstad et al., 2015). Although it will be worthwhile to replicate the moderation by age on dementia risk in future research, the similarities across health outcomes suggests that the vulnerability associated with loneliness is greater at younger ages and speaks against a greater cumulative effect with age. Alternatively, there may be a survival effect in that the association may be stronger at younger ages because the individuals vulnerable to loneliness would have already developed dementia at younger ages and thus at relatively older ages those who were going to develop dementia already did. Overall, however, the lack of moderation suggests that the risk associated with loneliness is not limited to specific demographic groups or to individuals with a genetic vulnerability.

As with any risk factor for dementia that is measured close to the outcome, there is the possibility that loneliness is a consequence of the disease process rather than a

risk factor (i.e., reverse causation). This issue is difficult to disentangle with short follow-up intervals because loneliness is assessed close to diagnosis. Wilson and colleagues, however, argued against reverse causality: loneliness was unrelated to the degree of neuropathology in the brain at autopsy (Wilson et al., 2007). The two sensitivity analyses in the present research support the view that this relation is not due to reverse causality. That is, when the sample was limited to participants who had at least 6 years of follow-up data (those who did not develop dementia within 6 years of the assessment of loneliness) and when participants with CIND at baseline were excluded, the association was similar to that of the full sample and still significant. This finding is noteworthy because all previous studies that found a significant association between loneliness and dementia had follow-up periods that ranged from 3 to 6 years (see Table 1). There may be more long-term effects of loneliness on cognitive health than accumulation of neuropathology.

The current findings support the literature that finds an association between loneliness and incident dementia. Previous studies have been diverse in terms of scale used to measure loneliness (e.g., scales that ranged from 1 to 5 items), how dementia was measured (e.g., performance measure vs diagnosis), follow-up period (range 3–10 years), and country of origin (e.g., European and Asian populations). And yet, despite these differences, relatively similar associations between loneliness and dementia risk emerged across studies, even if not all associations reached the threshold for statistical significance. That is, all of the effects in previous research (Table 1) were in the direction of greater risk despite not reaching this threshold, and in no case was loneliness protective. The consistency across countries is particularly striking. Despite presumably quite varied environments and norms for social interaction and engagement, the association was apparent in Europe, Asia, and the United States. This pattern suggests that subjective feelings of isolation have an effect on risk of cognitive impairment regardless of broader cultural context.

The present study had several strengths, including a large, relatively diverse sample and a fairly long follow-up period. These strengths need to be put in the context of some limitations of this research. First, we used a performance-based measure as an assessment of dementia in the HRS. This measure has been well validated, and the results in the current study were similar to what has been found when a clinical diagnosis of dementia is used instead (Wilson et al., 2007). Still, future research would benefit from more work with a clinical diagnosis as the outcome. Second, we did not identify pathways through which loneliness contributes to dementia risk. The analysis of the clinical and behavioral covariates suggested that these factors played a minor role in this association. Future research could test additional pathways through which loneliness increases risk. Third, we noted similarities across studies from different countries in comparison with the published literature, but we could not directly address the issue of cross-cultural generalizability. Future research would benefit from a systematic approach to this issue.

Loneliness has recently been identified as a significant public health problem (Cacioppo & Cacioppo, 2018), but one that can be addressed with financial and institutional support. The present research highlights one poor outcome associated with loneliness: Individuals with loneliness are more likely to develop dementia than less lonely individuals. Addressing this psychosocial risk factor will likely have a broad range of positive outcomes, including lowering risk and prevalence of dementia.

Supplementary Material

Supplementary data is available at *The Journals of Gerontology, Series B: Psychological Sciences and Social Sciences* online.

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Conflict of Interest

None reported.

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