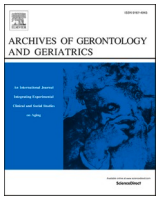
Archives of Gerontology and Geriatrics 125 (2024) 105483



Contents lists available at ScienceDirect

Archives of Gerontology and Geriatrics

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





Exploring the differential impacts of social isolation, loneliness, and their combination on the memory of an aging population: A 6-year longitudinal study of the CLSA

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HIGHLIGHTS

- This review examined the impact of social isolation and loneliness on memory in middle- and older-aged adults.
- The interaction between loneliness and social isolation had the largest adverse effect on memory, followed by social isolation alone, and loneliness alone.
- Interventions should account for individuals who are lonely and socially isolated, instead of just one or the other.

ARTICLE INFO

Keywords:
Social isolation
Loneliness
Memory
Aging
Cognition
CLSA

ABSTRACT

Memory plays a crucial role in cognitive health. Social isolation (SI) and loneliness (LON) are recognized risk factors for global cognition, although their combined effects on memory have been understudied in the literature. This study used three waves of data over six years from the Canadian Longitudinal Study on Aging to examine whether SI and LON are individually and jointly associated with memory in community-dwelling middle-aged and older adults (n = 14,208). LON was assessed with the question: "In the last week, how often did you feel lonely?". SI was measured using an index based on marital/cohabiting status, retirement status, social activity participation, and social network contacts. Memory was evaluated with combined z-scores from two administrations of the Rey Auditory Verbal Learning Test (immediate-recall, delayed-recall). We conducted our analyses using all available data across the three timepoints and retained participants with missing covariate data. Linear mixed models were used to regress combined memory scores onto SI and LON, adjusting for sociodemographic, health, functional ability, and lifestyle variables. Experiencing both SI and LON had the greatest inverse effect on memory (least-squares mean: -0.80 [95 % confidence-interval: -1.22, -0.39]), followed by LON alone (-0.73 [-1.13, -0.34]), then SI alone (-0.69 [-1.09, -0.29]), and lastly by being neither lonely nor isolated (-0.65 [-1.05, -0.25]). Sensitivity analyses confirmed this hierarchy of effects. Policies developed to enhance memory in middle-aged and older adults might achieve greater benefits when targeting the alleviation of both SI and LON rather than one or the other individually.

1. Introduction

Memory is a domain of cognitive function that governs the processes of: (1) encoding, or transforming internal emotions and external information (e.g., sensory input) into neural representations; (2) storing, or organizing these representations in the brain based on storage location, type of information, and duration (i.e., short-term or long-term); and (3) retrieving/recalling past information from storage by replicating the initial encoding operations (Craik & Rose, 2012). Memory declines can hinder a person's ability to engage in daily activities, including basic tasks like dressing and bathing, or more complex tasks like managing finances and participating in social activities (Boss et al., 2015).

Memory changes linked to aging are often viewed as a normal part of growing older, but these changes frequently signify major

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https://doi.org/10.1016/j.archger.2024.105483
Received 20 March 2024; Received in revised form 2 May 2024; Accepted 6 May 2024
Available online 7 May 2024
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neurocognitive disorders such as Alzheimer's disease, vascular dementia, and Lewy body dementia (Boss et al., 2015). Currently, over 55 million individuals globally are living with major neurocognitive disorders and this number is expected to rise to 139 million by 2050 (Brunier & Muchnik, 2021). These disorders have emerged as leading contributors to mortality and morbidity among aging populations (Park & Festini, 2017).

Age-related memory loss can be aggravated by preventable social factors like social isolation (SI) and loneliness (LON) (Fung et al., 2019; Kuiper et al., 2020). According to the discrepancy theory (Lara et al., 2019; Menec et al., 2020; Newall & Menec, 2019; Shankar et al., 2013), SI indicates deficiencies in structural social support. This type of support includes quantifiable and objective measures of social network size, frequency of social activity participation, and diversity in network composition or types of activities. No single gap in structural social support can adequately capture the depth or breadth of SI. For instance, a person with a small social network may not be considered socially isolated if they actively participate in numerous social events, are married or living common-law, and not retired (Menec et al., 2020; Shankar et al., 2011). To reflect the multidimensional nature of SI, researchers advocate measuring the construct by aggregating the impact of many deficiencies in structural social support, rather than by using a single deficiency (e.g., small social network size) to mark SI (Menec et al., 2020; Shankar et al., 2011). In contrast, LON is the negative emotional state emerging from one's subjective perception of incongruence between their actual and desired levels of structural support (Menec et al., 2020; Newall & Menec, 2019). LON is associated with higher depressive symptoms, greater withdrawal from social interactions, reduced environmental mastery, and diminished physical or cognitive capabilities (e.g., problem-solving, decision-making, and memory functions) (Kaldenberg, 2019; Papadopoulos et al., 2014; Pollard et al., 2003; Reinhardt, 2001). Previous research suggests SI and LON exhibit only small to moderate correlations, reinforcing the notion that they are distinct constructs according to the discrepancy theory (Lara et al., 2019; Menec et al., 2020; Newall & Menec, 2019; Shankar et al., 2013).

Various social and biological frameworks have explored the connection between SI, LON, and memory, including the 'use it or lose it' theory and neuroendocrinology of stress. The 'use it or lose it' theory suggests reduced interactions with social networks can contribute to memory loss because engagement in the physical, mental, and social activities essential for stimulating mental faculties declines (Hultsch et al., 1999; Yu et al., 2021). Moreover, evidence indicates that being socially isolated or lonely, coupled with the resulting psychological stress of being in such a state, can extend the activation of the hypothalamus-pituitary-adrenal axis, leading to hypercortisolism (Cacioppo et al., 2014). This hormonal imbalance can result in damage to synapses, neurons, and dendritic branching in the medial prefrontal cortex and hippocampus, all of which are regions closely tied to memory function and Alzheimer's disease (Adam et al., 2006; Boss et al., 2015; Gorelick, 2010).

SI and LON are increasingly acknowledged as important risk factors influencing cognitive function. However, several studies investigating their relationship with cognitive function have predominantly examined composite measures of global cognition or other cognitive domains such as language, abstract reasoning, perceptual-motor skills, and executive function (Jang et al., 2021; Luo et al., 2021; Power et al., 2019; Windsor et al., 2020), rather than focusing on memory. Thus, our study aimed to bridge the knowledge gap by specifically investigating SI and LON's association with memory, recognizing the latter domain's close relation with major neurocognitive disorders (Boss et al., 2015).

