Chronic loneliness and the risk of incident stroke in middle and late adulthood: a longitudinal cohort study of U.S. older adults

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eClinicalMedicine
2024;73: 102639

Published Online 24 June 2024
https://doi.org/10.1016/j.eclinm.2024.102639

Summary

Background Loneliness has been implicated as a stroke risk factor, yet studies have examined loneliness at only one time point. The association of loneliness changes and risk of incident stroke remains understudied. Our aim was to examine the association of loneliness with incident stroke, particularly the role of loneliness chronicity.

Methods This prospective cohort study examined data from the Health and Retirement Study during 2006–2018. For analyses examining baseline loneliness only, we included U.S. adults aged 50 years or older and stroke-free at baseline and excluded individuals missing data on loneliness and those who experienced death at baseline. For analyses examining loneliness changes over two time points, we included those aged 50 years or older at baseline and stroke-free through the exposure measurement period. Individuals missing a loneliness scale measure or those who experienced death during the exposure measurement period were excluded. Loneliness was measured with the 3-item Revised UCLA Loneliness Scale. We constructed loneliness scores (range 3–9), dichotomized loneliness measures (high vs low using a >6 cutoff), and loneliness patterns across two time points (consistently low, remitting, recent onset, consistently high). Cox regression models estimated associations of baseline loneliness (N = 12,161) with incident stroke over a 10–12-year period, and loneliness change patterns (N = 8936) with incident stroke over a subsequent 6–8-year period, adjusting for demographics, health behaviors and health conditions.

Findings Higher loneliness scores at baseline were associated with incident stroke for continuous (hazard ratio [HR]: 1.05, 95% confidence interval [CI]: 1.01–1.08) and dichotomized (HR: 1.25, 95% CI: 1.06–1.47) loneliness measures, and persisted after adjustment for social isolation but not depressive symptoms. Only individuals with a consistently high loneliness pattern over time (vs consistently low) had significantly higher incident stroke risk (HR: 1.56, 95% CI: 1.11–2.18) after adjusting for depressive symptoms and social isolation.

Interpretation Chronic loneliness was associated with higher stroke risk independent of depressive symptoms or social isolation. Addressing loneliness may have an important role in stroke prevention, and repeated assessments of loneliness over time may help identify those particularly at risk.

Funding National Institute on Aging (NIA U01AG009740).

Keywords: Loneliness; Longitudinal cohort study; Stroke; Older adults; Public health

Introduction

Stroke is one of the leading causes of long-term disability and mortality worldwide.[1] Although stroke mortality rates have declined globally over recent decades, rates of decline for stroke incidence has slowed and the global burden of stroke remains high.[1,2] As the world experiences an expanding aging population, the total economic and social impact of stroke is projected to rise.[2] Multiple risk factors (e.g., hypertension, diabetes, and smoking) for stroke have been identified, and efforts to address such risk factors have contributed to the decline in stroke incidence.[3] Although addressing established risk factors is key to stroke prevention, these factors do not fully account for observed risk. Thus, it is

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Research in context

Evidence before this study

Loneliness has been identified as a modifiable risk factor for stroke, which is one of the leading causes of long-term disability and mortality worldwide. We examined prior literature on the loneliness–stroke association through a comprehensive PubMed search for English-language studies published up to February 8, 2024. Search terms included "Loneliness AND Stroke," "Loneliness AND Cardiovascular Diseases," "Loneliness," and "lonel*." Very few studies have examined loneliness and risk of incident stroke, with one study demonstrating baseline loneliness with higher stroke incidence in the UK. Other studies have examined social isolation and loneliness combined, or on cardiovascular diseases, but not specific loneliness–stroke associations. Moreover, loneliness can be transient or chronic, and empirical studies of changes in loneliness are needed to better understand whether interventions for loneliness may be beneficial for stroke prevention.

Added value of this study

In this cohort study, higher loneliness scores at baseline were significantly associated with incident stroke in a nationally representative cohort of older U.S. adults (N = 12,161), independent of social isolation but not depressive symptoms. In analyses that examined loneliness change patterns (N = 8936), only individuals with consistently high loneliness over time (vs consistently low) had 56% significantly higher risk of incident stroke (95% CI: 1.11–2.18), independent of social isolation and depressive symptoms.

Implications of all the available evidence

To our knowledge, this study is the first to examine changes in loneliness on incident stroke in a large prospective cohort. These findings further support the notion that addressing loneliness may have an important role in stroke prevention, and repeated assessments of loneliness may help identify those particularly at risk.

imperative to identify additional modifiable risk factors that will further help combat the projected increasing burden of stroke.

