



Contents lists available at ScienceDirect

The Journal of Prevention of Alzheimer's Disease

journal homepage: www.elsevier.com/locate/tjpad

Original Article

Social isolation, loneliness, and their joint effects on cognitive decline and incident Alzheimer's disease: Findings from the Chicago health and aging project [☆]

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ARTICLE INFO

Keywords:

Social determinants of health
Vulnerable
Social isolation
Loneliness

ABSTRACT

Background: There has been contradictory evidence on the prospective associations between social isolation/loneliness (SI/L) and cognitive decline (CD). There is also a scarcity of large and diverse population-based cohort studies examining SI/L that have confirmed clinical diagnoses of Alzheimer's Disease (AD). Notably, beyond individual associations, whether the effects of SI/L compound and accelerate CD and incident AD are not known.

Objectives: We hypothesized that SI and L, independently, would be associated with CD and incident AD to a similar extent, and the association of SI with CD and incident AD would be higher in lonely older adults.

Design: Prospective cohort study.

Setting: Urban Chicago areas.

Participants: We analyzed data in the Chicago Health and Aging Project (CHAP), which comprised 7,760 biracial community-dwelling older adults [mean age (standard deviation (SD))=72.3 (6.3); 64 % Black & 63 % women; mean (SD) of follow-up=7.9 (4.3) years].

Intervention (if any): NA

Measurements: Linear mixed and logistic regression models were used to regress CD and incident AD separately on the SI index/L.

Results: SI index and L were significantly associated with CD, with one-point increase of beta estimate (SE, p-value) = -0.002 (0.001,0.022) and -0.012 (0.003,<0.001), respectively. Given that the SI index ranges from 0 to 5 and the L from 0 to 1, they had similar effect sizes. Similarly, there were significant associations between SI index and incident AD, odds ratio (95 % CI, p-value) = 1.183 (1.016–1.379,0.029), and between L and incident AD, 2.117 (1.227–3.655,0.006). When stratified by loneliness status, compared to older adults who were not isolated and not lonely, older adults who reported being socially isolated and not lonely experienced accelerated CD, -0.003 (0.001,0.004), despite no significantly increased odds of incident AD.

Conclusions: SI/L had significant associations with CD and incident AD. Notably, socially isolated older adults who reported not being lonely appeared to be most socially vulnerable to CD. These findings suggest a specific at-risk subgroup of socially vulnerable older adults for future targeted interventions to improve cognitive health.

1. Introduction

Social isolation and loneliness (SI/L), two social determinants of health recently garnering consistent attention due to the COVID-19 pandemic, have been associated with an increased rate of cognitive decline (CD) and development of Alzheimer's Disease/Alzheimer's Disease and

Related Dementias (AD/ADRDs) [1–5]. The convergence of SI/L with CD and AD presents imminent public health challenges that will only worsen with population aging. For example, the latest Lancet Commission 2024 identified SI as one of 14 risk factors, accounting for 46 % of the potential modifiable risk for dementia [6]. It is worth noting that SI/L are related yet distinct constructs [7,8]; SI is defined as the objec-

[☆] FUNDING: K.D. and K.B.R. are funded by NIH research grants.

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<https://doi.org/10.1016/j.tjpad.2024.100046>

Received 2 October 2024; Received in revised form 19 November 2024; Accepted 17 December 2024

Available online 1 January 2025

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tive lack of a robust social network, being unmarried, and participating in few activities with others [9], whereas L is defined as a negative emotional state resulting from the subjective experience of perceived unfulfilled social and intimate needs, feeling left out, and the lack of a sense of belonging, akin to being alone in the crowd [10]. Both SI/L are evolutionarily conserved stressors [11,12]. For SI, the Social Safety Theory proposes that developing and maintaining friendly social relationships is a fundamental human need, the lack of which is a critical feature of physiological stressors that increase disease risks [12]. The Evolutionary Theory of Loneliness posits that L could cause dysregulations in multiple physiological systems, thus increasing disease risks [11].

In the United States, addressing the issues of SI/L and CD/AD has become a national priority in public health agendas, particularly during and post-COVID-19. The American Psychiatric Association's monthly poll in 2024 reported that 1 in 3 Americans felt lonely at least once a week over the past year [13]. In 2023, the U.S. Surgeon General published a report highlighting the effects of loneliness on health, describing loneliness in America as a national epidemic and declaring loneliness a public health emergency [14]. The National Academies also published a report on SI/L in 2021, highlighting the research gaps, including the need for additional studies in this area [15]. Indeed, SI/L are two social determinants of health or health risk markers with detrimental effects comparable to those of other public health priorities [16], including smoking and alcohol consumption, and should be incorporated into the current public health priorities and campaigns [17].