To date, most research examining the association between SI/LON with memory has not explored the combined impact of SI and LON, but instead, treated each construct as an independent risk factor for memory (Estrella et al., 2021; Gilmour, 2011; Goldberg et al., 2021; Gow et al., 2013; Hülür, 2022; Hülür et al., 2022; Kang & Oremus, 2023; Kuiper et al., 2020; Lara et al., 2019; Pugh et al., 2021; Yu et al., 2021). However, combinations of SI and LON create unique health risk profiles that cannot be investigated in studies focusing on only one of these two deficiencies. Barnes et al. (2022), Menec et al. (2020), and Newal and Menec (2019) report individuals experiencing both SI and LON are characterized by older age, female gender, widowhood, and elevated risks of cardiovascular disease, depression, lower income, and increased medical costs, compared to those who are either socially isolated or lonely. Additionally, many studies on SI/LON and memory have used cross-sectional or short-term longitudinal designs ($\leq$ 3 years) (Gilmour, 2011; Gow et al., 2013; Lara et al., 2019; Kuiper et al., 2020), and have primarily focused on older adults aged 60 and above, neglecting middle-aged populations who may experience higher prevalence rates of SI and LON (Fung et al., 2019; Gilmour, 2011; Goldberg et al., 2021).

To address the knowledge gaps described above, the present study examined the association between four combinations of SI and LON (i.e., socially isolated and lonely, only socially isolated, only lonely, neither) and memory in middle-aged and older (45 to 85 years), community-dwelling adults in Canada, over six years of follow-up, with and without adjustment by sociodemographic factors, health comorbidities, functional ability, and lifestyle variables. We hypothesized that relative to the 'neither socially isolated nor lonely' group, individuals who were socially isolated and lonely would have the greatest declines in memory, followed in order by persons who were only lonely, and then by those who were only socially isolated. This hierarchy was proposed given that individuals' feelings and perceptions (LON) about a situation often have a more profound impact on their health than objective reality (SI) (Cimarolli & Boerner, 2005; Cimarolli & Boerner, 2005).

2. Methods

2.1. Data source

This research utilized data from the Tracking Cohort of the Canadian Longitudinal Study on Aging (CLSA). The initial sample recruited at baseline was 21,241 adults (Raina et al., 2019). Currently, baseline (BA), three-year follow-up (FUP1), and six-year follow-up (FUP2) data are available to researchers, covering the periods 2011–2015, 2015–2018, and 2018–2021, respectively.

The CLSA initially enrolled participants from the Canadian Community Health Survey 4.1 on Healthy Aging (Statistics Canada, 2008). Additional recruitment efforts involved mailouts to the rolls of provincial healthcare registration databases and random digit dialing of landline telephone numbers (CLSA, 2023). To be eligible, persons had to be aged between 45 and 85 years and fluent in English or French. Individuals were excluded if they lived in First Nations reserves/settlements, the three territories, or long-term care institutions (except independent living retirement homes and transitional living institutions). Full-time members of the Canadian military and non-permanent residents of Canada were also ineligible, as were persons judged to be cognitively impaired by CLSA staff during the recruitment interview. Further details about the CLSA and its recruitment strategy can be found elsewhere (Raina et al., 2009).

The Tracking Cohort was recruited from all ten provinces using a stratified random sampling procedure. The CLSA created 136 sampling strata based on age groups (45–54, 55–64, 65–74, and 75–85 years), sex (male or female), province of residence, education (less than post-secondary versus post-secondary education), and distance from study centres (CLSA, 2023). Participants recruited into the Tracking Cohort provided data through computer-assisted telephone interviews (CATI) that were conducted by trained interviewers (Raina et al., 2019).

The present study obtained ethics approval from the University of Waterloo's Office of Research Ethics (file # 43985); the CLSA's Data and Sample Access Committee approved access to the Tracking Cohort dataset. We reported our study in conjunction with the STROBE guidelines (von ELM et al., 2007) and included the reporting checklist in

Supplementary Material 1.

2.2. Study measures

2.2.1. Social isolation and loneliness

To measure SI, we utilized Menec et al.'s (2020) approach, which amalgamated CLSA questions pertaining to five commonly cited SI indicators into a 5-point scale: marital/cohabiting status, retirement status, living arrangement, frequency of social activity participation in the past year, and contact with social network members in the last six months. Menec et al.'s (2020) 5-point scale builds upon the widely used Berkman-Syme Social Network Index (Berman & Syme, 1979) and the Social Isolation Index (Steptoe et al., 2013), which are robust measures of structural social support (Valtorta et al., 2016). However, Menec et al.'s scale includes two additional sources of social isolation (i.e., living arrangements and retirement status) (Donovan & Blazer, 2020; Newall & Menec, 2020; Valtorta et al., 2016) and it was constructed specifically for assessing SI in the CLSA. Menec et al.'s scale awards one point for each of the following criteria: (1) both living alone and single/widowed/divorced/separated; (2) completely retired and reporting participation in one or less social activities per month; (3) reporting no visit or less than monthly visits with friends and neighbors; (4) reporting no visit or less than monthly visits with children; and (5) reporting no visit or less than monthly visits with family (relatives, siblings).

The breakdown of the 5-point scale showed that 60.9 % of our baseline participants were non-isolated (score 0), 29.7 % were mildly isolated (score 1), 9 % were moderately isolated (scores 2–3), and <1 % were severely isolated (scores 4–5). To ensure statistical power for each sub-level of social isolation, we followed Menec et al.'s (2020) guidance and dichotomized the index into non-isolated (scores 0–1) and socially isolated (scores 2–5). This 2+ cutoff was also employed in the Social Isolation Index (Steptoe et al., 2013) to capture a broader range and severity of social isolation, avoiding exclusive focus on the most severe cases (Newall & Menec, 2020; Valtorta et al., 2016). Additionally, the dichotomization method facilitated a systematic combination of social isolation and loneliness variables into four groups: only socially isolated, only lonely, both, and neither.

Turning to loneliness, the baseline CLSA questionnaire lacked an independent measure of loneliness. Therefore, we used a question from the 10-item Centre for Epidemiological Studies Depression Scale (CES-D-10): "In the last week, how often did you feel lonely?", which was the sole measure of LON in CLSA at baseline. Responses were scored on a 4-point Likert scale, with lower scores indicating higher loneliness levels (1= lonely all of the time [5–7 days]; 2= occasionally lonely [3–4 days]; 3= lonely some of the time [1–2 days]; 4= rarely or never lonely [less than 1 day]). Item scores of 1–2 were classified as being lonely and 3–4 were classified as not lonely, following other studies (Dahlberg et al., 2022; Newall & Menec, 2019) where this CES-D-10 question was employed to examine the combined effects of loneliness and social isolation.

To create the four exposure groups for SI/LON, we combined the separately dichotomized SI and LON measures as follows:

- Only socially isolated: scores 2–5 on the social isolation index and 3–4 on the loneliness measure;
- Only lonely: scores 0–1 on the social isolation index and 1–2 on the loneliness measure;
- Both isolated and lonely: scores 2–5 on the social isolation index and 1–2 on the loneliness measure; and
- Neither isolated nor lonely: scores 0–1 on the social isolation index and 3–4 on the loneliness measure.

