ORIGINAL ARTICLE

Loneliness and Risk of Alzheimer Disease

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Context: Social isolation in old age has been associated with risk of developing dementia, but the risk associated with perceived isolation, or loneliness, is not well understood.

Objective: To test the hypothesis that loneliness is associated with increased risk of Alzheimer disease (AD).

Design: Longitudinal clinicopathologic cohort study with up to 4 years of annual in-home follow-up.

Participants: A total of 823 older persons free of dementia at enrollment were recruited from senior citizen facilities in and around Chicago, Ill. Loneliness was assessed with a 5-item scale at baseline (mean±SD, 2.3±0.6) and annually thereafter. At death, a uniform postmortem examination of the brain was conducted to quantify AD pathology in multiple brain regions and the presence of cerebral infarctions.

Main Outcome Measures: Clinical diagnosis of AD and change in previously established composite measures of global cognition and specific cognitive functions.

Results: During follow-up, 76 subjects developed clinical AD. Risk of AD was more than doubled in lonely persons (score 3.2, 90th percentile) compared with persons who were not lonely (score 1.4, 10th percentile), and controlling for indicators of social isolation did not affect the finding. Loneliness was associated with lower level of cognition at baseline and with more rapid cognitive decline during follow-up. There was no significant change in loneliness, and mean degree of loneliness during the study was robustly associated with cognitive decline and development of AD. In 90 participants who died and in whom autopsy of the brain was performed, loneliness was unrelated to summary measures of AD pathology or to cerebral infarction.

Conclusion: Loneliness is associated with an increased risk of late-life dementia but not with its leading causes.

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SOCIAL ISOLATION, AS EVIdenced by objective indicators such as having a small social network,[1] being unmarried,[2,3] participating in few activities with others,[4-6] or some combination of these,[7,8] has been associated with increased risk of dementia and cognitive decline in several prospective studies. In contrast, little is known about the association of dementia with emotional isolation, or loneliness, which refers to perceived social isolation and feeling disconnected from others, that is, to dissatisfaction with social interactions rather than their absence. Although loneliness is related to social isolation, the correlation is far from perfect.[9] The only previous study of which we are aware was based on brief measures of loneliness and cognition and had mixed results, with loneliness related to increased risk of cognitive decline in some analyses but not others.[10] Thus, as previously noted,[11] it is uncertain how much feeling alone (ie, loneliness), as distinct from being alone (ie, social isolation), contributes to risk of dementia in old age.

We examined these issues using data from the Rush Memory and Aging Project, a longitudinal clinicopathologic study of risk factors for chronic conditions of old age. At baseline and annually thereafter for up to 4 years, participants underwent uniform evaluations that included assessment of loneliness with a modified version of the de Jong-Gierveld Loneliness Scale,[12,13] clinical classification of dementia and Alzheimer disease (AD), and detailed cognitive function testing. Those who died underwent a uniform postmortem evaluation of the brain to quantify AD pathologic abnormalities and cerebral infarction. In analyses, we tested the hypothesis that a higher level of loneliness is associated with an increased risk of AD. We also examined variables that might account for the association (eg, objective

measures of social isolation and depressive symptoms), the relation of loneliness to change in cognition, change in loneliness, and the relation of loneliness to the neuropathologic lesions most commonly associated with dementia in old age.

METHODS

PARTICIPANTS

The study subjects were participants in the Rush Memory and Aging Project.[14] Eligibility required absence of a clinical diagnosis of dementia at baseline and agreement to annual in-home clinical evaluations and brain donation at death. The study was approved by the institutional review board, Rush University Medical Center, Chicago, Ill.

We recruited participants from diverse settings in the Chicago area including continuous care retirement communities, subsidized housing facilities, local churches, and social service agencies. After a presentation on the project and distribution of information packets, persons were urged to discuss participation with family and friends. Those who expressed interest met later with project staff who provided more detailed information about study participation and obtained informed consent.

At baseline and annually thereafter, each participant underwent a uniform clinical evaluation. On the basis of this evaluation, which included a structured medical history, complete neurologic examination, and cognitive testing, an experienced clinician (J.F.K. and D.A.B. among others) evaluated participants for dementia and AD using the criteria of the joint working group of the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer Disease and Related Disorders Association (NINCDS-ADRDA).[15] As previously described,[14,16,17] these criteria consist of a history of cognitive decline and deficits in 2 or more cognitive domains, 1 of which must be memory to meet AD criteria.

