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Association of Loneliness With 10-Year Dementia Risk and Early Markers of Vulnerability for Neurocognitive Decline

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Abstract

Background and Objective: Loneliness is common and its prevalence is rising. The relationship of loneliness with subsequent dementia and the early preclinical course of Alzheimer disease and related dementia (ADRD) remains unclear. Thus, the primary objective of this study was to determine the association of loneliness with 10-year all-cause dementia risk and early cognitive and neuroanatomic imaging markers of ADRD vulnerability.

Methods: Retrospective analysis of prospectively collected data from the population-based Framingham Study cohorts (09/09/1948-12/31/2018). Eligible participants had loneliness assessed and were dementia-free at baseline. Loneliness was recorded using the Center for Epidemiologic Studies Depression Scale; defined conservatively as feeling lonely ≥ 3 days in the past week. The main outcomes were incident dementia over a 10-year period, cognition, and MRI brain volumes and white-matter injury.

Results: Of 2308 participants (mean age, 73 [SD, 9] years; 56% women) who met eligibility in the dementia sample, 14% (329/2308) developed dementia; 6% (144/2308) were lonely. Lonely (versus not lonely) adults had higher 10-year dementia risk (age-, sex-, and education-adjusted hazard ratio, 1.54; 95% CI, 1.06-2.24). Lonely participants younger than age 80 without APOE $\epsilon 4$ alleles had a three-fold greater risk (adjusted hazard ratio, 3.03; 95% CI, 1.63-5.62). Among 1875 persons without dementia who met eligibility in the cognition sample (mean age, 62 [SD, 9] years; 54% women), loneliness associated with poorer executive function, lower total cerebral volume, and greater white-matter injury.

Discussion: Over 10 years of close clinical dementia surveillance in this cohort study, loneliness was associated with increased dementia risk; this tripled in adults whose baseline risk would otherwise be relatively low based on age and genetic risk, representing a majority of the US population. Loneliness was also associated with worse neurocognitive markers of ADRD vulnerability, suggesting an early pathogenic role. These findings may have important clinical and public health implications given observed loneliness trends.

Classification of Evidence: This study provides Class I evidence that loneliness increases the 10-year risk of developing dementia.

ACCEPTED

Introduction

Loneliness is a risk factor for increased morbidity¹ and mortality² and can be reduced,³ yet its prevalence is rising—from 11% to 14% over a two-year period extending early into the COVID-19 pandemic in a US population-based sample,⁴ amounting to ~46 million lonely Americans.⁵ Estimated loneliness prevalence ranges higher for adults age 60 and older in US and international cohorts (13-43%).⁶⁻⁸ Given observed trends, a notable population health concern is that loneliness, especially if persistent, may be an important risk factor for dementia;^{6, 9, 10} but findings have been inconsistent.^{9, 11, 12}

Cohort studies have associated loneliness with increased risk of cognitive decline,⁶ dementia,^{10, 13} and Alzheimer disease and related dementia (ADRD) neuropathologic changes.^{14, 15} Other results do not support these associations.^{9, 11, 12} Yet—whether loneliness is an early ADRD contributor, symptom, or both—uncertainty about its association with incident dementia risk could underestimate the impact of increasing loneliness as well as limit understanding of ADRD development and underlying mechanisms. Estimates of dementia risk related to loneliness could be improved by using longitudinal studies with more frequent comprehensive clinical and neuropsychological assessments, neurobiological measures that correspond with preclinical ADRD vulnerability, and continuous surveillance for the clinically important endpoint of dementia in a large population-based sample with long duration of extensive monitoring and minimal loss to follow-up. Thus, we analyzed data from the Framingham Study (FS), one of the largest and longest-running longitudinal cohorts in the US, to determine how the baseline presence (versus absence) of loneliness in a population-based sample of adults associates with risk of developing dementia and indicators of susceptibility for neurocognitive decline. The primary research question of this study was to evaluate, among younger and older adult age groups, the prospective association of loneliness with 10-year incident dementia (confirmed by rigorous and continuous clinical dementia surveillance with adjudication by a dementia review panel of neurologists and neuropsychologists) and the cross-sectional association of loneliness with early markers of ADRD vulnerability: cognitive function (confirmed by

standardized and comprehensive neuropsychological evaluations), brain volumes (confirmed by MRI measures of total cerebral volume and hippocampal volume), and small-vessel cerebrovascular injury (confirmed by MRI measure of white-matter hyperintensities).