2.2.2. Memory

The CLSA assessed the memory domain of cognition using a modified version of the Rey Auditory Verbal Learning Test (RAVLT). The modification (tailored to keep within the time constraints of the Tracking Cohort interview) omitted an interference test and reduced the number of recall administrations from five to two (Tuokko et al., 2017). The modified RAVLT gauged episodic and working memory by generating two memory measures: (1) immediate recall memory (RAVLT I), for which participants were presented with a recorded list of 15 words and asked to recall as many of these words as possible within 90 s; and (2) delayed recall memory (RAVLT II), where participants were given 60 s to recall as many of the same 15 words as possible, after a 5-minute interval, without hearing the list again CLSA (2014).

The CATI software recorded responses to both RAVLT administrations and two trained CLSA staff members independently scored the responses, with a supervisor resolving any disagreements. The staff summed the number of correctly recalled words at each administration into raw test scores ranging from 0 to 15 for RAVLT I and II, respectively. Further details on the administration and scoring of RAVLT I and II are available elsewhere (CLSA, 2019). To standardize raw test scores into z-scores ($\mu = 0$, $\sigma = 1$), we identified a cognitively healthy subset of the Tracking Cohort (i.e., those without self-reported memory problems, dementia/Alzheimer's disease, epilepsy, cerebrovascular accident, stroke, multiple sclerosis, Parkinson's disease, and transient ischemic attack) and divided these participants into French and English subgroups. The sample sizes for the cognitively healthy subset were 12,233 at BA, 12,760 at FUP1, and 10,768 at FUP2. Mean and standard deviation values for RAVLT I and II raw scores were then calculated for each cognitively healthy subgroup, excluding participants who switched languages during testing. These calculated values were then used in Eq. (1) below to compute z-scores separately for all participants in each language subgroup (Yoo et al., 2023):

$$z = \frac{x - \mu}{\sigma} \quad (1)$$

where x= participant's raw score, μ= mean raw score in the healthy subsample, and σ= standard deviation of the mean raw score in the healthy subsample. After calculating the z-scores, the language subgroups were recombined into one sample for subsequent analyses. Lastly, the z-scores for RAVLT I and II were combined additively to derive a single combined memory score for each participant at each timepoint.

2.2.3. Covariates

Based on Kang and Oremus's (2023) recent systematic review, which identified 12 published articles exploring associations between SI/LON and memory (Estrella et al., 2021; Fung et al., 2019; Gilmour, 2011; Goldberg et al., 2021; Gow et al., 2013; Hülür, 2022; Hülür et al., 2022; Kuiper et al., 2020; Lara et al., 2019; Pugh et al., 2021; Shankar et al., 2013; Yu et al., 2021) and other source material (Evans et al., 2019; Jang et al., 2021; Newall & Menec, 2019; Read et al., 2020), the present study included four groups of covariates: (1) sociodemographic attributes (i.e., age, sex, education, province, area of residence, annual household income), (2) functional ability (i.e., 14 ADLs and IADLs), (3) lifestyle variables (i.e., alcohol consumption, smoking status), and (4) chronic health conditions (i.e., clinical depression and 37 other chronic conditions). Supplementary Material 2 contains a complete list of these covariates.

2.3. Data analysis

The analytical samples were drawn from the 14,658 participants who provided data at all three time periods. We conducted three sets of analysis: a primary analysis employing a modified 'all available data' approach, followed by two sensitivity analyses – one using non-modified 'all available data' and another using multiple-imputed data. All analyses were conducted using R v4.3.2 (The R Project for Statistical Computing, Vienna, Austria), with statistical significance set to $\alpha = 0.05$.

2.3.1. Analytical sample for primary analysis

From the 14,658 participants, we obtained 'all available data' on the main exposure and outcome variables, but not for the covariates, meaning those with at least one timepoint of complete data on SI, LON, and immediate-/delayed-recall memory were included in the analysis. An 'all available data' approach (AADA) can maximize the sample size and enhance statistical power by including information from partially observed cases, such as those with data at BA, but not at FUP1 and FUP2.

Since we included an extensive list of covariates (Supplementary Material 2) to adequately adjust for known confounders, 4611 participants had missing data on one or more of these covariates, although the proportion of missing data on most individual covariates was below 5 %. Rather than analyzing participants with complete covariate data only, we undertook a 'modified covariate approach' (MCA) and retained participants with missing covariate data in the analysis by substituting missing values with an additional response category labeled 'missing'. For instance, the 'annual household income' covariate, initially comprising four income categories, was adjusted to a five-level variable, with four levels directly related to income and a fifth category ('missing') assigned to participants with missing values on income.

Then, we combined the MCA and AADA approaches to derive the primary analytical sample, which included all available data for the SI, LON, and memory variables, along with the missing category for covariates. This resulted in 14,208 participants for the primary analysis. The procedure for obtaining the primary analytical sample is detailed in Fig. 1.

2.3.2. Sample for sensitivity analysis

Sensitivity analysis 1: To explore how missing covariate values might affect the results of regression modeling, we excluded participants with missing covariate data from the 'AADA + MCA' subgroup described in Section 3.3.1 above and undertook a sensitivity analysis with this sample. Participants included in the sensitivity analysis were required to have at least one wave of complete data for all main exposure variables (SI and LON), outcome variables (immediate- and delayed-recall memory), and confounding variables. The process for obtaining this 'AADA alone' sample (n = 12,234) is described in Fig. 1.

Sensitivity analysis 2: We undertook another sensitivity analysis to perform multiple imputation on the main exposure/outcome variables and covariates across the three time periods. The specific multiple imputation strategy we employed is detailed in Supplementary Material 3.

2.3.3. Descriptive assessments

We conducted descriptive univariate analyses with the primary analytical sample (i.e., 'AADA + MCA' sample; n = 14,208) to compare the distribution of the four SI/LON groups in relation to memory outcomes and covariates. Additionally, we compared the mean memory scores across levels of each covariate. For the purposes of descriptive analyses only, memory responses were categorized into three levels: 'average memory' (scores within 1.5 standard deviations below or above the mean for combined memory [RAVLT I + II z-scores], excluding those exactly 1.5 standard deviations away), 'high memory' (combined z-scores $\geq$ 1.5 standard deviations above the mean), and 'low memory' (combined z-scores $\geq$ 1.5 standard deviations below the mean). The means and standard deviations for the combination exercise were extracted from the healthy subset of participants, and all univariate analyses were undertaken with the Pearson chi-square test.