ASSESSMENT OF LONELINESS

We assessed loneliness at each evaluation with a modified version of the de Jong-Gierveld Loneliness Scale.[12,13] The original version of this scale has been shown to be internally consistent,[18,19] and associations with loss of a spouse,[20] institutional living,[18] and low self-esteem[13] support its construct validity. We made 3 modifications. First, because we wanted to assess emotional loneliness, we eliminated 5 items assessing social loneliness. Second, to improve the clarity of the scale, we combined 2 similar items and made minor wording changes to another item. Third, to enhance the sensitivity of the scale, we asked participants to rate agreement with each item on a 5-point scale rather than dichotomously. The 5 items included the following: "I experience a general sense of emptiness," "I miss having people around," "I feel like I don't have enough friends," "I often feel abandoned," and "I miss having a really good friend." Item scores were averaged to yield a total score that ranged from 1 to 5, with higher values indicating more loneliness.

ASSESSMENT OF SOCIAL ISOLATION

Two measures of social functioning were used as indicators of social isolation. Social network size was quantified with standard questions[21] about the number of children, family, and friends each person had and how often they interacted with them. Social network size was the number of these individuals seen at least once a month, as reported elsewhere.[7] Frequency of participation in social activity was assessed with 6 items about activities involving social interaction,[22] such as visiting a relative or friend. Each activity was rated on a 5-point scale, with 1 indicating once a year or less; 2, several times a year; 3, several times a month; 4, several times a week; and 5, every day or almost every day. The average item score was used in analyses.

ASSESSMENT OF OTHER COVARIATES

Depressive symptoms were assessed with a 10-item form[23] of the Center for Epidemiological Studies–Depression (CES-D) scale.[24] Items (eg, "I felt sad") were read to participants, who then indicated whether they had felt that way much of the time during the past week. The number of symptoms endorsed has been associated with morbidity and mortality in previous research in older persons.[25,26]

Frequency of participation in cognitively stimulating activities was assessed with a 9-item scale.[16] Subjects rated how often they had participated in 9 cognitive activities (eg, reading a magazine) in the past year on a 5-point scale, with 1 indicating once a year or less; and 5, every day or almost every day. The mean item score was used in analyses, as published elsewhere.[16]

Physical activity was measured with questions adapted[27] from the 1985 Health Interview Survey.[28] Subjects were asked if they had engaged in 5 physical activities (eg, walking for exercise) during the last 2 weeks and, if so, how many times and the duration of each occasion. Hours per week spent in the 5 activities was used as an indicator of physical activity level, as in previous research.[29]

We used 2 previously established[30] indicators of vascular burden at baseline: number of 3 vascular risk factors (eg, hypertension) and number of 4 vascular conditions (eg, stroke). Income was treated as the mean of a 10-item income rank score at 40 years and at baseline, ascertained with the show-card method.[21] Disability was assessed at baseline with the 6-item Katz scale.[31]

ASSESSMENT OF COGNITIVE FUNCTION

At each annual evaluation, 20 cognitive tests were administered by trained research assistants. The Mini-Mental State Examination was used for descriptive purposes. The remaining 19 tests consisted of 7 measures of episodic memory including immediate and delayed recall of Logical Memory Story A and of the East Boston Story, plus Word List Memory, Word List Recall, and Word List Recognition; 3 tests of semantic memory including Verbal Fluency Test and short forms of the Boston Naming Test and the National Adult Reading Test; 3 working memory tests including Digit Span Forward and Backward plus Digit Ordering; 4 measures of perceptual speed including Number Comparison, Symbol Digit Modalities Test (oral version), and 2 indexes from a modified Stroop Neuropsychological Screening Test; and 2 visuospatial tests including a 15-item version of Judgment of Line Orientation and a 17-item version of Standard Progressive Matrices. In analyses, we used composites based on 2 or more individual test results to reduced random variability. We formed a composite measure of global cognition based on all 19 test results. In addition, we constructed composite measures of episodic memory (7 tests), semantic memory (3 tests), working memory (3 tests), perceptual speed (4 tests), and visuospatial ability (2 tests), based in part on a factor analysis of the tests at baseline. Raw scores on individual tests were converted to z scores, using the baseline mean ± SD of the entire cohort, and averaged to yield the composite scores. Further information on the individual test results and the derivation of these composite measures is published elsewhere.[16,32]