Despite the advent of literature in the field, there are several remaining gaps in knowledge. Due to the different nature of constructs and measurements (i.e., objective versus subjective), SI/L are related yet distinct constructs and thus not interchangeable, yet studies continue to conflate them. Furthermore, there have been conflicting findings on the prospective associations of SI with CD/dementia and L and CD/dementia. For example, a recent meta-analysis found that in long-term studies (≥ 10 years), although high social engagement was modestly protective of dementia, loneliness was not associated with dementia risk [18]. Hence, SI and L may have differential associations with CD and incident AD. However, studies seldom examined the individual associations of SI/L with CD concurrently in a single study and compared their effect sizes head-on. Further complicating this issue, the few studies concurrently examined the individual associations SI/L on CD showed inconsistent findings. Furthermore, due to population-based studies imposing limitations on logistics and resources, there has been a lack of clinician-triaged clinical diagnoses of incident AD in these studies [19–21]. Lastly, possible synergistic effects between SI and L on CD/incident AD are unknown. It is plausible that SI's effects are exacerbated in older adults who are lonelier than their counterparts, which could enable researchers and policymakers to identify the most socially vulnerable subgroup of older adults for targeted interventions.

In this study, leveraging the rich 20-year data from the Chicago Healthy Aging Project (CHAP), an established prospective cohort of biracial community-dwelling older adults based in Chicago [1,22], comprising White and Black older adults, we aimed to:

- (1) Compare and contrast **a.** the presence/absence of association between SI/L and CD/incident AD and **b.** their effect sizes
- (2) Investigate **a.** the association between SI and L and **b.** if the association of SI with CD/incident AD differs by L status.

We hypothesized that SI and L, independently, would be associated with CD and incident AD to a similar extent, and the association of SI with CD and incident AD would be higher in lonely older adults.

2. Methods

2.1. Study design, setting, and population

The Chicago Health and Aging Project (CHAP) is an established prospective population-based cohort study designed to assess bio-

psycho-social and structural risk factors for age-related chronic conditions in older adults, specifically focusing on AD/ADRD. Detailed objectives and cohort study design were previously published [22]. Briefly, recruitment was started in 1993, enrolling participants from four Chicago neighborhoods with substantial proportions of non-Hispanic Black and White residents. The only two inclusion criteria for the cohort were living in the study catchment area and having a minimum age of 65 years at enrolment.

During in-home assessments, the trained research assistants administered questionnaires and neurocognitive tests every three years and up to six times throughout the study period. A detailed protocol has been previously published [23]. In brief, approximately one-third of the parent CHAP participants were selected for a clinical AD assessment during the study. For this paper, we analyzed data from participants with baseline SI/L measures and had at least two cognitive tests or one clinical assessment of incident AD. Hence, the total sample with CD as the outcome was $N = 7760$, and the sub-sample with a clinical assessment of incident AD was $N = 2100$.

2.2. Ethics approval and consent to participate

The Institutional Review Board of the Rush University Medical Center approved the study protocols, and all participants provided written consent for population interviews and clinical evaluations.

2.3. Availability of data and materials

Data that support study findings are available through data request and a data use agreement from the research resource data portal, <https://riha.rush.edu/dataportal.html>.

2.4. Loneliness

Loneliness was measured at baseline, i.e., during the first participant visits, using a single item from the modified version of the Center for Epidemiologic Studies—Depression Scale (CES-D): "I felt lonely." The CES-D has validated psychometric properties [24,25]. For the item, the participants were asked: "Have you felt this way much of the time during the past week?" with 1 = yes and 2 = no, with those answering "Yes" identified as lonely.

2.5. Social isolation

The social isolation index [9] has a five-point scale, with binary response options for each item; one point was assigned: 1. Unmarried/not cohabiting, 2. Less than monthly face-to-face contact with children, 3. Less than monthly contact face-to-face with other close relatives, 4. Less than monthly contact face-to-face with close friends, 5. No participation in social clubs, resident groups, religious groups, or committees. Hence, the sum of the five items resulted in the range of scores from 0 to 5, with 5 being the most socially isolated [9].

2.6. Cognitive tests

As described previously, the trained research assistants administered four cognitive tests to the participants during the in-home assessments [23]. The four tests included two tests of episodic memory, one test of executive function, and the MMSE. These tests were selected because they are psychometrically established, assess cognitive functions compromised in AD/ADRD (i.e., episodic memory, executive function), and meet the practical demands of the study (brevity and feasibility of administrations during in-home assessments for a population-wide epidemiological study and acceptable to older participants). After centering and scaling each test to the cohort's baseline means and standard deviations, we derived standardized scores for a global measure of cognitive function and domain-specific cognitive tests. Individual domain-specific

cognitive tests were based on two tests for memory and one executive function-based speed test. Subsequently, the global measure of cognitive function was calculated by averaging the four cognitive tests described in detail in CHAP's previous publications [26,27].