2.3.4. Regression analyses

We conducted multivariable, mixed effects regression analyses with R's lme procedure (within the nlme package), utilizing random intercept and time slope for our models, along with an autoregressive (AR1) within-participant correlation structure, the latter which assumes an exponential decline in within-participant correlation as the longitudinal time points get further apart. For our model selection procedure, we considered various candidate models, which explored different specifications for random effects, such as testing for random intercept only, random time slope only, and random intercept and slope together. From these candidate models, we identified the optimal model by assessing both the Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC), opting for the model with the lowest AIC/BIC values. Additionally, we examined various within-subject error structures, including conditional independence (the default correlation matrix of most mixed effects model procedures/functions), compound symmetry, exchangeable, unstructured, and AR1 correlation matrix types. We chose to utilize AR1 given its popularity in time series data or longitudinal studies where one finds a natural ordering of observations based on time, such as in our study with memory data.

Other correlation structures were not ideal for our data. For instance, compound symmetry and exchangeable structures assume uniform variances/correlations across all time points, while conditional independence assumes zero correlations within groups after considering other variables. Also, unstructured permits each observation to have its own correlation, providing excessive flexibility without imposing any constraint on the covariance structure.

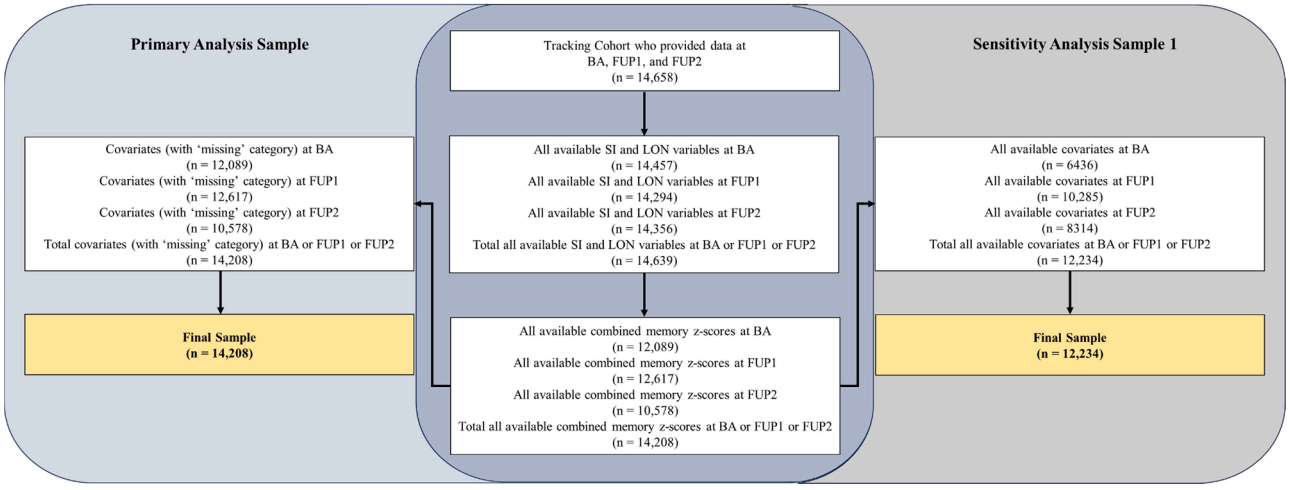


Fig. 1. Analytical sample extraction process
Notes.
Abbreviations: SI= social isolation; LON= loneliness; BA= baseline; FUP1= follow-up 1; FUP2= follow-up 2.

We formed a base model by regressing the combined memory scores onto SI/LON, age group, sex, educational level, province, follow-up time, and SI/LON*time interaction. The base model included covariates needed to account for the CLSA's complex survey design (CLSA, 2023).

To address possible confounding, we followed Yoo et al.'s (2023) approach and added four groups of covariates to the base model, in separate chunks, resulting in five adjusted models:

- Model 0 (base model) = SI/LON groups and age, sex, education, province, follow-up time, and SI/LON*time interaction
- Model 1= Model 0 + adjusting for other sociodemographic factors
- Model 2= Model 0 + adjusting for functional ability
- Model 3= Model 0 + adjusting for lifestyle variables
- Model 4= Model 0 + adjusting for health comorbidities
- Model 5 (full model)= Model 0+ adjusting for all above-mentioned covariates

The least-squares means (LSMEANS) option in lme was used in all models. LSMEANS are typically employed to calculate the means of fixed effects and compare the levels of dependent variables while controlling for the effects of covariates and interactions (Kiernan et al., 2011). In the context of our research, it allowed us to obtain the estimated marginal mean combined memory scores at each level of the SI/LON variable, while accounting for the effects of sex, age, education, province, follow-up time, and SI/LON*time. The LSMEANS option also computed the differences in means between levels, which represented the average estimated change in combined memory score between any two levels of the SI/LON variable (Kiernan et al., 2011; Menec et al., 2020). To control for family-wise errors that might occur during multiple comparisons, we applied the Benjamini-Hochberg (BH) correction (Benjamini & Hochberg, 1995). Detailed application of the BH method is shown in Table 3. The same regression analysis methods were applied to the primary and sensitivity analyses. For multiple imputation, separate regression analyses were performed on each of the 20-imputed datasets and Rubin's rules (Rubin, 1987) were used to combine the results into a single set of regression coefficients.

2.3.5. Clinical significance

To determine the clinical significance of our study results, we converted the LSMEANS estimates from our fully adjusted model (Model 5) to Cohen's *d* using Higgins et al.'s (2022) and Nakagawa and Cuthill's (2007) formulas. Then, the effect sizes were classified as clinically non-significant (<0.1) or significant (≥0.1) based on an average value of effect sizes (Cohen's $d = 0.1$) found in previous related systematic reviews on SI/LON, social support, memory, mild cognitive impairment, and global cognition (Evans et al., 2019; Kang & Oremus, 2023; Piolatto et al., 2022; Smith et al., 2021).

3. Results

3.1. Descriptive analyses

The results of the descriptive analyses for the 'AADA+ MCA' sample are shown in Tables 1 and 2. In this sample, 82.90 % of participants were neither socially isolated nor lonely; 7.88 % were only socially isolated; 7.98 % were only lonely; and 1.23 % were both isolated and lonely at BA. Similar patterns were observed at FUP1 and FUP2 (Table 1). Regarding memory, 87.59 % (BA), 86.38 % (FUP1), and 86.71 % (FUP2) of participants had average memory; 8.43 % (BA), 8.16 % (FUP1), and 7.25 % (FUP2) had high memory; and 3.98 % (BA), 5.47 % (FUP1), and 6.04 % (FUP2) had low memory (Table 2). Over follow-up, most participants either remained within the same SI/LON and memory response categories as at BA or they transitioned into a reference category (i.e., neither isolated nor lonely; average memory) (Fig. 2A – B, Fig. 3A – B).