ACCEPTED

Methods

Samples

This study included FS Original cohort participants attending their 25th biennial examination (1997-1999) and Offspring participants attending their seventh quadrennial examination (1998-2001). For the primary dementia analysis, eligible participants had a loneliness assessment and were aged at least 60 years (participants younger than age 60 are unlikely to have substantial 10-year risk of dementia)¹⁶. Persons were excluded if they had prevalent dementia or no dementia follow-up. The subsequent analysis evaluated the association of loneliness with early cognitive and neuroimaging indicators of AD/AD pathology. Because neuropsychological¹⁷ and MRI neuroanatomical¹⁸ changes are well-known to accompany underlying accumulation of AD/AD neuropathological changes many years prior to its clinical manifestation as dementia, eligible participants were aged 40-79 years and had a loneliness assessment and cognitive testing. Participants were excluded if they had prevalent dementia or stroke. Given our predetermined approach for secondary biological validation with this sample and subsequent results of exploratory interaction analyses, participants were also included in this sample if they had no genotypic information or an APOE ε4 allele. Imaging analyses used a subset who also had a brain MRI.

Standard Protocol Approvals, Registrations, and Patient Consents

All participants provided written informed consent. The Institutional Review Board of Boston University Medical Center approved the consent form and study protocol.

Exposure

Methods quantifying loneliness with the Center for Epidemiologic Studies Depression Scale (CES-D)¹⁹ in large longitudinal cohorts like FS have been previously described.^{6, 10} In brief, the CES-D asks

respondents to report whether each of twenty depressive symptoms was present during the past week “rarely or none of the time (less than 1 day)” (0 points), “some or a little of the time (1-2 days)” (1 point), “occasionally or a moderate amount of time (3-4 days)” (2 points), or “most or all of the time (5-7 days)” (3 points). Identical to similar cohort studies that used the CES-D item asking how often the respondent felt lonely,^{6, 10} participants were classified as “lonely” (3-7 days) or “not lonely” (0-2 days). This approach has yielded both positive and null results in similar community-based cohorts of older adults, and positive associations have demonstrated a pattern similar to “exposure-response” relationships whereby participants who have more severe and persistent loneliness are more likely to have greater AD RD risk.^{6, 10}

Although instruments assessing burden of depressive symptoms like the CES-D include items that ask about feelings of loneliness because of their co-occurrence,¹⁹ there is growing consensus that depression and loneliness are conceptually separate constructs that are statistically separable,^{6, 20} represent distinct clinical phenomena,²¹ involve distinct brain circuitry,^{22, 23} and have associations with AD RD neuropathological changes that are independent from one another^{14, 15, 24} and, in this context, have limited to at-most moderate overlap.^{6, 10} However, because loneliness (as a predisposing variable in depression) has been observed to have consistently moderate effects on depressive symptoms across studies regardless of sampling strategies, publication type, and publication year,²⁵ the CES-D loneliness item was selected as the main exposure variable while still accounting for depressive symptoms as a potential confounder using a modified version of the CES-D.

Incident Dementia Assessment

The primary outcome was clinical diagnosis of incident all-cause dementia during a 10-year follow-up period after baseline examination. The rigorous and continuous FS dementia surveillance methods have been published previously.²⁶ In brief, cognitive status has been monitored with Mini-Mental State

Examination²⁷ and neuropsychological testing since 1975 in the Original cohort and since 1987 in the Offspring cohort. A dementia review panel of study neurologists and neuropsychologists reviewed every possible dementia case and determined diagnosis date using extensive data, such as serial and prompted assessments, telephone interviews with family/caregivers, and medical records.²⁶ Diagnosis of dementia is based on criteria including the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV).²⁸ Cases detected before 2001 had repeat reviews after 2001 so updated diagnostic criteria could be applied. Continuous dementia surveillance occurred through December 31, 2018.

Cognitive Assessment

Clinic examination attendees had standardized neuropsychological testing administered by trained research assistants and neuropsychologists after clinical evaluation. Tests performed are reliable, widely used, and cover all domains of the Alzheimer's Disease Center's Uniform Data Set.²⁹ For the present study, we selected three separate measures to analyze that reflect key cognitive processes commonly affected early in AD/AR: Logical Memory Delayed Recall (memory), Trails Making Test B Minus A (executive function), and global cognition. For global cognition, we used a global cognitive score that was developed on a data sample collected at Offspring examination 7 with principal component analysis forcing a single component solution. The tasks included in the principal component analysis are the following: Trails Making Test A, Trails Making Test B, Logical Memory (Immediate and Delayed Recall), Visual Reproductions (Immediate and Delayed Recall), Paired Associate Learning (Delayed Recall), Hooper Visual Organization Test, and Similarities Test.³⁰ The global cognitive score is a weighted sum of standardized scores, where higher scores represent better performance. This method is identical to previous studies, is useful in addressing the neuropathologic and clinical heterogeneity of all-cause dementia in community-based samples of older adults,³¹ and is described in further detail elsewhere;³² its creation is summarized in supplemental **eTable 1**.