Recent studies have identified loneliness as a potential risk factor for stroke, associated with stroke risk via both short-term mechanisms (e.g., medication adherence), as well as longer-term increases in risk through mechanisms (e.g., inflammation pathways) causing damage to cardiovascular, metabolic, and immune systems.[4–6] The 2023 U.S. Surgeon General's advisory on social connection highlights loneliness as an epidemic, exacerbated by the COVID-19 pandemic and with widespread consequences for health.[7] A study among U.S. older adults found that the prevalence of loneliness, defined as having a score of ≥6 on the Revised UCLA Loneliness Scale, was at 24.6%.[8] Other studies have reported the prevalence of loneliness (i.e., reporting feeling lonely occasionally or at least sometimes) in the U.S. to be as high as 31–55% among middle-aged and older adults,[5,9–11] compared to 11–17% in the 1970s.[12] Although loneliness prevalence has increased since the 1970s, a recent study suggests that the proportion of older adults experiencing loneliness has been relatively stable in more recent decades.[11] Furthermore, several meta-analytic reviews have found that interventions designed to reduce loneliness may be effective (albeit modest), suggesting that loneliness may be a modifiable factor.[13–15] With high prevalence among the aging population, loneliness may thus be a viable, modifiable target for stroke prevention.[9] Loneliness is commonly conceptualized as a subjective personal experience, reflected as the gap between desired and available relationships.[16] It is important to differentiate loneliness from social isolation, which typically refers to the lack of social contact with others (e.g., absence of marital partners, friendship ties, and belonging to social groups).[17,18] Moreover, older adults are inclined to describe depressive symptoms in terms of loneliness, and this misclassification has also often impeded research on loneliness.[19] Although loneliness is typically included as a symptom in some questionnaire-based depression measures, it is considered a separate psychological construct and is not included in the standard *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) definition for depression.[20] Importantly, very few studies have accounted for both social isolation and depressive symptoms in studies of loneliness–stroke associations.

To our knowledge, the relationship between loneliness and stroke has rarely been examined, although considerable evidence has shown that loneliness is associated with other cardiovascular health outcomes independent of social isolation and depressive symptoms.[21–23] One study using data from the UK Biobank reported that loneliness at baseline (mean age: 56 years) was associated with higher stroke incidence over a period of mean 7.1 years of follow-up.[24] However, after accounting for all risk factors, the associations did not remain statistically significant in their fully adjusted model.[24] A prior systematic review also examined loneliness and social isolation as risk factors for coronary heart disease and stroke,[25] however none of the included studies explicitly examined the loneliness–stroke association. Examining loneliness at one time point (e.g., only at baseline) may provide an incomplete picture of the association of loneliness on stroke risk, for several reasons. Loneliness can be *situational* (i.e., a temporary experience) or *chronic* (i.e., a more stable state persisting

over long periods of time).[26] A temporary experience of loneliness may be driven by a stressful life event (e.g., retirement or death of a spouse), and may have different consequences for stroke than chronic loneliness.[26] A prior study examined how frequency of loneliness and social isolation across three timepoints was associated with incident cardiovascular disease (CVD) over a mean follow-up period of 5.4 years.[27] While loneliness was associated with higher risk of incident CVD, there was no evidence of a cumulative association for those who reported two or three (vs one) occasions of loneliness.[27] The study controlled for social isolation, but did not adjust for depressive symptoms nor considered patterns of loneliness. Additionally, the study did not examine how baseline or longitudinal changes in loneliness are associated with CVD outcomes over a long follow-up period to reduce potential reverse causality. Moreover, specific associations between loneliness and stroke incidence have rarely been examined, which limits our understanding of whether loneliness may be considered a modifiable risk factor for stroke prevention. Although there are numerous shared risk factors across stroke and other CVD outcomes,[28] the relative magnitude of effects may vary across heart disease and stroke.[29,30] Some studies have noted that there are also different risk factors by CVD subtype.[31] Furthermore, no study to our knowledge has examined whether changes in loneliness over time may be associated with stroke risk among middle-aged and older adults.

To address these important research gaps, we examined the association of loneliness with incident stroke, first considering baseline loneliness levels at one time point and then considering loneliness changes across two time points, using data from the Health and Retirement Study (HRS). Our primary goal was to understand whether chronicity plays a role in the association between loneliness and incident stroke. We hypothesized that individuals with chronic loneliness would be at highest risk for incident stroke. Our secondary goal was to understand whether loneliness would be associated with stroke via short-term mechanisms, by examining whether those with recent onset or remitting loneliness (i.e., have an earlier experience but not currently lonely) experience a differential risk in stroke, compared to those who are consistently not lonely. We hypothesized that the risk would be modestly elevated within the recent onset group, given the later onset of loneliness. We further hypothesize that loneliness is a distinct and significant risk factor for stroke independent of baseline depressive symptoms and social isolation.