2.7. Incident AD-clinical diagnosis of AD dementia

During each three-year study cycle, a stratified random sample based on age, sex, race/ethnicity, and cognitive level was selected for clinical evaluation of incident AD dementia. Clinical evaluations were structured and uniform, with the neurologists blinded to the parent cohort's population interview cognitive testing and stratified sampling categories [28]. Clinical evaluations included a structured medical history, neurologic examination, and 19 neurocognitive tests. Unaware of previously collected data, a board-certified neurologist diagnosed AD dementia according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer Disease and Related Disorders Association criteria [29]. A clinical diagnosis of AD dementia requires a history of CD and evidence of impairment in 2 or more cognitive domains. In this specific study, 2100 participants of the total sample were clinically evaluated for incident AD dementia.

2.8. Covariates

In all analyses, we controlled for pertinent covariates [30,31] collected at the baseline, i.e., age at the time of the interview, biological sex (men and women), race (non-Hispanic Black and non-Hispanic White), education (measured in the number of years of schooling completed), and follow-up time.

2.9. Statistical analyses

Baseline descriptive statistics were computed for demographic characteristics, including age, formal years of education completed, self-reported race/ethnicity, sex at birth, and global cognition.

To address aim 1, which was to compare and contrast a. the presence/absence of association between SI/L and CD/incident AD AND b. their effect sizes, we used a linear mixed effects regression model to model CD. These mixed models included random intercepts and slopes and allowed us to measure both within and across participant variability.³¹ Time since baseline SI/L assessment, in years, captured the annual rate of change in cognitive function over time, reported in beta estimate (SD, p-value). Incident AD was modeled using logistic regression that included sampling weights to adjust for the study design, reported in odds ratio (95 % confidence interval (CI), p-value). Effect sizes for the SI index reflect a one-point increase in the index (range from 0 to 5), while the effect sizes for L reflect the difference between experiencing and not experiencing L (range from 0 to 1).

We performed a Pearson's correlation analysis of the two constructs to address aim 2a., the association between SI and L. Lastly, to address aim 2 b. if the association of SI with CD/incident AD differs across L status, we ran models similar to those used to address aim 1, adding the interaction term SI*L. Subsequently, we performed *a priori* stratified analyses based on L status (Yes=1, lonely; No=0, not lonely), repeated for all statistical models.

All regression models were performed with SAS, and graphical representations were performed using the R program. Each linear mixed effects regression model was adjusted for all covariates indicated above and included the interaction of all covariates with time since baseline. All logistic models were adjusted for all covariates, including time since follow-up. The percent accelerated annual rate of CD is calculated using the formula " $(\beta$ for Time x SI index OR L / β for Time since baseline)*100". Since we conceptualized all hypotheses *a priori* to be tested based on a defined set of regression models, a two-tailed p-value of 0.05 and below was considered statistically significant.

Table 1a

Demographics Characteristics of the Total Sample with Cognitive Decline as the Outcome.

| Characteristics | N = 7760 |
|------------------------------|-------------|
| Age | 72.3 (6.3) |
| Education | 12.4 (3.6) |
| Women | 4860 (63 %) |
| Black | 4983 (64 %) |
| Baseline Cognition | 0.28 (0.73) |
| Lonely | 1180 (15 %) |
| Social Isolation Index Score | 1.54 (1.14) |
| Time to follow-up, years | 7.9 (4.3) |

Note Mean (SD); n (%).

Table 1b

Demographics Characteristics of the Sub-Sample with Incident AD as the Outcome.

| Characteristics | N = 2891 |
|--------------------------|----------------|
| Age | 77 (6) |
| Education | 12.9 (3.4) |
| Women | 1800 (62.26 %) |
| Black | 1586 (55 %) |
| Lonely | 450 (16 %) |
| Isolation | 1.57 (1.08) |
| Baseline AD | 0 (0 %) |
| Incident AD at follow-up | 442 (15 %) |
| Time to follow-up, years | 3.83 (0.94) |

Note Mean (SD); n (%).

3. Results

3.1. Baseline demographics

As shown in Table 1a, the total sample had 7760 older adults. The mean age (standard deviation) was 72.3 (6.3), with 4860 (63 %) women and 4983 (64 %) Black older adults. Years of education had a mean (standard deviation) of 12.4 (3.6). 1180 (15 %) reported being lonely, and the mean (standard deviation) for the Social Isolation Index Score was 1.54 (1.14). Table 1b shows the demographics for the sub-sample of which incident AD assessments were available.