ASSESSMENT OF AGE-RELATED NEUROPATHOLOGY

A standard protocol was used for brain removal, sectioning and preserving of tissue, and quantifying AD pathology and cerebral infarctions, as described in detail elsewhere.[14,33] We used 3 previously established composite measures of AD pathology in analyses. A measure we labeled "global AD pathology" was based on counts of neuritic plaques, diffuse plaques, and neurofibrillary tangles identified by a modified Bielschowsky silver stain in 5 brain regions, with standard scores averaged across pathology types and regions. To obtain more systematic and molecularly specific indexes of AD pathology, we used systematic sampling schemes to quantify the percent area occupied by β-amyloid immunoreactive plaques and the density of τ-immunoreactive neurofibrillary tangles in each of 8 brain regions: superior frontal cortex, dorsolateral prefrontal cortex, inferior temporal cortex, angular gyrus cortex, anterior cingulate cortex, calcarine cortex, entorhinal cortex, and hippocampal formation (cornu ammonis field 1, subiculum). Standard scores of each pathologic type in each region were averaged to yield composite measures of β-amyloid and tangles.[33] Cerebral infarctions were identified as described elsewhere.[34] For analyses, subjects were divided into those with vs without 1 or more chronic cerebral infarctions.

DATA ANALYSIS

Cox proportional hazards models adjusted for age, sex, and years of formal education were used to test the hypothesis that higher degrees of loneliness are associated with an increased risk of AD. The initial model included a term for loneliness. This model was repeated in separate subsequent analyses that controlled for social network size and social activity frequency, cognitive activity, physical activity, race/ethnicity, income level, disability, and vascular risk factors and conditions.

To evaluate the role of depressive symptoms, we separated the item about feeling lonely from the remaining CES-D items. We then calculated the change in the estimate for loneliness after controlling for the 9-item CES-D and the change in the estimate for the 9-item CES-D after controlling for loneliness.

Mixed-effects models,[35] described in more detail elsewhere,[36,37] were used to test the hypothesis that higher degree of loneliness is associated with more rapid cognitive decline. Each model included terms for time (in years since baseline) and time squared to capture linear and nonlinear change; terms for loneliness and its interaction with time; and terms for age, sex, level of educational achievement, and their interactions with time. The term for loneliness indicates the effect of 1 point of the loneliness scale on level of cognition at baseline, and the interaction of loneliness with time indicates the effect of 1 point of loneliness on annual rate of linear change. We conducted separate analyses for each of the 5 specific measures of cognitive domain.

We used generalized estimating equation models[38] to assess change in loneliness during the study. The first model included terms for time (in years since baseline) and time squared. The second model included terms for baseline cognition and its interaction with time, to test the association of cognition with baseline level of loneliness and rate of change in loneliness; and terms to control for age, sex, and level of educational achievement. We then examined the relation of mean degree of loneliness during the study to development of AD and global cognitive decline.

Among those who died and in whom autopsy of the brain was performed, we tested the relation of loneliness to each measure of pathology in separate linear regression models. We then regressed the last valid global cognitive score before death on loneliness and a given index of pathology, with separate analyses for each pathologic index.

Model assumptions were examined graphically and analytically and found to be adequately met. Programming was done with SAS software (SAS Institute Inc, Cary, NC).[39]

RESULTS

DESCRIPTION OF COHORT

Data for these analyses were collected from November 30, 2000, to May 5, 2006. Of 1023 subjects at baseline, we excluded 67 who met dementia criteria, 23 who died before the first annual follow-up evaluation, and 76 who had not been in the study long enough to reach the first follow-up point. This left 857 subjects, of whom 791 (92.3%) completed at least 1 follow-up evaluation (mean of 3.3 evaluations per subject [range, 2-5 evaluations], which represents 97.6% of possible evaluations in survivors). At baseline, mean±SD age of the subjects was 80.7±7.1 years, and their mean±SD level of educational achievement was 14.5±3.0 years; 75.7% were women, and 91.0% were white and non-Hispanic; 66% lived in retirement homes, 30% in single-family dwellings, and 4% in assisted-living settings or nursing homes.