Methods

Study population

The HRS is a nationally representative, longitudinal sample of individuals in the U.S. aged 50 years and older and their spouses of any age. The HRS initially had three cohorts (1992, 1993 and 1998), which were merged in 1998 and followed biennially thereafter.[32] HRS respondents answered questions on how changing health and economic circumstances are associated with aging.[33] In 2006, the HRS introduced a Psychosocial and Lifestyle Questionnaire, using a leave-behind self-administered questionnaire format.[34] A rotating random 50% subsample of the longitudinal panel received the questionnaire in each wave, where Subsample A began in 2006 and Subsample B began in 2008. We assessed loneliness across two waves of data for both subsamples (repeated every four years for each subsample).[34] As loneliness was first measured in the leave-behind questionnaire, which began in 2006 or 2008, this defined our baseline T1. T2 was in 2010/2012 when each subsample completed the second questionnaire. The overall repeated exposure period was subsequently defined in 2006–2012. Details of the leave-behind sampling timeline are provided in Fig. 1 for the baseline only analyses, and in Fig. 2 for the loneliness change analyses. Additional technical details of the study design and implementation have been previously published.[35] This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

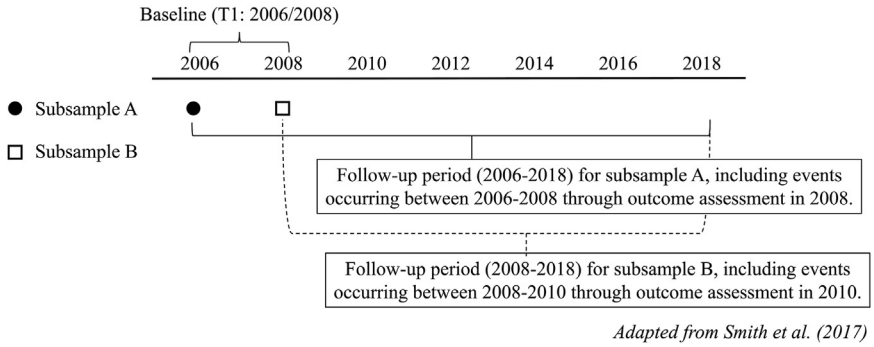
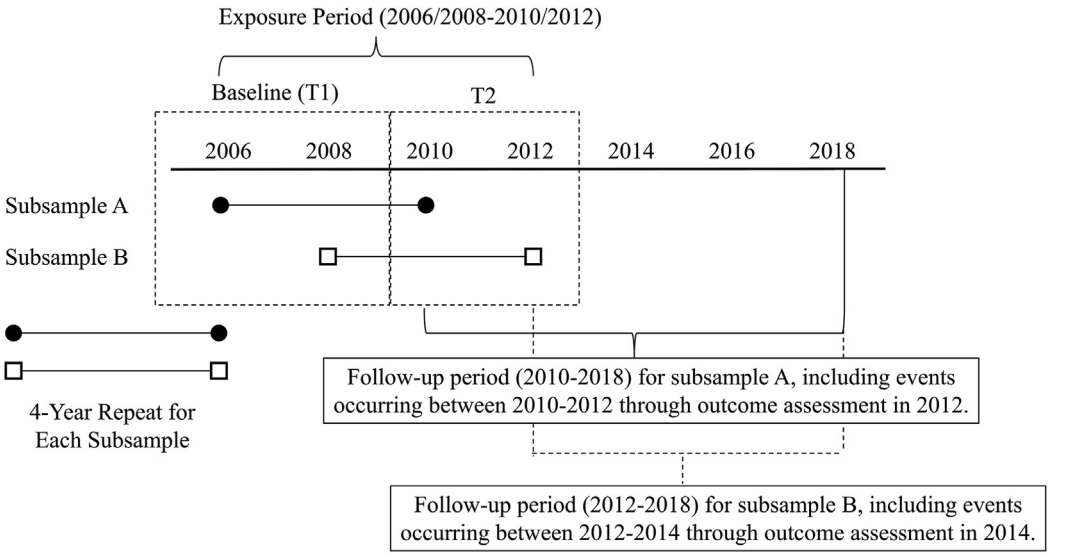


Fig. 1: Details of the leave-behind questionnaire sampling timeline for loneliness examined at only one time point.



Adapted from Smith et al. (2017)

Fig. 2: Details of the leave-behind questionnaire sampling timeline for loneliness examined across two time points.

Inclusion and exclusion criteria

For the first set of analyses considering baseline loneliness only, we defined 2006–2018 as our follow-up period, with stroke events occurring between 2006 and 2008 only available for Subsample A through the outcome assessment in 2008. We restricted our sample to participants aged ≥50 years who did not report having had a stroke prior to or in T1. Out of 14,283 eligible HRS respondents, we excluded individuals missing the loneliness measure in T1 (N = 1944, 12.8%), those who had a stroke in T1 (N = 165, 1.1%), and those who died in T1 (N = 13, 0.09%). Our sample for this set of analyses included 12,161 individuals (eFigure S1).

For the second set of analyses considering loneliness changes over two time points, we defined 2010–2018 as our follow-up period, with outcomes assessed in 2012 (i.e., stroke events occurring between 2010 and 2012) only available for Subsample A. Again, we restricted our sample to participants aged ≥50 years in T1 who did not report having a stroke prior to or in the exposure measurement period (T1-T2). Out of 13,002 eligible HRS respondents, we excluded individuals missing a loneliness scale measure in T1-T2 (N = 3419, 26.3%), those who had a stroke in T1-T2 (N = 423, 3.3%), and those who died in T1-T2 (N = 224, 1.7%). Our sample for this set of analyses included 8936 individuals (eFigure S2).