Overall, SI and LON were significantly and inversely associated ($p <$ 0.001) with memory across BA, FUP1, and FUP2 (Table 1). For instance, the prevalence of low memory was approximately two times higher in the isolated and lonely group ('both') compared to the neither isolated nor lonely group ('neither') at BA ('neither'= 3.58 %; 'both'= 6.51 %) and FUP1 ('neither'= 5.08 %; 'both'= 10.69 %), and three times higher at FUP2 ('neither'= 5.24 %; 'both'= 16.04 %) (Table 1). Moreover, the 'both' group exhibited a higher prevalence of low memory compared to those experiencing SI alone or LON alone at FUP1 ('only SI'= 7.50 %; 'only LON'= 6.84 %; 'both'= 10.69 %) and FUP2 ('only SI'= 8.58 %; 'only LON'= 8.48 %; 'both'= 16.04 %). However, the three SI/LON groups had a similar prevalence of low memory at BA ('only SI'= 6.04 %; 'only LON'= 5.28 %; 'both'= 6.51 %) (Table 1).

The descriptive analyses examining the four SI/LON groups and memory also revealed notable differences in the distribution of covariates. For example, the 'neither' SI/LON group was characterized by being younger, having higher educational attainment, greater annual household income, lower functional impairment, no clinical depression, and fewer chronic health conditions (not related to depression) compared to the groups who were socially isolated, lonely, or both (Table 1). Similarly, memory scores tended to be higher in younger individuals with higher education; greater annual household income; and lower levels of functional impairment, depressive symptoms, and other health comorbidities (Table 2).

3.2. Regression analyses

The regression analyses for the primary analytical sample (Table 3) found a consistent hierarchical pattern of inverse associations between the SI/LON groups and memory across the base model and all five adjusted models. The 'neither' group had the highest memory scores, followed by the 'only SI' group and the 'only LON' group. The 'both' group had the lowest memory scores. For instance, in the base model, the memory LSMEANS estimates were as follows: 'neither'= -0.26; 'only SI'= -0.31; 'only LON'= -0.41; and 'both'= -0.51. These memory LSMEANS estimates showed statistically significant differences in the following pairwise comparisons of SI/LON groups: (1) 'neither' versus 'only LON' (difference= -0.15 [BH-corrected p-value= 0.00]); (2) 'neither' versus 'both' (difference= -0.25 [BH-corrected p-value= 0.00]); (3) 'only SI' versus 'only LON' (difference= 0.10 [BH-corrected p-value= 0.02]); and (4) 'only SI' versus 'both' (difference= 0.20 [BH-corrected p-value= 0.01]) (Table 3).

Figs. 4A and 4B illustrate how memory changed over time in each of the four SI/LON groups. Memory scores worsened in the 'both' group over 6 years of follow-up but improved in the other three groups. These patterns remained consistent across all unadjusted and adjusted models (Table 3).

Turning to the covariate chunks, the negative effects of all SI/LON groups on memory were amplified after adjusting for functional impairment (memory LSMEANS for 'neither' [$LSMEANS_{neither}$]= -0.51; $LSMEANS_{only\ SI}$= -0.56; $LSMEANS_{only\ LON}$= -0.65; $LSMEANS_{both}$= -0.74) (Model 2) and in the full model ($LSMEANS_{neither}$= -0.65; $LSMEANS_{only\ SI}$= −0.69; $LSMEANS_{only\ LON}$= -0.73; $LSMEANS_{both}$= -0.80) (Model 5, Table 3). In contrast, adjusting for lifestyle variables (Model 3) resulted in nearly the same memory LSMEANS as the base model. The statistically significant memory differences between the 'only SI' and 'only LON' groups as well as between the 'only SI' and 'both' groups in the base model became non-significant when adjusting for sociodemographic (Model 1) or health factors (Model 4), and in the full model (Model 5). Across all six models, we did not find statistically significant differences in memory between the 'neither' versus 'only SI' groups and between the 'only LON' versus 'both' groups (Table 3).

When comparing the results of the primary analysis to the sensitivity analyses described above, the memory differences between the 'only SI' and 'only LON' groups weakened and became non-significant in the 'AADA alone' sensitivity analysis. In the multiple-imputed sensitivity analysis, only the memory difference between the 'neither' and 'only

Table 1
Distribution of combined memory and covariates by social isolation/loneliness groups.