METRIC PROPERTIES OF LONELINESS SCALE

The measure of loneliness had an approximately normal distribution at baseline (mean±SD, 2.3±0.6; skewness, 0.5). Scores ranged from 1.0 to 4.6, with higher values indicating more loneliness. The Cronbach coefficient α was .78, which is comparable to the original scale[18,19] and indicates a moderate level of internal consistency. Loneliness was negatively related to social network size ($r=-0.21$; $P<.01$), frequency of social activity ($r=-0.18$; $P<.01$) and cognitive activity ($r=-0.23$; $P<.01$), and education ($r=-0.19$; $P<.01$), and was positively related to depressive symptoms ($r=0.47$; $P<.01$) and age ($r=0.16$; $P<.01$).

LONELINESS AND INCIDENT ALZHEIMER'S DISEASE

During follow-up, 76 subjects developed dementia that met clinical criteria for AD (71 with probable AD and 5 with possible AD[15]). Those who developed AD were older, more likely to be men, and had lower household incomes than did unaffected persons, and they had a lower level of cognitive function, higher levels of loneliness and disability, and lower levels of social and cognitive activity (**Table 1**). Six subjects who developed other forms of dementia were excluded from analyses of incident AD.

In a Cox proportional hazards model that controlled for age, sex, and level of educational achievement, risk of clinical AD increased by approximately 51% for each point on the loneliness scale (relative risk [RR], 1.51; 95% confidence interval [CI], 1.06-2.14). Thus, a person with a high degree of loneliness (score 3.2, 90th percentile) was about 2.1 times more likely to develop clinical AD during follow-up compared with a person with a low degree of loneliness (score 1.4, 10th percentile).

Indicators of social isolation, including social network size and frequency of social activity, have been associated with dementia or cognitive decline in older persons.[1-8] Therefore, we repeated the original model with terms added for social network and social activity. In this analysis, the relation of loneliness to disease incidence persisted (RR, 1.45; 95% CI, 1.01-2.09), more frequent social activity was associated with reduced AD risk (RR, 0.52; 95% CI, 0.34-0.79), and social network size was not related to risk (RR, 1.01; 95% CI, 0.97-1.05). The effect of loneliness in the original model was also unchanged when we eliminated subjects with infrequent (<15th percentile) social activity (estimate, 1.58; 95% CI, 1.07-2.33) or a small (<15th percentile) social network (estimate, 1.53; 95% CI, 1.04-2.25).

Loneliness was inversely related to level of cognitive activity in this cohort and has been associated with level of physical activity in previous research.[40] Because frequency of cognitive and physical activity has been associated with risk of AD,[29,41] we repeated the original analysis, controlling first for participation in cognitive activities and then for physical activities. The association of loneliness with incidence of AD was reduced by about 15% after controlling for cognitive activity (RR, 1.41; 95% CI, 0.99-2.01) and was unaffected by controlling for physical activity (RR, 1.54; 95% CI, 1.08-2.19).

In subsequent analyses, we examined other potentially confounding demographic and health-related factors. The association of loneliness with AD was unchanged after controlling for race/ethnicity (RR, 1.52; 95% CI, 1.07-2.15), income (RR, 1.47; 95% CI, 1.01-2.15), disability on the Katz scale (RR, 1.51; 95% CI, 1.06-2.15), and vascular risk factors and conditions (RR, 1.51; 95% CI, 1.07-2.15).

Table 1. Characteristics of Participants Who Did Not Develop AD and Those Who Did*

Characteristic	Participants Without AD (n = 716)	Participants With AD (n = 76)	*P* Value
Age at baseline, y	80.3 (7.1)	85.1 (5.9)	<.01
Educational achievement, y	14.5 (2.9)	14.8 (3.4)	.35
Female sex, %	77.2	61.8	<.01
African American race, %	6.0	4.0	.47
Income score	5.7	4.7	.03
MMSE score	28.2 (1.8)	25.8 (3.0)	<.01
Nine-item CES-D score	1.1 (1.5)	1.1 (1.7)	.97
Loneliness score	2.2 (0.6)	2.5 (0.6)	<.01
Social network size	7.0 (6.0)	6.4 (5.1)	.41
Social activity score	2.6 (0.6)	2.3 (0.5)	<.01
Cognitive activity score	3.2 (0.7)	2.8 (0.8)	<.01
Physical activity score	2.9 (3.4)	3.3 (4.2)	.42
Disability, %†	10.5	24.0	<.01
Vascular risk factors, %‡	79.5	85.5	.21
Vascular conditions, %‡	29.1	34.2	.35

Abbreviations: AD, Alzheimer disease; CES-D, Center for Epidemiological Studies–Depression scale; MMSE, Mini-Mental State Examination.
*Data are given as mean (SD) unless otherwise indicated.
†Percentage of subjects unable to perform 1 or more activities of daily living, Katz scale.
‡Percentage of subjects with 1 or more vascular risk factors or vascular conditions.