Ethics

The HRS is sponsored by the National Institute on Aging and conducted by the University of Michigan. Participants provided written informed consent and the HRS was approved by the University of Michigan Institutional Review Board. The Harvard T.H. Chan School of Public Health human subjects committee determined the present study to be exempt from institutional review board review as it uses the publicly available de-identified HRS data.

Exposure ascertainment

The HRS loneliness scale is a simplified three–item scale, derived from prior exploratory and confirmatory factor analyses of the 20-item Revised UCLA Loneliness Scale (R-UCLA).[36] To create the loneliness score, the item responses were reverse-coded and summed across the three items, with scores ranging from 3 to 9.[36] The three-item R-UCLA scale has been shown to have solid psychometric properties, including good reliability and validity.[36] We examined loneliness using the continuous loneliness summary score, and also dichotomized the score into high (>6) or low (≤6). This cutoff has shown good concordance with the one-item loneliness measure on the Center for Epidemiologic Studies-Depression (CES-D) Scale (used as an artificial standard to determine lonely vs not lonely).[37] For individuals missing 1–2 items on the loneliness scale, the summary score was calculated using the available items, weighted appropriately for the number of items available.

For the analyses of change, we constructed four loneliness change patterns using combinations of dichotomized loneliness scores at the two exposure time points. We defined "*consistently low*" as having low loneliness scores at both T1 and T2; "*recent onset*" as having a low loneliness score at T1 and a high score at T2; "*remitting*" as having a high loneliness score at T1 and a low score at T2; and "*consistently high*" as having high loneliness scores at both T1 and T2.

Stroke ascertainment

We ascertained fatal or non-fatal incident stroke events as the first occurrence of stroke, based on self- or proxy-reported doctor's diagnosis ("Has a doctor ever told you that you had a stroke?"). For participants who died or were unavailable for a direct interview, interviews were conducted with proxy informants (predominantly spouses). Reports of transient ischemic attacks were not systematically assessed and therefore not coded as strokes, nor was stroke subtype information available.[38] Prior work with HRS data has shown that associations between known risk factors and self-reported stroke incidence in the HRS corresponded well with associations reported in studies using clinically verified strokes.[38] Furthermore, self-reported strokes in the HRS corresponded well with strokes coded according to the *International Classification of Diseases (ICD)* in the Centers for Medicare and Medicaid Services records, with 74% sensitivity and 93% specificity.[39]

Social isolation

We created a social isolation measure based on the Berkman-Syme Social Network Index, assessing social isolation at baseline across four domains of social activity: marital status, volunteer activity, contact with children and neighbors.[40] Following prior work on social integration, we assigned one point for each domain in which respondents were considered isolated. For marital status, married respondents were assigned zero and all others were assigned one point. If a respondent participated at least 1 h in the past year volunteering in religious, educational, health-related, or other charitable organizations, the respondent was assigned zero. Respondents who did not volunteer any hours were assigned one point. Respondents were assigned zero if they had contact with children, defined as weekly or more frequent contact (by phone, mail, or in person), and one point otherwise. Contact with neighbors was based on whether the respondents reported getting together with neighbors to chat or socialize. Respondents reporting weekly or more frequent contact were assigned zero, and one point otherwise.[41] The sum of non-missing values for all domains was used as the individual's social isolation score, with higher scores indicating more social isolation (ranging from 0 to 4). If respondents were missing all domains, the social isolation score was set to missing.[41]

Depressive symptoms

We used the validated, modified 8-item version of the CES-D scale to assess depressive symptoms at baseline.[32] In each biennial questionnaire, participants were asked to respond (yes/no) whether they experienced each of eight symptoms in the past week. A summary score was created by summing the number of "yes" answers across the eight items (with two positive items reverse-scored).[32] One item on the CES-D asked whether the respondent felt lonely, and was deleted prior to calculating the total CES-D score. We used the continuous CES-D summary measure (ranging from 0 to 7) in the analyses. The Cronbach's alpha for the CES-D scale with the loneliness item removed was 0.78, which is considered acceptable.[42]

Potential confounders and mediators

We considered several sociodemographic characteristics, health behaviors and health conditions at T1 as potential confounders. At T1, participants self-reported the following demographic and socioeconomic information: age (continuous), sex (male or female), race and ethnicity (categorized as non-Hispanic Black, non-Hispanic White, Hispanic or other [American Indian, Alaskan Native, Asian and Pacific Islander]), highest level of education (less than high school, high school graduate/GED/some college, four-year college and above) and household income (continuous).