Brain MRI Assessment

Preclinical ADRD MRI measures restricted only to cortical subregions might be less sensitive to the full range of underlying ADRD neuropathology in a population-based sample;³³ thus, our imaging analyses used the following key measures most likely to represent early ADRD cerebral vulnerability in the form of atrophy or microangiopathic white-matter injury: total cerebral volume, hippocampal volume, and white-matter hyperintensities. Participants were scanned during the baseline examination period using a Siemens Magnetom MRI (1.5T). Full details of acquisition, image analysis, and quantification of MRI variables have been described elsewhere, including imaging parameters and sequences, measurement protocols, segmentation methods, reliability, and reproducibility.³⁴ Volume measures were corrected for head size using the ratio of each measure over total cranial volume, multiplied by 100.^{34, 35} All MRI variables were standardized in analyses. Additional details of imaging acquisition and quantification methods are provided in the supplemental **eMethods**.

Covariates

Educational achievement was assessed using a four-level variable (no high school degree, high school degree only, some college, college degree or more). Additional adjustments for depressive symptoms, social isolation, antidepressant medication use, and common vascular risk factors were performed in secondary sensitivity analyses. Regarding depressive symptoms, a re-evaluation of the original CES-D's factor structure³⁶ used a factor solution of three factors (somatic symptoms, negative affect, anhedonia) and demonstrated that, although the loneliness item was retained as a measure of negative affect, the weight of the loneliness item was the lowest within this factor and was relatively consistent across diverse participants, including undergraduate, community, rehabilitation, and clinical samples as well as an epidemiologic sample comparable to the FS cohorts. Thus, depressive symptoms were accounted for with

a modified CES-D score; it excluded the loneliness item, summed points for remaining questions (range 0-57 points), and was a continuous log-transformed variable to account for non-normal distribution.³⁷ Regarding social isolation, the self-reported Berkman-Syme Social Network Index (SNI) was used to control for social isolation based on social network size.¹ Identical to prior methods,^{38,39} the SNI classified individuals based on summed score cutoffs as “socially isolated (0-1 points) or “not socially isolated” (2-4 points).

For interaction analyses, APOE ε4 allele carrier status was included as an independent genetic covariate instead of a polygenic risk score given its greater clinical and epidemiologic utility for considering the role of genetic predisposition in the present study.⁴⁰ APOE genotype was determined by isoelectric focusing of collected plasma and confirmed by DNA genotype.⁴¹

Statistical Analysis

To characterize age differences in the association of loneliness with dementia risk, the primary dementia analysis was performed for the entire sample and stratified by age group: age less than 80 and age 80 and older. The decision to characterize age differences by stratifying the sample at age 80 was made a priori based on knowledge of extant literature reporting associations of loneliness with greater cortical amyloid and regional tau accumulation using PET imaging,^{14,15} previous FS investigations suggesting loneliness-related dementia risk^{10,39} and risk of neurocognitive markers of early AD/ADRD vulnerability⁴² varied between younger and older adults, and loneliness prevalence estimates demonstrating a slight increase by age for young-old adults (age 65-79) and a more notable increase for oldest-old adults age 80 and above.⁴³

For the primary dementia analysis, overall and by age, Cox proportional hazards regression models estimated age-, sex-, and education-adjusted hazard ratios for 10-year dementia risk comparing

participants who were lonely with those who were not lonely. To systematically assess for effect modification, interactions were evaluated using Cox models with interaction terms for each of the following variables by loneliness: sex, education level, and APOE ϵ 4 status. Then, stratified Cox regression models were performed as indicated by significant interaction terms. The proportional hazards assumption was upheld for reported models, assessed by analyzing Schoenfeld residuals.