- Primary analyses analyzing continuous SI index score
- Analyses addressing Aim 1: comparing and contrasting a. the presence/absence of association between SI/L and CD/incident AD, and b. their effect sizes
- Total sample:
- Association of continuous SI index score/L with CD

Table 2a shows a significant 2-way interaction between the SI index and time (left panel), with the beta estimate (SE, p-value) = -0.002 (0.001,0.022). Thus, for each unit increase in SI index, the annual rate of CD was faster by 0.002 Standard Deviation Units (SDU). Compared to non-socially isolated (SI index =0), the most socially isolated older adults (SI index=5) had approximately a 19.62 % [i.e., (β =-0.002x5/ β =-0.059)*100] accelerated rate of CD.

In a separate model (right panel), there was similarly a significant 2-way interaction between loneliness and time -0.012 (0.003,<0.001). Thus, compared to older adults who were not lonely, in lonely older adults, the annual rate of CD was faster by 0.012 SDU, i.e., approximately 19.67 % [i.e., (β =-0.012/ β =-0.062) *100] accelerated rate of CD.

3.2. Association of SI index and L with incident AD

Table 2b showed a significant association between SI index and incident AD (left panel), odds ratio (95 % CI, p-value) = 1.183 (1.016-1.379,0.029), and between L and incident AD (right panel),

Table 2a

Total sample: Association of social isolation index and loneliness, independently, with cognitive decline.

| Total Sample Estimate (SD, p-value) | | | |
|--|------------------------|------------------|------------------------|
| N = 7680 | | N = 7696 | |
| Time | -0.059 (0.003, <0.001) | Time | -0.062(0.002, <0.001) |
| social isolation index | -0.065 (0.006, <0.001) | loneliness | -0.092 (0.018, <0.001) |
| social isolation index*time | 0.002 (0.001, 0.022) | loneliness *time | -0.012 (0.003, <0.001) |

NOTE: The linear mixed effects regression models were adjusted for age (centered at 75), education (centered at 12), female sex, African American race, and included the interaction of these characteristics with time since baseline.

Table 2b

Total sample: Association of social isolation index and loneliness, independently, with incident AD.

| Total Sample OR (95 % CI, p-value) | | | |
|---------------------------------------|----------------------------|------------|----------------------------|
| N = 2884 | | N = 2871 | |
| social isolation index | 1.183 (1.016–1.379, 0.029) | loneliness | 2.117 (1.227–3.655, 0.006) |

NOTE: The logistic regression models were adjusted for age (centered at 75), education (centered at 12), female sex, African American race/ethnicity, and time since baseline.

Table 3a

Total sample: Association of social isolation and loneliness with cognitive decline, in the same model, and their interaction

| | Total Sample Estimate (SD, p-value) N = 7638 |
|---|--|
| Time | -0.057 (0.003, <0.001) |
| social isolation index | -0.054 (0.006, <0.001) |
| social isolation index *time | -0.003 (0.001, 0.007) |
| loneliness | -0.048 (0.034, 0.167) |
| loneliness*time | -0.021 (0.006, <0.001) |
| social isolation index* loneliness | -0.009 (0.016, 0.550) |
| social isolation index* loneliness*time | 0.005 (0.003, 0.050) |

NOTE: The linear mixed effects regression models were adjusted for age (centered at 75), education (centered at 12), female sex, African American race/ethnicity, and included the interaction of these characteristics with time since baseline.

2.117 (1.227–3.655, 0.006). The most socially isolated older adults (SI index=5) had a 91.5 % increased odds of incident AD (0.183×5*100 %=91.5 %), whereas lonely older adults had a 111.7 % increased odds of incident AD (1.117×100 %=111.7 %).

• Main Findings:

SI/L were significantly associated with CD to a similar extent, i.e., similar effect sizes, while for incident AD, L conferred a slightly higher risk than SI.

- Analyses addressing Aim 2a: investigating the association between SI and L
- Cross-tabulation of SI Index Score and L status

As shown in Fig. 1, as older adults in this cohort reported higher levels of SI, the percentage of older adults who also reported loneliness increased. The correlation coefficient, i.e., β , was 0.166 with a 95 % confidence interval of (0.144, 0.188) and a p-value < 0.0001.

- Main Findings: The more socially isolated older adults were also lonelier, with a positive linear gradation.
- Analyses addressing Aim 2b: determining if the association of SI with CD/incident AD differs across L status
- Total sample:
- Association of the interaction/synergistic effects of SI/L with CD

Table 3a shows the 3-way interaction, social isolation index*loneliness*time, was borderline significantly associated with longitudinal

Table 3b

Association of social isolation and loneliness with incident AD, in the same model, and their interaction

| | Total Sample OR (95 % CI, p-value) N = 2870 |
|------------------------------------|---|
| social isolation index | 1.175 (0.981–1.407, 0.076) |
| loneliness | 2.687 (0.831–8.690, 0.095) |
| social isolation index* loneliness | 0.871 (0.537–1.412, 0.571) |

NOTE: The logistic regression models were adjusted for age (centered at 75), education (centered at 12), female sex, African American race/ethnicity, and time since baseline.