Self-reported measures of health behaviors and health conditions were also measured at T1.[43–45] Self-reported health behaviors included: engaging in vigorous physical activity (more than once a week, once a week, one to three times a month, hardly ever or never), alcohol consumption (none, moderate: <3 drinks per day or <18 per week, heavy: ≥3 drinks per day or ≥18 per week), body mass index (BMI: continuous, kg/m^2 derived from self-reported height and weight) and smoking status (non-smoker, former smoker, current smoker). Health conditions were assessed using dichotomized responses (yes/no) to the question, "Has a doctor ever told you that you had a (health condition)?" for each of the following health conditions at T1: heart condition (i.e., "heart attack, coronary heart disease, angina, congestive heart failure, or other heart problems"), diabetes, and hypertension. Self-reported health conditions in the HRS have been shown to have substantial agreement with medical records data and good external validity.[45,46] Additionally, we considered the above health behaviors and health conditions at T2 as potential mediators in a sensitivity analysis for the loneliness change analyses only.

Statistics

We first examined the distribution of covariates for the overall sample and by loneliness group categories, for each set of analyses. After ascertaining that the proportional hazards assumption was not violated, we used Cox regression models to estimate hazard ratios (HR) and accompanying 95% confidence intervals (CIs) for the association between loneliness and incident stroke. We used clustered standard errors to account for the clustering of observations within marital dyads. In the first set of analyses, we examined both the association of loneliness levels (continuously measured) and dichotomized loneliness at baseline with incident stroke. In the second set of analyses, we examined loneliness changes

across two time points on incident stroke, with the consistently low category as our reference group.

We ran a series of models for all analyses. In Model 1, we adjusted for age, race and ethnicity, and sex only. In Model 2, we additionally adjusted for sociodemographic confounders (educational level and household income) measured at T1. In Model 3, we further adjusted for health conditions (diabetes, heart conditions and hypertension) and health behaviors (BMI, smoking, alcohol consumption, physical activity) at T1. We assessed for effect modification by sex, race and ethnicity by including multiplicative interaction terms with loneliness measures.

We further conducted three sensitivity analyses to assess robustness of our findings. First, we examined whether the association of loneliness with incident stroke risk was independent of depressive symptoms and social isolation. Second, we examined whether associations with stroke were sensitive to how the loneliness score was dichotomized, by repeating the main analyses with a lower cutoff (>5 or ≤5). Third, we used stabilized inverse probability weighting (IPW) to address potential selection bias due to differential dropout.[47] For the analyses of change, we conducted a fourth sensitivity analysis where we repeated the main analyses additionally adjusting for health conditions at T2, to examine changes in associations due to potentially mediating health behavioral pathways.

Missingness in the overall dataset was around three percent, with the largest percentage of missing values attributed to the social isolation measure (2.8%). For those with missing values on the health condition variables, we first replaced missing values using information collected at the previous wave, if available. For all additional missing values on the exposure and covariates, we imputed the missing values using the multiple imputation by chained equations (MICE) procedure with the mi command in STATA, with the main analyses applied to 10 imputed datasets.[48] Missing values on stroke were not imputed. We conducted all analyses using Stata version 14 (Stata Corp, College Station, TX, USA).

Role of funding source

The HRS (Health and Retirement Study) is sponsored by the National Institute on Aging (NIA U01AG009740) and is conducted by the University of Michigan. The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Table 1 describes the demographic and health characteristics of the overall analytical sample and by loneliness change group. Descriptive statistics for the baseline loneliness analyses are presented in eTable S1. For the first set of analyses examining baseline loneliness (N = 12,161), 1237 incident strokes were observed during 10–12 years of follow-up (2006–2018). In the second set of analyses examining loneliness change (N = 8936), 601 incident strokes were observed during 6–8 years of follow-up (2010–2018). Based on the second set of analyses, the average age of the analytical sample at baseline (T1) was 67.4 years and the majority of individuals were female (60.6%), non-Hispanic White (79.8%), and 84.8% had consistently low loneliness scores over time. As shown in Table 1, baseline characteristics differed across the loneliness change groups. Compared to the consistently low group, individuals in the consistently high group were younger (65.4 vs 67.6 years), had less than high school education (25.6 vs 18.1%), were less likely to engage in vigorous physical activity (73.4 vs 54.2%) and were more likely to have a health condition. Sociodemographics, health conditions and health behaviors also differed between the remitting and recent onset groups, compared to the consistently low group. Loneliness at T1 was weakly correlated with depressive symptoms (r = 0.34) and social isolation (r = 0.23) at T1, and moderately correlated with loneliness at T2 (r = 0.57). The correlation between social isolation and depressive symptoms at baseline was r = 0.19.

Association of baseline loneliness with risk of incident stroke

Results of the analyses of baseline loneliness are presented in Table 2. In our fully adjusted model, a one-unit increase in the loneliness score was associated with a five percent higher risk for incident stroke (hazard ratio [HR]: 1.05, 95% confidence interval [CI]: 1.01–1.08). When using the dichotomized loneliness measure, individuals categorized as lonely had 25% higher risk (fully adjusted HR: 1.25, 95% CI: 1.06–1.47), compared to those not categorized as lonely (reference). The tests for interactions showed no evidence of effect modification by sex or race and ethnicity in the association between baseline loneliness and incident stroke.