LONELINESS, DEPRESSIVE SYMPTOMS, AND AD

Because feeling lonely is a symptom of depression and lonely persons are prone to experience depressive symptoms,[42] we conducted additional analyses in an effort to disentangle these related constructs. In these analyses, we excluded 1 item about loneliness (ie, "I felt lonely") from the 10-item CES-D scale (mean ± SD of 9-item CES-D scale, 1.2 ± 1.6). Controlling for the 9-item CES-D score reduced the association of loneliness with AD risk by about 16% (RR, 1.41; 95% CI, 0.97-2.06). By way of comparison, the 9-item CES-D score had a marginal association with AD risk (RR, 1.13; 95% CI, 0.98-1.30), which was reduced by more than half after controlling for loneliness (RR, 1.02; 95% CI, 0.92-1.24). In addition, subjects who acknowledged feeling lonely on the CES-D item (n = 146) were 86% more likely to develop AD than were those without the symptom (RR, 1.86; 95% CI, 1.10-3.14). Controlling for this symptom reduced the association of the 9-item CES-D score with AD risk by more than half (RR, 1.06; 95% CI, 0.90-1.24), whereas controlling for the 9-item CES-D score reduced the item effect by less than 18% (RR, 1.66; 95% CI, 0.90-3.07).

LONELINESS AND COGNITIVE DECLINE

To evaluate the contribution of preexisting cognitive impairment to the association of loneliness with risk of AD, we examined the relation of loneliness to cognitive decline, the principal clinical expression of the disease, in mixed-effects models controlled for age, sex, and level of educational achievement (**Table 2**). In these analyses, the terms for time and time squared indicate the mean annual change in the cohort. Loneliness was inversely related to baseline level of function on each cognitive measure. In addition, with this baseline effect controlled for, loneliness was associated with more rapid decline in global cognition, semantic memory, perceptual speed, and visuospatial ability, as shown by the interactions of loneliness with time.

REPEATED MEASUREMENT OF LONELINESS

Loneliness was assessed at each annual evaluation, resulting in a mean of 3.3 assessments per subject (range, 2-5 assessments). We used generalized estimating equation models to characterize change in loneliness and to test its relation to level of global cognition at baseline. There was no evidence of linear (estimated effect of time, –0.02; SE, 0.02; $P = .40$) or nonlinear (estimated effect of time squared, 0.01; SE, 0.01; $P = .11$) change in loneliness. In a subsequent analysis, baseline level of global cognition was related to loneliness at baseline (estimate, –0.26; SE, 0.05; $P < .01$) but not to change in loneliness (estimate, –0.01; SE, 0.02; $P = .69$).

In view of the stability of loneliness during the study, we averaged each subject's scores across evaluations to better capture the enduring tendency to be lonely. Scores ranged from 1.0 to 4.6 (mean ± SD, 2.3 ± 0.6) and were strongly related to baseline loneliness ($r = 0.85$; $P < .01$). Higher level of loneliness on this cumulative measure was robustly associated with higher likelihood of developing

Table 2. Relation of Loneliness to Change in Cognitive Function*

Cognitive Measure	Model Term	Estimate (SE)	*P* Value
Global cognition	Time	−0.02 (0.01)	.20
	Time squared	−0.01 (<0.01)	<.01
	Loneliness	−0.15 (0.03)	<.01
	Loneliness × time	−0.01 (0.01)	.03
Episodic memory	Time	−0.02 (0.02)	.35
	Time squared	−0.01 (0.01)	.29
	Loneliness	−0.14 (0.04)	<.01
	Loneliness × time	0.00 (0.01)	.79
Semantic memory	Time	−0.03 (0.02)	.04
	Time squared	0.00 (<0.01)	.69
	Loneliness	−0.14 (0.03)	<.01
	Loneliness × time	−0.02 (0.01)	.01
Working memory	Time	0.00 (0.02)	.97
	Time squared	−0.02 (0.01)	<.01
	Loneliness	−0.14 (0.04)	<.01
	Loneliness × time	−0.02 (0.01)	.09
Perceptual speed	Time	−0.04 (0.02)	.05
	Time squared	−0.02 (0.01)	<.01
	Loneliness	−0.16 (0.04)	<.01
	Loneliness × time	−0.02 (0.01)	.03
Visuospatial ability	Time	0.01 (0.03)	.85
	Time squared	0.00 (0.01)	.58
	Loneliness	−0.13 (0.04)	<.01
	Loneliness × time	−0.03 (0.01)	.04

Abbreviation: SE, standard error.
*From separate mixed-effects models controlled for age, sex, and level of educational achievement.