To characterize the role of loneliness in early ADRD susceptibility prior to the onset of dementia, a second sample was derived based on significant age-group-by-modifier subsets in the dementia analysis. The new sample consisted of participants who had neuropsychological testing at the baseline evaluation; most had a baseline brain MRI obtained. We used adjusted multivariable linear regression models in this second sample to assess whether loneliness status was an independent predictor of selected neurocognitive measures. All models adjusted for age, age², sex, educational achievement, and time interval from loneliness assessment to when the cognitive or MRI measure was acquired. Beta coefficient estimates were expressed in standard deviations units (SDU), so each 1-unit change corresponds to a standard deviation difference in each measure.

For sensitivity analysis, the primary dementia, cognition, and imaging models (Model 1) were additionally adjusted in sequential models to account for baseline depressive symptoms (Model 2), social isolation (Model 3), antidepressant medication use (Model 4), and vascular risk factors (Model 5). Participants with missing covariate data were excluded from these sensitivity analyses. To investigate the possibility that loneliness is a very early ADRD symptom (rather than an ADRD potentiator), we examined primary dementia models after excluding persons with prevalent mild cognitive impairment; separately, we also delayed the follow-up period to begin 5 years after baseline and span 5 years, allowing for a more conservative assessment of the role of loneliness before ADRD clinical expression. Additional sensitivity analyses used a three-level ordinal term for loneliness in the primary dementia, cognition, and

imaging models. To evaluate risk by dementia subtype, we used the primary dementia models to separately assess risk of developing Alzheimer's disease and vascular dementia.

Statistical significance was determined using a 2-sided α level of .05 without appropriate indication to correct for multiple comparisons given that each planned comparison tested a different specific hypothesis in the present study's main analyses.⁴⁴ Exploratory interaction analyses in the dementia sample used an α level of .10 to increase sensitivity, consistent with prior FS studies assessing effect modification.⁴⁵ Analyses were performed using SAS 9.4 (SAS Institute Inc). This study followed Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines (**eSupplemental Materials**).

Data Availability

The FS datasets analyzed for the present study are available through formal data use agreements. Any investigator may access the data through the process outlined at framinghamheartstudy.org.

Results

Association of Loneliness and 10-Year Risk of Incident Dementia

In the dementia analytic sample, there were 2308 participants (576 Original and 1732 Offspring members) who met inclusion criteria (**Figure 1A**); mean age was 73 years (SD, 9 years), 56% were women, and 53% had at least some college education (**Table 1**). Participants aged 80 and older were more likely to have prevalent cardiovascular disease and no college degree. At baseline, almost all Mini-Mental State Examination scores were in the cognitively unimpaired range (median score, 29 [interquartile range, 27-30]; range, 15-30). Twenty percent of participants had at least one APOE ϵ 4 allele. Age-based subgroups had similar social network size and low depressive symptoms. The prevalence of participants reporting loneliness at least 1 day in the past week—452 of 2308 (20%)—was comparable to similar cohorts of older adults.^{6-8, 46, 47} Overall, 144 of 2308 (6%) participants felt lonely 3 or more days in the past week.

During the 10-year follow-up period (median 10.00 [interquartile range, 5.50-10.00] years), 329 of 2308 (14%) participants were diagnosed with dementia (189 Original and 140 Offspring members). Thirty-one of 144 (22%) lonely participants developed dementia. In the overall dementia sample, adjusting for age, sex, and educational achievement, loneliness was significantly associated with higher dementia incidence (hazard ratio, 1.54; 95% CI, 1.06-2.24) (**Table 2** and **Figure 2A**). There was no significant association between loneliness and incident dementia in participants aged 80 years and above; however, among participants younger than age 80, those who were lonely were more than twice as likely to develop dementia (hazard ratio, 2.27, 95% CI 1.32-3.91). In the subsequent assessment of effect modification in the younger group, an interaction with APOE ϵ 4 status was identified (**Table 2**). Loneliness was associated with a three-fold increased hazard of incident dementia in the younger group of participants who did not carry an APOE ϵ 4 allele (hazard ratio, 3.03; 95% CI, 1.63-5.62) (**Figure 2B**).