	Baseline ($n = 12,090$)					Follow-up 1 ($n = 12,617$)					Follow-up 2 ($n = 10,578$)				
	Neither (82.9 %)	Only SI (7.9 %)	Only LON (8.0 %)	Both (1.2 %)	Total	Neither (83.0 %)	Only SI (6.7 %)	Only LON (9.0 %)	Both (1.3 %)	Total	Neither (79.6 %)	Only SI (9.8 %)	Only LON (8.8 %)	Both (1.8 %)	Total
Combined memory score (%)	87.71***	86.46	87.98	84.56	87.59	86.63***	85.60	85.45	80.50	86.38	87.19***	84.86	85.41	81.82	86.71
Average	8.71	7.03	6.74	9.40	8.43	8.29	6.90	7.71	8.81	8.16	7.58	6.56	6.12	2.14	7.25
High	3.58	6.04	5.28	6.51	3.98	5.08	7.50	6.84	10.69	5.47	5.24	8.58	8.48	16.04	6.04
Low															
Age groups (%)															
45–54	31.63***	21.09	27.67	24.83	30.40	14.62***	11.19	11.57	11.32	14.08	5.12***	3.38	3.54	4.28	4.79
55–64	33.52	31.58	34.30	30.20	33.39	35.95	29.40	34.09	36.48	35.35	33.53	33.17	31.65	30.48	33.28
65–74	21.20	27.49	20.73	21.48	21.66	30.12	36.67	28.13	29.56	30.37	36.21	33.17	29.08	33.69	35.24
75–85	13.49	19.62	17.10	23.49	14.38	17.20	19.40	22.26	19.50	17.83	20.21	23.14	24.46	20.86	20.88
Missing	0.16	0.21	0.21	0.00	0.17	2.11	3.33	3.94	3.14	2.37	4.93	7.14	11.27	10.70	5.80
Sex (%)															
Male	47.81**	54.98	41.45	46.98	47.86	47.48***	55.95	38.48	50.31	47.26	45.68**	51.98	38.84	43.32	45.65
Female	52.19	45.02	58.55	53.02	52.14	52.46	43.93	61.35	49.69	52.66	54.32	48.02	61.16	56.68	54.35
Missing	0.00	0.00	0.00	0.00	0.00	0.07	0.12	0.18	0.00	0.08	0.00	0.00	0.00	0.00	0.00
Education (%)															
Less than post-secondary	28.02***	34.42	33.99	38.93	29.13	26.08***	29.64	32.25	32.70	26.96	24.27**	27.10	29.29	23.53	24.98
Post-secondary	70.92	64.74	65.39	61.07	69.87	72.97	69.76	66.52	66.67	72.09	74.70	72.13	69.21	75.40	73.97
Missing	1.07	0.84	0.62	0.00	1.00	0.95	0.60	1.23	0.63	0.95	1.03	0.77	1.50	1.07	1.05
Annual household income (%)															
< $20k	3.26***	5.56	9.64	16.11	4.11	3.03***	4.40	9.64	13.21	3.84	2.98***	3.76	7.73	12.30	3.64
$20k to < $50k	22.37	31.27	32.12	32.21	23.97	21.82	30.60	32.34	35.85	23.53	22.52	28.64	37.02	40.64	24.72
$50k to < $100k	36.73	34.10	33.68	26.17	36.15	36.81	33.81	29.89	23.90	35.82	35.61	33.56	27.68	24.06	34.51
≥ $100k	32.55	22.88	18.13	15.44	30.42	32.80	26.19	19.72	17.61	30.98	30.92	26.81	16.52	12.83	28.93
Missing	5.10	6.19	6.42	10.07	5.35	5.55	5.00	8.41	9.43	5.82	7.97	7.23	11.05	10.16	8.21
Province (%)															
Ontario	25.12**	17.31	21.24	14.77	24.07	23.46***	18.10	20.60	14.47	22.73	23.75**	16.68	19.85	20.86	22.66
Alberta	9.41	7.45	10.26	6.71	9.29	10.35	8.57	9.82	10.69	10.18	10.44	9.45	11.27	9.09	10.39
British Columbia	10.86	13.42	10.16	14.09	11.04	12.71	22.50	14.37	14.47	13.54	12.86	16.39	13.63	12.30	13.26
Manitoba	6.89	5.77	5.70	5.37	6.69	6.61	3.33	6.22	5.03	6.34	5.90	3.57	6.44	3.74	5.68
New Brunswick	6.21	7.87	6.74	4.70	6.36	5.96	7.98	5.70	8.81	6.10	5.92	6.56	6.44	5.88	6.03
Newfoundland	5.46	6.19	5.39	6.04	5.52	5.14	5.48	4.38	4.40	5.08	4.74	4.82	5.26	4.81	4.79
Nova Scotia	7.63	9.44	6.22	8.72	7.68	7.41	8.21	6.66	11.95	7.45	7.65	8.68	5.90	8.02	7.60
Prince Edward Island	5.44	5.88	4.35	6.04	5.39	4.81	6.55	4.29	8.18	4.92	5.34	4.82	4.40	2.67	5.16
Quebec	16.97	19.94	24.46	28.19	17.94	17.70	14.76	22.17	14.47	17.86	17.85	25.65	21.14	29.41	19.11
Saskatchewan	6.02	6.72	5.49	5.37	6.02	5.84	4.52	5.78	7.55	5.77	5.56	3.38	5.69	3.21	5.31
Missing	0.00	0.00	0.00	0.00	0.00	0.02	0.00	0.00	0.00	0.02	0.00	0.00	0.00	0.00	0.00
Area of residence (%)															
Rural	23.02	25.81	21.55	23.49	23.13	17.95	19.40	16.13	17.61	17.88	17.47*	20.93	14.48	16.58	17.53
Urban	66.26	63.59	67.36	65.77	66.13	73.50	71.19	75.02	71.07	73.46	74.77	70.97	76.82	76.47	74.61
Missing	10.73	10.60	11.09	10.74	10.74	8.54	9.40	8.85	11.32	8.66	7.77	8.10	8.69	6.95	7.87
Functional Ability (%)															
No ADL/IADL impairment	7.73***	8.08	11.09	9.40	8.05	9.30***	10.00	14.81	16.35	9.93	12.09***	12.44	16.42	10.70	12.48
Mild impairment	91.16	89.51	86.53	83.22	90.56	86.98	84.29	79.40	77.36	86.00	84.45	82.35	73.61	73.80	83.10
Moderate impairment	0.70	1.57	1.66	6.04	0.91	1.49	3.10	2.63	3.14	1.72	1.95	2.41	6.22	10.16	2.51
Severe/total impairment	0.24	0.52	0.31	1.34	0.28	0.54	0.83	1.14	1.26	0.63	0.96	1.64	3.11	3.74	1.27
Missing	0.17	0.31	0.41	0.00	0.20	1.69	1.79	2.02	1.89	1.73	0.56	1.16	0.64	1.60	0.64
Alcohol consumption (in past 12 months) (%)															
Never	12.25***	15.63	16.79	16.78	12.94	12.25***	15.36	15.16	20.13	12.82	15.23***	17.74	20.92	29.41	16.23
≤ 1 time per month	14.29	17.73	18.55	22.82	15.00	13.09	15.48	17.88	20.75	13.78	12.74	14.46	17.70	16.58	13.41
1 to 3 times per month	18.34	16.16	18.34	18.79	18.17	18.14	16.07	20.16	20.75	18.22	17.35	17.16	17.60	18.72	17.38
≥ 1 time(s) a week	55.06	50.37	46.32	41.61	53.83	56.31	52.98	46.63	37.74	54.98	54.31	50.24	43.24	35.29	52.60
Missing	0.06	0.10	0.00	0.00	0.06	0.21	0.12	0.18	0.63	0.21	0.37	0.39	0.54	0.00	0.38
Smoking status (for past 30 days) (%)															

(*continued on next page*)

Table 1 (*continued*)

	Baseline (n = 12,090)					Follow-up 1 (n = 12,617)					Follow-up 2 (n = 10,578)				
	Neither (82.9 %)	Only SI (7.9 %)	Only LON (8.0 %)	Both (1.2 %)	Total	Neither (83.0 %)	Only SI (6.7 %)	Only LON (9.0 %)	Both (1.3 %)	Total	Neither (79.6 %)	Only SI (9.8 %)	Only LON (8.8 %)	Both (1.8 %)	Total
Never	60.45***	62.43	57.51	53.02	60.28	93.55***	92.02	90.97	84.28	93.10	94.63***	93.54	91.09	88.24	94.10
≥ 1 cigarette in the past 30 days	1.57	1.47	1.76	3.36	1.60	1.73	1.07	2.45	0.63	1.74	1.23	1.16	2.25	1.60	1.32
≥ 1 cigarette every day	5.96	8.81	10.47	16.78	6.67	4.71	6.90	6.57	15.09	5.15	4.10	5.30	6.65	10.16	4.55
Missing	32.03	27.28	30.26	26.85	31.45	0.02	0.00	0.00	0.00	0.02	0.04	0.00	0.00	0.00	0.03
Clinical depression (%)															
No	92.24***	88.25	65.91	57.72	89.40	92.73***	90.83	65.38	61.01	89.73	95.06***	92.57	71.14	64.71	92.17
Yes	5.80	7.97	32.54	40.94	8.54	7.12	9.05	34.18	46.66	10.1	4.93	7.43	28.75	35.29	7.81
Missing	1.97	3.78	1.55	1.34	2.07	0.15	0.12	0.44	0.00	0.17	0.01	0.00	0.11	0.00	0.02
Chronic health conditions (%)															
None	10.81***	7.87	7.67	6.04	10.26	7.08***	4.88	4.47	3.14	6.65	4.77***	3.57	1.39	3.21	4.33
≥ 1 chronic conditions	85.43	87.30	87.05	87.25	85.73	92.78	94.76	95.18	96.86	93.18	95.21	96.34	98.28	96.79	95.62
Missing	3.76	4.83	5.28	6.71	4.00	0.13	0.36	0.35	0.00	0.17	0.01	0.10	0.32	0.00	0.05