Results from the three sensitivity analyses mirrored our main results, although some attenuated associations for loneliness and incident stroke were evident. Controlling for social isolation did not change the results; findings were minimally attenuated by depressive symptoms (eTable S2). Using a >5 cutoff to dichotomize loneliness attenuated the effect estimates, but associations remained (eTable S3). The analyses using inverse probability weighting provided similar results and suggest our findings were not largely affected by loss to follow-up (eTable S4).

Association of loneliness change across two time points with risk of incident stroke

In the fully adjusted model, individuals categorized as having "consistently high" loneliness across T1-T2 had higher risk (HR: 1.56, 95% CI: 1.11–2.18) than those categorized as having "consistently low" loneliness

	Overall	Loneliness change pattern categories			
	Sample	Consistently low	Remitting	Increasing	Consistently high
Individuals, n (%)	8936	7576 (84.8)	496 (5.6)	485 (5.4)	379 (4.2)
Sociodemographic characteristics					
Age (in years), mean (SD)	67.4 (9.0)	67.6 (8.9)	66.3 (8.9)	67.9 (9.4)	65.4 (9.4)
Sex, n (%)					
Female	5412 (60.6)	4502 (59.4)	325 (65.5)	330 (68.0)	255 (67.3)
Male	3524 (39.4)	3074 (40.6)	171 (34.5)	155 (32.0)	124 (32.7)
Race and ethnicity, n (%)					
Hispanic or other	834 (9.3)	669 (8.8)	70 (14.1)	54 (11.1)	41 (10.8)
Non-Hispanic black	967 (10.8)	787 (10.4)	79 (15.9)	58 (12.0)	43 (11.4)
Non-Hispanic white	7134 (79.8)	6119 (80.8)	347 (70.0)	373 (76.9)	295 (77.8)
Highest level of education, n (%)					
Less than high school	1739 (19.5)	1370 (18.1)	143 (28.8)	129 (26.6)	97 (25.6)
High school	5035 (56.4)	4284 (56.6)	273 (55.0)	257 (53.0)	221 (58.3)
College and above	2161 (24.2)	1922 (25.4)	80 (16.1)	98 (20.2)	61 (16.1)
Income (in 1000s US dollars), mean (SD)	44.9 (142.2)	46.8 (153.1)	31.2 (33.0)	38.5 (61.1)	32.9 (38.3)
Health behaviors					
Vigorous physical activity, n (%)					
More than once a week	2388 (26.7)	2142 (28.3)	89 (17.9)	95 (19.6)	62 (16.4)
Once a week	832 (9.3)	728 (9.6)	39 (7.9)	41 (8.5)	24 (6.3)
One to three times a month	674 (7.5)	594 (7.8)	3 (6.3)	34 (7.0)	15 (4.0)
Hardly ever or never	5037 (56.4)	4108 (54.2)	336 (67.7)	315 (65.0)	278 (73.4)
Alcohol consumption, n (%)					
None	4036 (45.2)	3328 (43.9)	251 (50.6)	258 (53.2)	199 (52.5)
Moderate (<3 drinks per day or <18 per week)	4210 (47.1)	3664 (48.4)	202 (40.7)	199 (41.0)	145 (38.3)
Heavy (≥3 per day or ≥18 per week)	690 (7.7)	584 (7.7)	43 (8.7)	28 (5.8)	35 (9.2)
BMI (kg/m2), mean (SD)	28.9 (6.0)	28.8 (5.8)	30.2 (7.2)	29.5 (6.8)	30.1 (7.5)
Smoking, n (%)					
Non-smoker	4111 (46.0)	3511 (46.3)	216 (43.6)	205 (42.3)	179 (47.2)
Former smoker	3950 (44.2)	3347 (44.2)	217 (43.8)	216 (44.5)	170 (44.9)
Current smoker	875 (9.8)	718 (9.5)	63 (12.7)	64 (13.2)	30 (7.9)
Health conditions					
Has heart condition, n (%)	1856 (20.1)	1529 (20.2)	123 (24.8)	113 (23.3)	91 (24.0)
Has diabetes, n (%)	1620 (18.1)	1294 (17.1)	115 (23.2)	111 (22.9)	100 (26.4)
Has hypertension, n (%)	4935 (55.2)	4109 (54.2)	304 (61.3)	291 (60.0)	231 (61.0)
Depressive symptoms and social isolation					
Social isolation, mean (SD)	1.5 (1.0)	1.4 (0.9)	2.0 (0.9)	1.8 (0.9)	2.1 (0.9)
Depressive symptoms, mean (SD)	1.1 (1.6)	0.8 (1.4)	2.4 (2.2)	1.9 (2.1)	3.0 (2.4)

Percentage of missing values prior to imputation: Age 0.01%; Race and Ethnicity 0.01%; Highest Level of Education 0.01%; Income 0.01%; Vigorous Physical Activity 0.06%; BMI (body mass index): 1.2%; Has Heart Condition 0.01%; Has Diabetes 0.01%; Depressive Symptoms 1.1%. All others: no missing values.