CD in the total sample, with the beta estimate (SE, p-value) = 0.005 (0.003, 0.050).

- Association of the interaction/synergistic effects of SI/L with incident AD

Table 3b shows that the interaction term “social isolation index*loneliness” was not significantly associated with incident AD, 0.871 (0.537–1.412, 0.571).

- Sample stratified by L status

3.3. Association of SI with CD by L status

As shown in Table 4a, a higher social isolation index was associated with accelerated CD among those who reported being not lonely, -0.003 (0.001, 0.004), but not in those who reported being lonely, 0.003 (0.003, 0.294). Thus, for each unit increase in SI index, the annual rate of CD was faster by 0.003 Standard Deviation Units (SDU) in lonely older adults. Compared to the non-socially isolated (SI index=0), the most socially isolated older adults (SI index=5) who were also not lonely had approximately a 28.42 % [i.e., ($\beta = -0.003 \times 5 / \beta = -0.057$)*100] accelerated rate of CD.

- Sample stratified by L status: Association of SI with incident AD by L status

Table 4b shows no significant association between baseline SI index and incident AD, regardless of L status.

- Main Findings: When stratified by L status, compared to older adults reporting not being lonely, older adults who reported being lonely

Loneliness and Isolation at Baseline

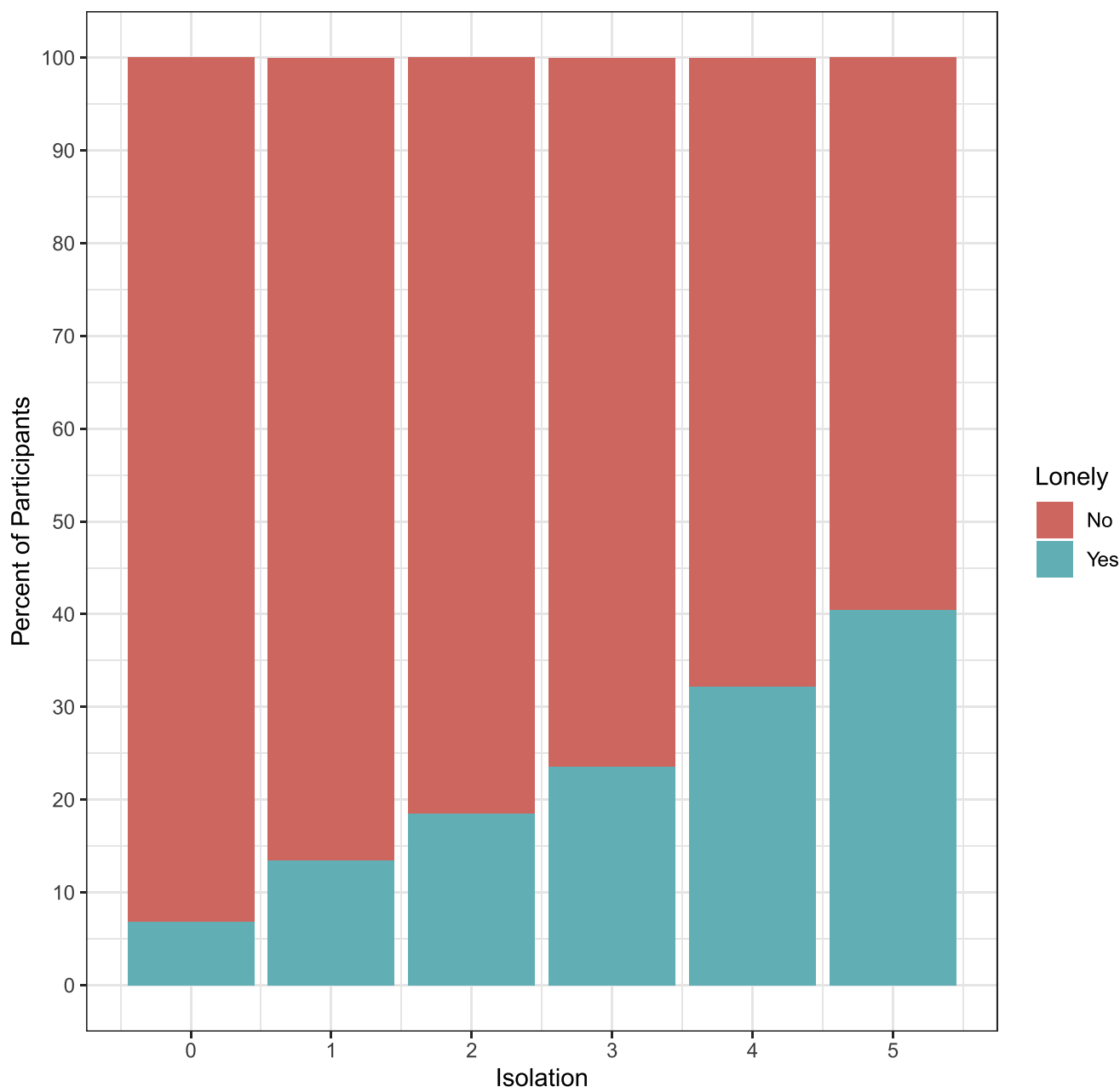


Fig. 1. Older adults with a higher social isolation index score also had a higher percentage of reported being lonely.

Table 4a

Sample stratified by loneliness status: Association of social isolation with cognitive decline by loneliness status.

| | Not lonely subgroup Estimate (SD, p-value) N = 6475 | Lonely subgroup Estimate (SD, p-value) N = 1163 |
|-----------------------------|---|---|
| Time | -0.056 (0.003, <0.001) | -0.077 (0.008, <0.001) |
| social isolation index | -0.055 (0.006, <0.001) | -0.059 (0.016, <0.001) |
| social isolation index*time | -0.003 (0.001, 0.004) | 0.003 (0.003, 0.294) |

NOTE: The linear mixed effects regression models were adjusted for age (centered at 75), education (centered at 12), female sex, African American race, and included the interaction of these characteristics with time since baseline.

Table 4b
Sample stratified by loneliness status: Association of social isolation with incident AD by loneliness status.

| | Not lonely subgroup OR (95 % CI, p-value) N = 2425 | Lonely subgroup OR (95 % CI, p-value) N = 445 |
|------------------------|--|---|