Note. For descriptive analyses, memory responses are categorized into three levels: 'average', 'high', and 'low' memory. The cut-offs for high and low memory were established as having scores that are ≥1.5 standard deviations above versus below the mean for combined memory (RAVLT I + II), respectfully.
Abbreviations: SI= social isolation; LON= loneliness; ADL= activities of daily living; IADL= instrumental activities of daily living.
*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$. The p-values are obtained from a series of Chi-square tests, which assessed whether there are significant associations between SI/LON and combined memory, and between SI/LON and covariates, controlling for follow-up time, by comparing the observed frequencies with the expected frequencies under the assumption of independence.

LON' groups remained statistically significant. Multiple imputation approach imputes variables with uncertainty, resulting in somewhat variable imputed values (i.e., opposite of mean imputation). This can lead to wider confidence intervals compared to analyses using all available data, despite the sample size increasing (though not by much in this paper). Despite these changes in statistical significance across the primary and sensitivity analyses, all three analyses consistently demonstrated that the SI/LON groups followed the same pattern of best to worst memory scores across all six regression models: 'neither' → 'only SI' → 'only LON' → 'both'. This underscores the robustness of the hierarchy across different covariate sets and diverse analytical approaches.

Finally, after applying the Cohen's $d = 0.1$ threshold in the primary analysis Model 5 to evaluate the clinical relevance of our study findings, we found clinically significant negative associations between memory and the 'both SI and LON' group (Cohen's d= -0.31 [95 % CI: -1.22, -0.39]) and the 'only LON' group (Cohen's d= -0.12 [95 % CI: -1.13, -0.33]), but not with the 'only SI' group (Cohen's d= -0.03 [95 % CI: -1.09, -0.29]).

4. Discussion

We investigated the association between SI and LON, both independently and in combination, and memory over six years of follow-up in middle-aged and older adults. Our study's descriptive results mirror the findings from other studies, such as Menec et al. (2020), Hülür (2022), and Smith and Victor (2019). For instance, aligning with Menec et al.'s (2020) findings, our study showed that the 'only LON' category had a higher proportion of women compared to the other SI/LON groups. In terms of age, educational levels, and health comorbidities (excluding depression), the 'neither' group was the youngest, most highly educated, and had the lowest number of chronic conditions; however, these variables did not exhibit patterns or hierarchies across the other three SI/LON groups, which was also observed in Menec et al.'s (2020) research. Regarding functional impairment, the 'neither' group and 'both' group, respectively, displayed the least and the most severe functional impairment, but no significant differences existed between the 'only SI' and 'only LON' groups.

In addition, similar to the findings in Hülür (2022) and Smith and Victor's (2019) research, our study showed that the 'neither' group had the most favorable outcomes for annual household income and clinical depression, followed by the 'only SI' group, then the 'only LON' group, and lastly the 'both' group. The above-mentioned patterns for age, sex, income, functional ability, clinical depression, and other health comorbidities were consistent across BA, FUP1, and FUP2 (Table 1). Overall, the present study's descriptive analyses indicated that participants exhibited distinct socio-demographic and health characteristics based on the specific combinations of SI and LON they experienced.

Turning to memory, our regression analyses suggested that being socially isolated, lonely, or both were linked to lower memory scores relative to being neither isolated nor lonely. However, as illustrated in Fig. 4A and B, the strength of the inverse impact on memory appears to diminish over time in the 'neither', 'only SI', and 'only LON' groups (Fig. 4A and B). In fact, mean memory scores in the 'neither' and 'only SI' groups were higher at FUP2 compared to BA and FUP1 (refer to Fig. 5).

The observed pattern of increasing memory scores occurred alongside changes in participant age distribution, with a higher proportion of participants aged 65–74 and 75–85 years in FUP2 compared to both FUP1 and BA assessments (35.24 % and 20.88 % in FUP2; 30.37 % and 17.83 % in FUP1; 21.66 % and 14.38 % in BA) (Table 1). Considering the well-documented association between advancing age and memory decline, it is important to address the potential factors contributing to the widening increases in memory scores over time. One possible explanation for these increases in memory scores, despite the aging of the participant cohort, could be related to an attrition bias in the memory outcome, where a higher dropout rate was observed in the lowest memory group compared to those with better memory at baseline. This discrepancy in dropout rates was seen at both FUP1 (attrition rate for high memory [ARHM]= 6.5 %; attrition rate for average memory [ARAM]= 8.1 %; attrition rate for low memory [ARLM]= 14.8 %) and FUP2 (ARHM= 20.3 %; ARAM= 23.3 %; ARLM= 34.7 %). Therefore, the observed "improvements" in memory over six years were likely due to the fact that fewer individuals with low memory scores at

Table 2
Distribution of covariates by combined memory.