Association of Loneliness With Early Cognitive and Neuroanatomic Markers of ADRD Vulnerability

To better understand the relationship between loneliness and ADRD vulnerability in dementia-free adults, we used the cognition sample which consisted of 1875 participants who met inclusion criteria (41 Original and 1834 Offspring members) (**Figure 1B**); mean age was 62 years (SD, 9 years), 54% were women, and 67% had at least some college education (**Table 1**). Loneliness was associated with poorer cognition in the executive function domain; lonely participants scored 0.23 SDU lower than participants who were not lonely (**Table 3**). A subset of the cognition sample was used to examine the relationship between loneliness and neuroanatomic measures. Baseline brain MRI was obtained for 1643 of 1875 (88%) participants (**Figure 1B**). The MRI subset also excluded 32 participants who had other neurological conditions; the remaining 1611 participants were representative of the full cognition sample (**Table 1**). Lonely (versus not lonely) participants were more likely to have lower total cerebral volume and greater white-matter hyperintensity burden. Lonely participants had total cerebral volumes that were 0.25 SDU lower and white-matter hyperintensity volumes that were 0.28 SDU greater (**Table 3**). There were no significant associations between loneliness and the global cognitive score, Logical Memory Delayed Recall, or hippocampal volume.

Sensitivity Analysis

Primary findings in the dementia analysis persisted after excluding 88 participants with baseline mild cognitive impairment (hazard ratio, 1.92; 95% CI, 1.29-2.85) and after advancing follow-up by 5 years (hazard ratio, 1.83; 95% CI, 1.08-3.12). Loneliness remained consistently associated for the younger group (including the APOE ϵ 4-negative subset) after additional adjustments for depressive symptoms, social isolation, antidepressant medication use, and common vascular risk factors (supplemental **eTable 2**). Similarly, loneliness was still associated with greater white-matter hyperintensities after additional

adjustments (supplemental **eTable 3**). The magnitude of the association between loneliness and total cerebral volume reduced with adjustment for social isolation. Loneliness was no longer associated with cognition after adjustment for depressive symptoms. Using an ordinal term for loneliness in primary models produced similar results overall (supplemental **eTable 4 and eTable 5**) with the exception that reporting loneliness 1-2 days/week in the older age group was also associated with increased dementia risk. Examining the association of loneliness with incidence of separate dementia subtypes, loneliness was associated with dementia due to Alzheimer's disease. The association was not observed for dementia due to vascular dementia, though the hazard ratio remained in the expected direction (supplemental **eTable 6**).

Classification of Evidence

The primary research question of this study was to evaluate, among younger and older adult age groups, the prospective association of loneliness with 10-year incident dementia (confirmed by rigorous and continuous clinical dementia surveillance with adjudication by a dementia review panel of neurologists and neuropsychologists) and the cross-sectional association of loneliness with early markers of AD/AR vulnerability: cognitive function (confirmed by standardized and comprehensive neuropsychological evaluations), brain volumes (confirmed by MRI measures of total cerebral volume and hippocampal volume), and small-vessel cerebrovascular injury (confirmed by MRI measure of white-matter hyperintensities). This study provides Class I evidence that loneliness increases the 10-year risk of developing dementia.

Discussion

This cohort study found that loneliness was associated with an increased 10-year incidence of all-cause dementia, reaffirming the elevated dementia risk of loneliness demonstrated by others^{9, 12} but also revealing a tripling in risk for lonely adults younger than age 80 without an APOE ϵ 4 allele. This association between loneliness and 10-year dementia risk may be at least partly due to the involvement of loneliness in the earliest stages of AD RD neuropathogenesis, as suggested by our subsequent findings characterizing how loneliness in dementia-free adults relates with early cognitive and imaging measures of AD RD vulnerability. Among APOE ϵ 4-negative adults younger than age 80, the highest-risk subgroup identified, loneliness associated with: (1) poorer executive function (a cognitive domain that includes processes like attention, judgment, organization, planning, and decision-making); (2) lower total cerebral volume (a global neuroanatomic measure that is often more sensitive to the broad range of neuropathologies underlying cognitive decline in population-based samples than using only cortical subregions);³³ and (3) a greater volume of white-matter hyperintensities (indicating greater extent of small-vessel cerebrovascular injury). Taken together, these results implicate reporting loneliness ≥ 3 days in the past week as an important potentially-modifiable psychosocial factor for middle-age and young-old APOE ϵ 4-negative adults early in the AD RD neuropathologic process leading up to the clinical presentation and diagnosis of dementia.