Table 1: **Characteristics of the analytical sample at baseline at wave 1 (2006/2008) for analyses examining loneliness across two time points.**

(Table 2). Similar associations were observed for individuals categorized as having "recent onset" (HR: 1.30, 95% CI: 0.95–1.77) or "remitting" (HR: 1.30, 95% CI: 0.95–1.79) loneliness, although these were not statistically significant. This observation may be due to the low case counts for these loneliness categories. Tests for interactions showed no evidence of effect modification by sex or race and ethnicity.

Results from the four sensitivity analyses again mainly mirrored our main results. Our findings were robust to inclusion of social isolation, depressive symptoms, and both simultaneously (eTable S2). Using a >5 cutoff for the loneliness score, the hazard ratio was meaningfully attenuated in the consistently high group (eTable S3). Our findings were not largely affected by loss to follow-up (eTable S4), nor by the inclusion of health behaviors and conditions at T2 (eTable S5).

Discussion

In this cohort of middle-aged and older U.S. adults, we observed that lonely individuals at baseline had a higher

	Individuals, n (%)	Cases	Person-years[a]	Model 1[b], HR (95% CI)	Model 2[c], HR (95% CI)	Model 3[d], HR (95% CI)
Loneliness measured at baseline (One timepoint, N = 12,161)						
Loneliness score (Continuous)	12,161 (100)	1237	140,138	1.07 (1.04, 1.11)	1.06 (1.03, 1.10)	1.05 (1.01, 1.08)
Loneliness (dichotomized)						
Loneliness score (>6)	1297 (10.7)	169	14,788	1.37 (1.16, 1.61)	1.31 (1.12, 1.55)	1.25 (1.06, 1.47)
Loneliness score (≤6)	10,864 (89.3)	1068	125,350	1.00 (ref)	1.00 (ref)	1.00 (ref)
Loneliness change over two timepoints (>6 cutoff, N = 8936)						
Consistently high	379 (4.2)	37	2934	1.74 (1.25, 2.43)	1.69 (1.21, 2.36)	1.56 (1.11, 2.18)
Recent onset	485 (5.4)	44	3764	1.41 (1.04, 1.91)	1.39 (1.02, 1.88)	1.30 (0.95, 1.77)
Remitting	496 (5.6)	42	3878	1.42 (1.04, 1.94)	1.37 (1.00, 1.87)	1.30 (0.95, 1.79)
Consistently low	7576 (84.8)	478	59,438	1.00 (ref)	1.00 (ref)	1.00 (ref)

Abbreviations: CI, confidence interval; HR, hazard ratio. [a]For baseline loneliness only, total 140,138 person-years of follow-up; and for loneliness changes over two time points, total 70,014 person-years of follow-up. [b]Model 1 adjusted for age, sex and race and ethnicity. [c]Model 2 adjusted for age, sex, race and ethnicity, educational level and income. [d]Model 3 adjusted for age, sex, race and ethnicity, educational level, income, and health conditions and behaviors (physical activity, drinking, body mass index (BMI), smoking status, diabetes, heart conditions and hypertension) at T1 (2006/2008).

Table 2: **Cox proportional hazard ratios for the association of loneliness and incident stroke.**

risk of incident stroke after adjusting for a broad range of potential confounders. When examining loneliness change over two time points, those categorized as having "consistently high" loneliness were at higher risk for incident stroke than those in the category "consistently low" loneliness. The heightened risk for incident stroke remained after additionally adjusting for depressive symptoms and social isolation. The "remitting" and "recent onset" loneliness groups did not show a clear pattern of increased risk of stroke. Taken together, these findings not only substantiate our overall hypothesis that loneliness is associated with an elevated risk of incident stroke, but also supports the role of chronicity in these associations. Furthermore, our findings suggest that the effects of loneliness on stroke occur over the longer term, given that short-term increases or decreases in loneliness were not differentially associated with stroke risk.

Three mechanisms generally describe how loneliness can impact stroke risk: physiological, behavioral, and psychosocial.[23] Potential physiological mechanisms previously described in the literature include risk of elevated blood pressure, increased hypothalamic-pituitary-adrenocortical activity, and diminished immunity.[49] Potential behavioral mechanisms include unhealthy behaviors such as poor medication adherence, smoking and alcohol use, and lower quality of sleep.[50] Although we did not formally assess for mediating pathways, we adjusted for health behaviors and conditions at T2 in our sensitivity analyses. We found that risk estimates were only modestly attenuated, suggesting that these factors may explain only a modest proportion of the observed associations between loneliness and stroke risk. Another explanation may be that the associations of loneliness on incident stroke are not largely explained by physiological pathways. It has been argued that the hypothesized mechanisms are based on weak empirical evidence, limited to mostly cross-sectional studies and small sample sizes.[51] A prior study examined loneliness on cardiometabolic outcomes in two nationally representative cohorts of older adults, finding no associations in loneliness changes and simultaneous changes in blood pressure and hemoglobin A1C.[51] However, these findings were still restricted to a narrow range of cardiometabolic measures and did not assess for longer-term effects of loneliness.[51,52] Although it is beyond the scope of this study, further work is needed to establish stronger empirical evidence on the potential physiological mechanisms (e.g., inflammation or metabolic pathways)[53,54] underlying the loneliness–stroke association.