AD and more rapid global cognitive decline, even in models that simultaneously adjusted for all covariates (**Table 3**).

LONELINESS, AD PATHOLOGIC FEATURES, AND CEREBRAL INFARCTION

In a final series of analyses, we examined the possibility that loneliness is an early sign of the neuropathologic lesions most commonly associated with loss of cognition in old age. Of 135 eligible participants who died during the study, brain autopsy was performed in 106 (78.5%), the results of which were available in 90 at the time of these analyses (reported as mean ± SD): age at death, 86.1 ± 5.8 years; postmortem interval, 8.4 ± 8.7 hours. At the last clinical evaluation (9.1 ± 7.2 months before death), the Mini-Mental State Examination score was 24.4 ± 7.5, and 30% of subjects had a clinical diagnosis of AD.

In separate linear regression models controlled for age, sex, and level of educational achievement, baseline loneliness score was unrelated to a global measure of AD pathology identified by silver stain (estimated slope, −0.01; SE, 0.11; $P = .94$), the percent area occupied by β-amyloid–immunoreactive plaques (estimated slope, −0.01; SE, 0.02; $P = .70$), the density of τ-immunoreactive neurofibrillary tangles (estimated slope, 0.00; SE, 0.01; $P = .31$), or the presence of cerebral infarction (estimated slope, 0.17; SE, 0.14; $P = .22$). In subsequent analyses (**Table 4**), both loneliness and the neuropathologic measures showed the expected inverse associations with global cognition proximate to death, making it less likely that the lack of correlation between loneliness and pathology is due to measurement limitations or insufficient power. Results were comparable in analyses using the cumulative measure of loneliness during the study period instead of baseline loneliness (data not shown).

COMMENT

In a cohort of about 800 elderly persons followed up annually for up to 4 years, lonely individuals were more than twice as likely to develop an AD-like dementia syndrome than were those who were not lonely, even after controlling for level of social isolation. Among participants who died and in whom a brain autopsy was performed, loneliness was not related to AD pathologic findings or cerebral infarction. The results suggest that loneliness may contribute to risk of an AD-like dementia in late life and does so through some mechanism other than AD pathology and cerebral infarction.

Previous research on the relation of social resources to loss of cognition has primarily focused on social isolation,[1-8] that is, the physical absence of other persons. In these studies, larger social network,[1] being married,[2,3] engaging in activities that involve social interaction,[4-6] or some combination of these[7,8] have been associated with a decreased risk of dementia or cognitive decline, though some null results have been reported as well.[3,43,44] In contrast, there has been less research on perceived social isolation and results have been inconclusive. Thus, dissatisfaction with social relationships was associated with an increased risk of dementia in one study,[1] but another study did not observe this effect.[3]

Loneliness was associated with impaired cognitive function at baseline, consistent with some[45] but not other[10] previous study findings. After controlling for baseline cognition, loneliness was also associated with more rapid cognitive decline in multiple functional domains. This result is consistent with the only previous study known to us of loneliness and cognitive decline, which found loneliness to be associated with an increased risk of cognitive decline during 10 years of observation.[10] These results were based on fewer than 200 participants, however, and loneliness was unrelated to cognitive decline over shorter observation periods, perhaps in part owing to limited statistical power and because loneliness was assessed with a single question and cognition was assessed with a brief global measure.

The basis of the association of loneliness with AD and cognitive decline is uncertain. One possibility is that loneliness is a consequence of dementia, perhaps as a behavioral reaction to diminished cognition or as a direct result of the pathology contributing to dementia. Yet, the level of cognition at baseline was not associated with a change in loneliness and there was no mean increase in loneliness despite a mean decrease in cognition. Further, loneliness was unrelated to β-amyloid plaques, neurofibrillary tangles, or cerebral infarctions, the leading causes of late-life dementia. These data do not support the idea that loneliness is a reaction to incipient dementia or an early sign of its pathology, though further research on this complex issue is needed.