Although our results were consistent with the direction of prior associations reported between loneliness and dementia in population-based samples of older adults,^{9, 12, 13} the estimated risk of incident dementia in younger APOE ϵ 4-negative participants was much higher than other studies. For example, our estimate was greater than the 40% increased dementia risk found in the Health and Retirement Study among comparable lonely individuals age 65 and older who were also followed for 10 years but had their cognitive status assessed with three tasks from a brief telephone interview designed for screening dementia.¹³ Notably, our findings are also consistent with a recent FS study using only Offspring cohort

participant data that observed *persistent* loneliness in mid-life (defined as reporting loneliness ≥ 1 day in the past week at the sixth and seventh quadrennial examinations) was associated with higher lifetime risk of dementia and Alzheimer's disease (dementia hazard ratio was 1.91; 95% CI, 1.25-2.90).¹⁰ This risk with persistent loneliness was similarly elevated for APOE $\epsilon 4$ noncarriers (hazard ratio, 2.32; 95% CI, 1.49-3.62), though not as high as the three-fold risk increase observed in the present study of loneliness reported at a single time-point, at baseline, which may have clinical and public health relevance for brief screening assessments of risk. Compared to prior studies, our investigation's risk estimates may be due to a combination of larger sample size, different loneliness assessments and definitions, parsimonious approach to enhancing sensitivity using high-risk subgroups, or longer follow-up beginning at an age range more likely to develop dementia in subsequent years. Although loneliness was measured using a single-item assessment from an instrument originally designed to evaluate depressive symptoms, our findings reasonably suggest that the increased dementia risk observed in lonely adults may be due to related increases in early AD/AR vulnerability through pathways involving multifocal brain atrophy, extensive microvascular injury, and consequent cognitive decline.

Whether loneliness is an early symptom of neurodegenerative disease or an early contributor to neuropathology and cognitive decline remains unclear. On the one hand, considering loneliness as an early symptom of neurodegeneration, the present findings may reflect the earliest manifestations of cortical beta amyloid¹⁴ and tau¹⁵ accumulation in brain areas that are both affected early in the course of AD/AR and are involved in the perception of loneliness and other neurobehavioral functions.²³ On the other hand, if loneliness is mainly a causal factor in cognitive decline, the present findings may be indicative of loneliness driving (or compounding) vascular, neuroendocrine, inflammatory, and cytotoxic injury biological pathways that have been proposed to be specific to the distress of loneliness²¹ or increased functional communication in neural systems implicated in generating one's perception of loneliness (e.g., the default mode network).²³ Regardless, although the present study is observational, it

supports an upstream contributory role for loneliness given that participants without dementia were followed for 10 years—longer than might be typically expected for dementia to develop if mild cognitive or neurobehavioral symptoms were present due to underlying ADRD pathologic changes. This was additionally supported by sensitivity analyses conducted to assess for the potential of reverse causality.

Our finding that lonely young-old adults without APOE ϵ 4 allele had elevated dementia risk may be due to APOE ϵ 4 carriers having a higher genetic load for ADRD, so loneliness may not have been as influential in determining dementia risk. Loneliness might have also had a role in reducing APOE ϵ 2 and ϵ 3 expression through proposed stress and immune dysregulation pathways,⁴⁸ leading to lower apolipoprotein E in blood and the brain and consequently greater susceptibility to amyloid beta aggregation and ADRD pathogenesis. Moreover, the absent association between loneliness and dementia among individuals over age 80 may be attributable to loneliness having a less prominent role in ADRD when other age-related biological factors account for a greater proportion of incident dementia over age 80 (e.g., tauopathy, TDP-43 proteinopathy, arteriosclerosis, and hippocampal sclerosis).⁴⁹ Thus, for younger individuals without inherent genetic risk factors, loneliness and related psychosocial determinants of health may be more influential than traditional ADRD clinical risk factors, acting through pathways independent, or compounding, of biology.

Overall, these results have implications for dementia risk stratification, the relevance of basic loneliness screening, and the potential to underestimate dementia risk in lonely young-old adults without known genetic risk factors. As the proportion of lonely adults increases within societies, so does the potential to underestimate the associated risk of developing dementia. The current study not only observed a robust independent relationship between loneliness, incident dementia, and early ADRD vulnerability, but also a notably higher risk for a specific subgroup that includes the estimated 61% of Black adults and 74% of

White adults in the US who do not possess an APOE ϵ 4 allele.⁵⁰ One of the strengths of neurologists and other healthcare providers is a broad perspective of the biological, clinical, and public health implications of the present findings as well as an appreciation for the value of interdisciplinary strategies to address loneliness. These results raise the importance of future studies to further investigate mechanisms, possible interventions, and tools to efficiently screen for loneliness in routine clinical care (e.g., asking the question used in this study: In the past week, how often have you felt lonely?).

A strength of the present analysis is the rich data source including two distinct but similar cohorts followed over many decades with minimal loss to follow-up. To minimize potential bias from unmeasured confounding that could influence loneliness patterns over time, analyses accounted for baseline differences between cohorts and other factors that could simultaneously affect loneliness and dementia risk, or loneliness and AD/AR-related neurocognitive measures.