| social isolation index | 1.160 (0.967–1.392,0.105) | 1.088 (0.712–1.663,0.694) |

NOTE: The logistic regression models were adjusted for age (centered at 75), education (centered at 12), female sex, African American race/ethnicity, and time since baseline.

and socially isolated experienced a 28.42 % accelerated rate of CD, although there were no increased odds of incident AD.

- Sensitivity Analyses further controlling for activities of daily living and comorbidities

Sensitivity analyses show similar results, except the effect size and p-value of SI with incident AD were weakened to 1.143 (0.982–1.332, 0.082).

4. Discussion

SI/L were significantly associated with both CD and incident AD. Furthermore, the more socially isolated older adults were also lonelier, with a positive linear gradation in the association. Notably, compared to other subgroups, older adults who were the most socially isolated but reported not being lonely experienced a higher accelerated rate of CD. Specifically, compared to non-isolated older adults, the most socially isolated experienced a 19.62 % accelerated rate of CD. Compared to non-isolated older adults, those who were most socially isolated and did not report loneliness experienced an accelerated rate of cognitive decline (CD) by almost 10 %, reaching 28.42 %.

Our findings on L being significantly associated with CD and incident AD and their associated effect sizes concur with most of the extant literature, including the pilot study published two decades ago by our group [1]. On the other hand, though to a lesser extent, there was also contradictory evidence suggesting the lack of an association between L and CD/AD [32,33]. However, these previous findings might be attributed to differences in the nations examined and their demographics, the measures/indicators of SI/L used [34], and small sample sizes in previous studies [5], rendering lower statistical power to detect significance. A recent meta-analysis found a consensus of significant association between L and CD/AD [5]. Similarly, another recent meta-analysis also concluded that L precedes CD [5]/dementia (26 % higher odds) [3]. However, the HRS study found increased odds of dementia of up to 40 % [4], the Framingham Heart Study of up to 54 % [35] and 31 % in Europe [36]. Similarly, a recent meta-analysis found that lower SI levels were associated with better late-life cognitive function, regardless of the measures and domains of cognitive function, gender, and the number of years of follow-up [37].