Given that the associations of loneliness with stroke risk persisted even after adjustment for several physiological and behavioral risk factors, psychosocial mechanisms including depression, anxiety, dysphoria or social withdrawal might help explain our observations.[55] In our sensitivity analyses for baseline loneliness only, the associations between loneliness and stroke was attenuated after adjustment for depressive symptoms. These findings are consistent with prior work that demonstrated loneliness assessed at a single time point was associated with higher risk of incident stroke, although associations were attenuated after adjusting for social isolation, depressive symptoms and other conventional risk factors.[24] However, adjustment for depressive symptoms did not explain the associations between chronic loneliness and incident stroke. Those who are chronically lonely may represent individuals with an inability to develop satisfying social relationships, which may result in longer-term interpersonal difficulties.[26] Another interpretation of these findings may be that chronic loneliness is an indicator for other unobserved social behaviors, such as neuroticism or other personality-related factors.[56] These personality factors may also be associated with long-term interpersonal difficulties that result in a dispositional loneliness, putting individuals with chronic loneliness at higher risk for incident stroke.[57]

This study has several strengths. This longitudinal study is one of the first to examine the associations of loneliness chronicity on incident stroke in a nationally representative population of older adults in the U.S., an important research question given the high prevalence of loneliness among the aging population. We were also able to disentangle the effects of loneliness on stroke risk independently from both social isolation and depression. Second, we assessed loneliness using a validated loneliness score, which may be better than single-item measures or direct questions that include the term 'loneliness.' The latter two measures may lead to a biased estimation of the prevalence of loneliness, because loneliness can be seen as a stigmatizing concept and respondents may avoid characterizing themselves as such.[58] Individuals may also not be consciously aware that they are lonely, which can also lead to biased estimation of loneliness using direct questions.[37]

Some limitations of our study must be discussed. Our sample was confined to older adults in the U.S. and may not be generalizable to younger populations or non-U.S. populations. Although we adjusted for many potential confounders, there is still the possibility of unmeasured confounding in our observational study. Another limitation is that because clinically relevant cutoffs have not been established, we used an arbitrary cutoff to dichotomize loneliness. In our sensitivity analysis with a lower cutoff, we see that the effect estimates decrease substantially for the consistently high group. Although there is a lower prevalence of individuals in the consistently high group, we do not believe we are underpowered to detect effect estimates for this category, given that our findings remain consistent across different exposure classifications. Lastly, in our study, we were only able to examine the effects of loneliness changes over a 4-year period across two time points in relation to incident stroke over a 6–8-year follow-up period. It remains unclear whether the 4-year exposure window used to assess loneliness change in this study is sufficient to ascertain the role of loneliness change in the etiology of stroke. Future studies are warranted to evaluate whether longer-term changes in loneliness status may further support the dose–response effect observed in our results, or whether shorter-term nuanced changes in loneliness may result in lower risk for incident stroke.

In conclusion, loneliness can result in a higher risk for incident stroke and those experiencing chronic loneliness may be particularly at risk. Addressing loneliness may have an important role in the prevention of incident stroke. Future studies should examine more comprehensive loneliness trajectories over time to examine whether the association is sustained, examine the underlying mechanisms between loneliness and incident stroke, and whether interventions targeting loneliness are effective in preventing stroke.

Contributors

YS conceptualized and designed the study, had directly accessed and verified the underlying data, conducted data analysis, wrote the first and revised drafts. IK advised on the statistical approach and contributed to the critical revision of the manuscript. LDK advised on study design and analytic approach, contributed to curating and synthesizing the literature, and contributed to the critical revision of the manuscript. LFB advised on study design and statistical approach, and contributed to the critical revision of the manuscript. HT provided primary supervision, advised on the statistical approach, had directly accessed and verified the underlying data, and contributed to the critical revision of the manuscript. All authors had full access to the data and accept final responsibility for the decision to submit the manuscript for publication.

Data sharing statement

Data used in this study is publicly available through the Institute for Social Research at the University of Michigan, Ann Arbor (https://hrsdata.isr.umich.edu/data-products/public-survey-data) to researchers for scientific purposes upon request.

Declaration of interests

No conflicts of interest to declare.

Acknowledgements

The HRS (Health and Retirement Study) is sponsored by the National Institute on Aging (NIA U01AG009740) and is conducted by the University of Michigan. The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102639.

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