Limitations

Like other studies using data from FS Original and Offspring cohorts, this sample is composed of mostly White individuals. Although the sample was smaller than some prior studies,¹³ it was large enough to address the questions of interest and in a cohort with comprehensive follow-up spanning over six decades. Although information on additional symptoms related to loneliness were not available for participants and was not included (e.g., feeling left out or misunderstood), the CES-D's loneliness item is sufficiently distinct from the other CES-D items that the possibility of substantial overlap with depression or confounding from depressive symptoms that may manifest differently across age groups and various phenotypes of depression was likely low to moderate;³⁶ thus, this approach was considered to be adequate and appropriate. Although loneliness is slightly more prevalent in the older age group (consistent with similar community-based samples of older adults),^{6-8, 46} it remains possible that "depression without

loneliness” had a more influential role than “loneliness without depression” in this age group. Although the possibility for reverse causality cannot be ruled out in this cohort study (i.e., our findings could have been the result of underlying ADRD neuropathology manifesting as feelings of loneliness years or decades before clinical diagnosis), studying causal relationships between loneliness and incident dementia is not readily amenable to randomized clinical trials, and hence conclusions may rely on cohort studies.

Conclusions

In this cohort study, loneliness was associated with higher 10-year risk of incident dementia; notably, lonely APOE $\epsilon 4$ -negative younger adults had a three-fold increased risk. This elevated risk is possibly due to associations identified between loneliness and early cognitive and neuroanatomical markers of AD RD vulnerability, raising potential population health implications for observed trends in loneliness.

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Figure 1. Sample Derivation

A. Dementia

B. Cognition

The sample derivation flow diagrams for the Framingham Heart Study participants in the (A) dementia and (B) cognition analytic samples.

Figure 2. Ten-Year Cumulative Incidence of Dementia by Loneliness Status

Cumulative incidence curves for the primary outcome, 10-year incident all-cause dementia; (A) overall and (B) for the subgroup of participants ages 60–79 without an *APOE* $\epsilon 4$ allele. Median follow-up time for lonely participants, 5.94 (interquartile range, 2.90–10.00) years; for participants who were not lonely, 10.00 years (interquartile range, 5.89–10.00). NA indicates not available.

Table 1. Sample Characteristics

Characteristic	Dementia Sample ^a			Cognition Sample ^b
	Overall (n=2308)	Age ≥80 (n=560)	Age 60-79 ^a (n=1748)	Age 40-79 (n=1875)
Cohort, No. (%)				
Original	576 (25%)	503 (90%)	73 (4%)	41 (2%)
Offspring	1732 (75%)	57 (10%)	1675 (96%)	1834 (98%)
Age, years	73 (9)	85 (4)	69 (6)	62 (9)
Sex, No. (%)				
Female	1298 (56%)	367 (66%)	931 (53%)	1005 (54%)
Male	1010 (44%)	193 (34%)	817 (47%)	870 (46%)
Education, No. (%)				
No high school degree	277 (12%)	151 (27%)	126 (7%)	74 (4%)
High school degree only	795 (35%)	217 (39%)	578 (34%)	536 (29%)
Some college	605 (27%)	111 (20%)	494 (29%)	574 (30%)
College degree or more	594 (26%)	76 (14%)	518 (30%)	691 (37%)
Mini-mental state examination, median (IQR)	29 (27-30)	28 (26-29)	29 (28-30)	29 (28-30)
Loneliness in the past week, No. (%) ^c				
<1 day (0 points)	1856 (80%)	396 (71%)	1460 (84%)	1550 (83%)
1-2 days (1 point)	308 (13%)	109 (19%)	199 (11%)	248 (13%)
3-4 days (2 points)	100 (4%)	38 (7%)	62 (4%)	55 (3%)
5-7 days (3 points)	44 (2%)	17 (3%)	27 (2%)	22 (1%)
Loneliness 3 or more days in the past week (≥2 points), No. (%)	144 (6%)	55 (10%)	89 (5%)	77 (4%)
Modified CES-D (range 0-57) ^d	5.3 (6.5)	6.8 (7.0)	4.8 (6.2)	5.1 (6.3)
Berkman-Syme Social Network Index (range 0-4)	2.5 (1.0)	2.3 (1.0)	2.6 (1.0)	2.5 (1.1)
APOE ε4 carrier status, positive, No. (%)	441 (20%)	93 (17%)	348 (21%)	NA
Hypertension, No. (%) ^e	1463 (64%)	430 (78%)	1033 (59%)	812 (43%)
Prevalent diabetes mellitus, No. (%)	251 (15%)	12 (27%)	239 (15%)	188 (11%)
Prevalent cardiovascular disease, No. (%) ^f	593 (26%)	254 (45%)	339 (19%)	219 (12%)
Cognitive function				
Global cognitive score	NA	NA	NA	-0.05 (1.00)
Logical memory delayed recall	NA	NA	NA	10.5 (3.6)
Trails making test B minus A, median (IQR)	NA	NA	NA	0.68 (0.45-1.03)
Brain atrophy and injury ^g				
Total cerebral volume, % of TCV	NA	NA	NA	77 (3)
Hippocampal volume, % of TCV	NA	NA	NA	0.54 (0.04)
White matter hyperintensity volume, % of TCV, median (IQR)	NA	NA	NA	0.04 (0.02-0.08)