It is worth noting that all comparisons of effect sizes would be in the context of the different ranges of the SI index (range: 0–5), whereas for L, it is from 0 to 1. Hence, the effect sizes of a one-point increase in L would be compared to the effect sizes of a 5-point increase (and hence x5 the original effect sizes) in the SI index for all interpretations. We found a 117 % increased risk of incident AD in lonely older adults and an 18 % increased risk of incident AD for each point increase in the SI index. Hence, scaling the SI index to the range of the L scale by multiplying SI effect sizes by five, the most socially isolated older adults had a 90 % increased risk of AD, compared to the 117 % increased risk of incident AD in lonely older adults. As a result, the detrimental independent effects of SI/L on CD were comparable, though slightly higher with L and incident AD. Congruent with our findings, a study analyzing

the health retirement study (HRS) cohort found loneliness to have contributed to a greater risk of developing dementia than being objectively alone [4,38]. The authors suggested that the discrepancy in the desired versus received/perceived social interactions could be more influential in conferring the risk of dementia than being physically isolated from others [4,38]. This finding suggested that though both constructs are essential risk factors preceding CD and incident AD, perceived isolation confers a slightly greater risk of incident AD than being physically isolated.

Interestingly, the findings remain mostly similar upon further controlling for mobility limitations and comorbidities, except that the effect size and p-value of SI with incident AD were weakened to 1.143 (0.982–1.332, 0.082). These findings suggest mobility limitations and comorbidities may underpin the association between SI and incident AD. Compared to the HRS using the UCLA-3-item loneliness scale versus CHAP's 1-item loneliness, the 1-item loneliness we used in CHAP had a similar predictive ability. One of the main limitations of previous studies, including the HRS, is in deriving cognitive status from cognitive screening questions and cut-off scores. Conversely, here in CHAP, the clinical assessments performed by neurologists yielded robust research diagnoses by triaging multiple pieces of clinical information typically not collected in population-based studies and specifically identified cases of AD.

The more socially isolated older adults were more likely to have reported feeling lonely, with a positive and linear gradient in the association. While there were other scholars describing loneliness as a trait [41] or a psychological process [42,43], some scholars had characterized loneliness as perceived social isolation [44,45]. Our association seems to support the latter. In attempting to identify the most socially vulnerable subgroup of older adults, older adults who were more socially isolated but not reported being lonely experienced the highest accelerated rate of CD despite not having higher odds of incident AD. Many studies on SI/L focused on one or the other constructs, with only a few examining both constructs concurrently in a single study [19–21]. To our knowledge, only two studies have examined these potential synergistic effects, though presenting somewhat diverging findings on cognitive domains [21] while no interaction effect on cognitive status [20], which is mostly in line with our findings.

There are a few plausible interpretations as to how and why older adults who were the most socially isolated but not lonely experienced the highest accelerated rate of CD. Based on the evolutionary theory of loneliness, being socially connected is a universal and fundamental human requirement for survival, especially in the Paleolithic period when early humans lived in caves [8,39,40]. Since we found a significant and graded association between SI and L in this cohort, older adults who were more socially isolated also reported more feelings of loneliness, and the most isolated older adults were thus the loneliest. Contrary to our hypothesis that this subgroup of older adults would have been the most vulnerable to CD/incident AD, we did not find supporting evidence for this hypothesis. Again, based on the evolutionary theory of loneliness, it is plausible that in this subgroup of older adults, due to the innate distress survival signals conveyed by both SI and L crossing a

threshold of tolerance, prompting them to take actions to mitigate these stressors, which might include seeking support/resources and/or other protective factors to mitigate the detrimental effects of both SI and L [8,39,40]. Conversely, for the subgroup of older adults who were socially isolated but did not feel lonely, they may not have acknowledged their feelings and innate human needs for social connections, thus psychologically unable to close their mental gaps in the actual connections they had and the innate human desired connections they needed, which is in line with the definition of loneliness, resulting in the emergence of a cognitive vulnerability factor. According to a psychological pathway demonstrated in anxiety disorder that is in line with the stress generation models [46,47], such a cognitive vulnerability factor can reduce perceived control and thus activate the amygdala, subsequently increasing the activation of the hypothalamic-pituitary-adrenal (HPA), which controls stress response [46]. Interestingly, such physiological dysregulations, including increased HPA axis outputs of cortisol and inflammatory markers, have been shown in recent studies, including ours, to be associated with SI and L [48–52]. Alternatively, this cognitive vulnerability factor may also cause older adults to have further social withdrawal and thus exclude self from seeking out valuable resources and protective factors that can mitigate SI. These downstream factors, alone or in combination, may exacerbate the detrimental effects imposed by SI and thus explain the accelerated rate of CD.

Last but not least, despite being significantly associated with CD and incident AD individually, the lack of an interaction effect of SI and L on incident AD suggests that none of the SI and L subgroup combinations had higher odds of being significantly associated with incident AD, though the presence of significant interaction effect on CD. There are a few possibilities, including reduced sample size and reduced follow-up time when analyzing incident AD as an outcome, compared to CD, which had a larger sample size and a longer duration, in which we detected significant interaction effects. Thus, in this study, there might have been reduced power to detect statistical significance when examining incident AD (VS CD), and/or the effect modification requires a longer time to manifest for this specific cognitive outcome, which is reasonable given that incident AD is preceded by CD.