Table 3. Relation of Cumulative Loneliness to Incident Alzheimer Disease (Models A and B) and Global Cognitive Decline (Models C and D)*

Model Term	Model A RR (95% CI)	Model B RR (95% CI)	Model C Estimate (SE); *P* Value	Model D Estimate (SE); *P* Value
Cumulative loneliness	2.10 (1.45-3.06)	1.84 (1.11-3.07)		
Cumulative loneliness			–0.20 (0.03); <.01	–0.09 (0.04); .02
Cumulative loneliness × time			–0.03 (0.01); <.01	–0.05 (0.01); <.01

Abbreviation: CI, confidence interval; RR, relative risk; SE, standard error.
*Estimated from proportional hazards (A and B) or mixed-effects (C and D) models adjusted for age, sex, and level of educational achievement (A and C) and for social activity, social network, physical activity, cognitive activity, depressive symptoms, income, race/ethnicity, disability, and vascular risk factors and conditions (B and D).

Table 4. Relation of Loneliness and Neuropathology to Level of Global Cognition Proximate to Death*

Model Terms	Estimate (SE); *P* Value				
Loneliness	–0.30 (0.15); .05	–0.32 (0.15); .03	–0.34 (0.15); .03	–0.32 (0.13); .01	–0.28 (0.16); .09
Global Alzheimer disease pathology		–0.44 (0.16); <.01			
β-Amyloid burden			–0.07 (0.03); <.01		
Tangle density				–0.07 (0.01); <.01	
Cerebral infarction					–0.40 (0.21); .06

*Estimated from separate linear regression models adjusted for age at death, sex, and level of educational achievement.

An alternative explanation is that loneliness might somehow compromise neural systems underlying cognition and memory, thereby making lonely individuals more vulnerable to the deleterious effects of age-related neuropathology (ie, decreasing neural reserve). Thus, animals subjected to social isolation show decreased dendritic arborization in the hippocampus and prefrontal cortex[46] and down-regulation of brain-derived neurotrophic factor,[47] accompanied by impaired memory[47] and concept formation.[48] In human beings, loneliness has been associated with impaired social skills.[49] Thus, neural systems underlying social behavior might be less elaborated in lonely persons and, as a result, be less able to compensate for other neural systems compromised by age-related neuropathology. Further clinicopathologic and clinicoradiologic research is needed to investigate these and other possibilities.

Findings for social isolation were mixed. More frequent participation in social activities was associated with a decreased risk of AD, consistent with previous research on dementia[4-6] and cognitive decline.[7,8] Social network size, which has been related to cognitive decline or dementia in some studies[1,7,8] but not others,[3,44] was not associated with incident AD, however. Overall, these data suggest that both the quantity of social interaction and the quality of social attachments affect risk of late-life dementia.

Loneliness and depressive symptoms are separable on psychometric[50] and conceptual[42] grounds but are moderately correlated and appear to reciprocally influence one another with time.[42] We found that the loneliness item on the depression scale predicted AD risk better than the sum of the remaining 9 items. Further, controlling for depressive symptoms reduced the association of loneliness with AD risk, but the reduction was modest (<20%) compared with the more substantial reduction (>50%) in the association of depressive symptoms with risk after controlling for loneliness. These data suggest that the association of loneliness with dementia is at least partly independent of depressive symptoms and imply that loneliness may be an important component of the association of depressive symptoms with AD.

Confidence in these findings is strengthened by several factors. Clinical classification of dementia and AD was based on uniform evaluations and widely accepted criteria implemented by experienced clinicians, reducing the likelihood that diagnostic bias or imprecision affected results. The availability of approximately 3 or 4 evenly spaced observations per subject and previously established composite measures of cognition enhanced our ability to reliably assess individual paths of cognitive decline in multiple functional domains. High rates of participation in follow-up clinical evaluations and brain autopsy reduced the likelihood that results were biased by selective attrition. Results were consistent with different measures of loneliness, cognition, and AD pathology.

These findings have important limitations. They are based on a predominantly white volunteer cohort; the mean observation period was less than 3 years; and there were only 76 cases of incident AD and 90 autopsies performed. It will be important to replicate these findings in studies with longer observation periods and more diverse participants.

In conclusion, the perception of being alone was associated with cognitive decline and development of an AD-like dementia even after controlling for objective indexes of social isolation and other covariates. Neither AD pathology nor cerebral infarction could account for the association, suggesting that novel neurobiologic mechanisms may be involved.

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Author Contribution: Dr Wilson had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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