Abbreviations: CES-D, Center for Epidemiologic Studies Depression Scale; JNC, Joint National Commission; NA, not applicable; TCV, total cranial volume

Data are presented as mean (SD) unless otherwise indicated.

^a The dementia analytic sample excluded participants age<60 and with missing loneliness information, prevalent dementia, or no dementia follow-up.

^b The cognition analytic sample consisted of participants ages 40-79 without an APOE ε4 allele and excluded participants with missing loneliness information, prevalent dementia, and no neuropsychological testing.

^c For CES-D loneliness item, “I felt lonely” during the past week less than 1 day (0 points), 1-2 days (1 point), 3-4 days (2 points), 5-7 days (3 points).

^d Modified CES-D is the sum score of CES-D items remaining after exclusion of the loneliness item.

^e Stage 1 or higher JNC-VII hypertension, or antihypertensive medication use.

^f Includes coronary heart disease, congestive heart failure, peripheral vascular disease, ischemic cardiomyopathy, stroke, and transient ischemic attack.

^g Among participants in the cognition sample, 1611/1875 (86%) were included in the MRI analytic subsample.

Table 2. Adjusted 10-Year Risk of Incident All-Cause Dementia By Loneliness Status

			Lonely vs Not Lonely
Dementia Incidence^a	No. at Risk	No. of Cases of Dementia	Hazard Ratio (95% CI)
Overall	2271	329	1.54 (1.06–2.24)
Age ≥80	555	198	1.16 (0.69–1.94)
Age 60-79 ^b	1716	131	2.27 (1.32–3.91)
Age 60-79 by APOE ε4 status ^c			
At least one APOE ε4 allele	341	40	0.92 (0.22–3.85)
No APOE ε4 alleles	1294	84	3.03 (1.63–5.62)

^a Predictor: Lonely (3+ days/week) versus not lonely (<3 days/week). All models adjust for age, sex, and educational level.

^b The dementia analytic sample excluded participants age<60.

^c Among all participants in the dementia analytic sample, 1635 had any genotypic information. For participants age 60-79, a significant interaction between loneliness status and APOE ε4 allele carrier status was present.

Table 3. Multivariable-Adjusted Models of Cognitive and Neuroanatomical Measures as a Function of Loneliness Status: Participants Age 40-79 Without an APOE ε4 Allele

		Lonely vs Not Lonely	
Outcome ^a	No. of participants	Estimate (SE)	P value
Cognitive function			
Global	1840	-0.16 (0.09)	.08
Logical memory delayed recall	1871	0.07 (0.11)	.53
Trails making test B minus A ^b	1853	-0.23 (0.11)	.03
Brain atrophy and injury ^c			
Total cerebral volume, % of TCV	1611	-0.25 (0.10)	.01
Hippocampal volume, % of TCV	1611	0.05 (0.13)	.70
White matter hyperintensity volume, % of TCV ^b	1589	0.28 (0.11)	.01

Abbreviation: TCV, total cranial volume.

^a Predictor: Lonely (3+ days/week) versus not lonely (<3 days/week). Data are presented as beta estimate in standard deviation units and standard error (SE). Models used participants in the cognition analytic sample (n=1875), which includes participants age 40-79 without an APOE ε4 allele. All models adjust for age, age², sex, educational level, time interval between from collection of loneliness measure to when cognitive function or brain MRI were measured.

^b Log transformed to decrease skewness of distribution.

^c Among participants in the cognition sample, 1611/1875 (86%) were included in the MRI analytic subsample.

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