This study had several limitations. Since this is a secondary analysis of previously collected data, we were limited to analyzing the 1-item loneliness from the CES-D scale. However, cross-validating the association of L with CD using the three-item loneliness scale and the single-item measure, a previous study found no difference in findings and conclusions using either the 1-item or 3-item scales [36], which is similar to our findings here compared to HRS findings using the 3-item scale. Future studies should validate our findings, primarily employing the UCLA loneliness scale [53] or the DeJong Gierveld Loneliness Scale, which measures two different loneliness dimensions, i.e., emotional and social loneliness [54,55], both of which have multi-item and multi-response options. Furthermore, the CHAP study sample comprised two racial groups from a selected area of the United States, limiting the generalizability of findings and thus requiring validations in other cohorts with similar and other racial compositions. Stigma [56], especially in minority communities, might have resulted in loneliness being underreported in Black older adults. Conversely, our research assistants of the same race as the participants were trained in effective communication with older adults, thus minimizing this potential issue. We are also mindful of the distinct nature of the constructs yet related relationship between loneliness and depressive symptoms, and thus the potential confounding effects conferred by depressive symptoms. Notably, this cohort has a strong correlation of 0.63 between the two constructs, presenting collinearity concerns. Coupled with the loneliness item being part of the CES-D, we did not include depressive symptoms in our models.

This study had several notable strengths. First, despite Black older adults having a higher risk for and a steeper increase in incident AD/ADRD in the United States in the next 40 years, there is a scarcity of diversity in the aging cohorts examining this specific topic. Hence,

this study mitigated this issue and demonstrated the generalizability of SI/L as a crucial modifiable social risk factor for CD in a biracial cohort comprising Black and White older adults, on which public health strategies may intervene. Extant studies also typically examined either SI or L and CD or incident AD separately; conversely, we examined both SI/L constructs and outcomes, i.e., CD/incident AD concurrently *and* their interactions in a single prospective multi-year follow-up cohort. Furthermore, the large sample size of > 7000 community-dwelling older adults residing in the U.S. is one of the largest studies on this topic internationally. Lastly, this prospective 20-year study cohort and longitudinal design with multiple waves of follow-ups enabled the investigations of the temporal relationships among the variables and examined CD and incident AD, which require a long period to manifest.

This work may inform future research in targeting a specific at-risk subgroup of older adults who appeared to be most socially vulnerable to the combined detrimental effects of SI and L, i.e., socially isolated older adults who are not lonely. For example, programs such as the Meals on Wheels and I-CONNECT programs [57] may assess loneliness levels in socially isolated older adults and place additional emphasis on those who did not report loneliness. These findings thus have the potential to inform early detection and intervention research in tackling the imminent public health issues of SI/L and CD. Future work validating these findings in cohorts with similar and other racial compositions is necessary to advance the field. Specifically, an important focus for future work will be examining SI/L in rural settings. While rural communities are typically perceived as close-knit, SI/L could be more pronounced due to obstacles to social interaction among older residents [58]. Policies and programs addressing SI/L must be geographically tailored, and variations in risk factors must be considered within rural areas [59]. For example, strong church and family engagement may potentially mitigate SI/L [60]. Additionally, as our other recent studies have shown [51,52,61], it is also timely to examine the biological underpinnings of the association between SI/L and CD.

Funding

The authors thank all the participants in the Chicago Health and Aging Project. They also thank the staff of the Rush Institute of Healthy Aging. The National Institutes on Aging of the National Institute of Health under Award Numbers P30AG072972, T32AG050061, R01AG058679, R01AG073627, and UH2AG083289 supported this study. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Health.

Declaration of competing interest

K.D. and K.B.R. are funded by the NIH research grants and report no conflicts of interest. All other authors report no conflicts of interest.

CRediT authorship contribution statement

Ted K.S. Ng: Writing – review & editing, Writing – original draft, Investigation. **Todd Beck:** Writing – review & editing, Formal analysis. **Kyle R. Dennis:** Writing – review & editing, Formal analysis. **Pankaja Desai:** Writing – review & editing. **Kristin Krueger:** Writing – review & editing. **Klodian Dhana:** Writing – review & editing. **Robert S. Wilson:** Writing – review & editing. **Denis A. Evans:** Writing – review & editing, Funding acquisition. **Kumar B. Rajan:** Writing – review & editing, Funding acquisition, Conceptualization.

Acknowledgments

We thank the CHAP study team and participants for their time and participation.

Declaration of Generative AI and AI-assisted technologies in the writing process

AI was not used in the preparation of this manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjpad.2024.100046.

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