	Baseline ($n = 12,090$)				Follow-up 1 ($n = 12,617$)				Follow-up 2 ($n = 10,578$)			
	Combined memory scores											
	Average (87.6 %)	High (8.4 %)	Low (4.0 %)	Total	Average (86.4 %)	High (8.2 %)	Low (5.5 %)	Total	Average (86.7 %)	High (7.3 %)	Low (6.0 %)	Total
Age groups (%)												
45–54	30.93***	32.88	13.31	30.40	14.49***	17.01	3.19	14.08	4.80***	8.34	0.47	4.79
55–64	33.86	34.35	21.00	33.39	36.05	42.37	13.77	35.35	34.02	43.29	10.64	33.28
65–74	21.24	23.36	27.44	21.66	30.78	28.77	26.38	30.37	36.18	33.51	23.94	35.24
75–85	13.83	9.32	37.21	14.38	16.66	11.18	46.23	17.83	20.12	13.95	40.22	20.88
Missing	0.13	0.10	1.04	0.17	2.02	0.68	10.43	2.37	4.90	0.91	24.73	5.80
Sex (%)												
Male	48.51**	28.46	74.62	47.86	48.05***	22.93	71.01	47.26	46.13**	21.90	67.29	45.65
Female	51.49	71.54	25.36	52.14	51.88	76.77	28.99	52.66	53.87	78.10	32.71	54.35
Missing	0.00	0.00	0.00	0.00	0.06	0.29	0.00	0.08	0.00	0.00	0.00	0.00
Education (%)												
Less than post-secondary	29.05***	21.30	47.61	29.13	26.74***	17.59	44.35	26.96	24.91***	15.38	37.40	24.98
Post-secondary	69.89	78.12	51.98	69.87	72.32	81.73	54.20	72.09	74.05	83.31	61.66	73.97
Missing	1.07	0.59	0.42	1.00	0.95	0.68	1.45	0.95	1.04	1.30	0.94	1.05
Annual household income (%)												
< $20k	3.99***	3.24	8.52	4.11	3.76***	2.92	6.52	3.84	3.38***	2.87	8.29	3.64
$20k to < $50k	23.79	20.61	35.14	23.97	23.17	17.78	37.83	23.53	24.52	17.73	35.99	24.72
$50k to < $100k	36.35	34.35	35.55	36.15	36.09	34.99	32.90	35.82	34.81	35.98	28.33	34.51
≥ $100k	30.66	35.03	15.38	30.42	31.32	38.58	14.35	30.98	29.36	36.51	13.62	28.93
Missing	5.21	6.77	5.41	5.35	5.66	5.73	8.41	5.82	7.93	6.91	13.77	8.21
Province (%)												
Ontario	24.25	21.10	26.40	24.07	22.48*	24.39	24.20	22.73	22.93	21.90	19.72	22.66
Alberta	9.34	9.42	7.90	9.29	10.14	11.86	8.41	10.18	10.50	10.30	8.92	10.39
British Columbia	10.84	13.94	9.36	11.04	13.86	13.22	8.99	13.54	13.27	13.04	13.46	13.26
Manitoba	6.68	6.87	6.65	6.69	6.38	5.25	7.39	6.34	5.69	6.13	5.01	5.68
New Brunswick	6.38	5.40	7.90	6.36	6.15	5.34	6.52	6.10	6.04	5.22	6.89	6.03
Newfoundland	5.30	5.89	9.56	5.52	4.94	5.83	6.23	5.08	4.83	4.56	4.54	4.79
Nova Scotia	7.68	7.26	8.52	7.68	7.50	6.41	8.26	7.45	7.60	7.82	7.36	7.60
Prince Edward Island	5.36	5.50	5.82	5.39	5.00	3.79	5.36	4.92	5.17	4.43	5.95	5.16
Quebec	18.22	18.25	11.23	17.94	17.87	18.08	17.54	17.86	18.80	21.12	21.13	19.11
Saskatchewan	5.96	6.38	6.65	6.02	5.68	5.83	7.10	5.77	5.18	5.48	7.04	5.31
Missing	0.00	0.00	0.00	0.00	0.02	0.00	0.00	0.02	0.00	0.00	0.00	0.00
Area of residence (%)												
Rural	23.23	22.28	22.66	23.13	17.99	16.03	18.84	17.88	17.73	17.08	15.18	17.53
Urban	66.12	66.83	64.86	66.13	73.34	75.90	71.59	73.46	74.45	74.45	77.00	74.61
Missing	10.65	10.89	12.47	10.74	8.66	8.07	9.57	8.66	7.82	8.47	7.82	7.87
Functional Ability (%)												
No ADL/IADL impairment	8.17**	6.97	7.90	8.05	9.87***	9.43	11.59	9.93	12.52***	11.34	13.30	12.48
Mild impairment	90.48	91.95	89.40	90.56	86.14	87.46	81.59	86.00	83.37	86.70	74.80	83.10
Moderate impairment	0.91	0.69	1.46	0.91	1.67	1.17	3.33	1.72	2.31	1.17	7.04	2.51
Severe/total impairment	0.25	0.19	0.83	0.28	0.56	0.29	2.17	0.63	1.22	0.39	2.97	1.27
Missing	0.19	0.20	0.42	0.20	1.76	1.65	1.30	1.73	0.58	0.39	1.88	0.64
Alcohol consumption (in past 12 months) (%)												
Never	12.46***	13.05	23.08	12.94	12.61**	10.30	19.86	12.82	15.81***	15.25	23.47	16.23
≤ 1 time per month	14.83	15.60	17.67	15.00	13.61	14.29	15.65	13.78	13.17	14.34	15.81	13.41
1 to 3 times per month	18.13	21.20	12.68	18.17	18.00	21.48	16.81	18.22	17.31	18.12	17.37	17.38
≥ 1 time(s) a week	54.51	50.15	46.57	53.83	55.59	53.64	47.39	54.98	53.36	52.15	42.25	52.60
Missing	0.07	0.00	0.00	0.06	0.19	0.29	0.29	0.21	0.35	0.13	1.10	0.38
Smoking status (for past 30 days) (%)												
Never	60.84***	53.29	62.79	60.28	93.10*	92.61	93.77	93.10	94.08*	93.61	94.99	94.10
≥ 1 cigarette in the past 30 days	1.57	2.06	1.25	1.60	1.75	1.85	1.30	1.74	1.45	0.65	0.31	1.32
≥ 1 cigarette every day	6.52	7.46	8.52	6.67	5.13	5.54	4.93	5.15	4.44	5.74	4.69	4.55
Missing	31.08	37.19	27.44	31.45	0.02	0.00	0.00	0.02	0.03	0.00	0.00	0.03
Clinical depression (%)												
No	89.52***	91.17	82.95	89.40	89.91***	91.25	86.23	89.73	92.38***	93.22	87.95	92.17
Yes	8.47	7.36	12.48	8.54	10.04	8.75	13.04	10.10	7.61	6.78	11.90	7.81
Missing	2.01	1.47	4.57	2.07	0.16	0.00	0.72	0.17	0.01	0.00	0.16	0.02
Chronic health conditions (%)												
None	10.27**	11.68	7.07	10.26	6.63***	9.14	3.33	6.65	4.31*	5.87	2.82	4.33
≥ 1 chronic conditions	85.70	85.38	87.11	85.73	93.24	90.86	95.80	93.18	95.64	94.13	97.18	95.62
Missing	4.02	2.94	5.82	4.00	0.14	0.00	0.87	0.17	0.05	0.00	0.00	0.05

Note. For descriptive analyses, memory responses will be categorized into three levels: 'average', 'high', and 'low' memory. The cut-offs for high and low memory were established as having scores that are ≥1.5 standard deviations above versus below the mean for combined memory (RAVLT I + II), respectfully.
Abbreviations: ADL= activities of daily living; IADL= instrumental activities of daily living.
*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$. The p-values are obtained from a series of Chi-square tests, which assessed whether there are significant associations between

combined memory and covariates, controlling for follow-up time, by comparing the observed frequencies with the expected frequencies under the assumption of independence.

baseline remained in the Tracking Cohort by FUP2.

Another factor to consider is that the proportion of participants who smoke declined over time, with 94.10 % reporting never having smoked at FUP2, while only 4.55 % reported smoking one or more cigarettes daily. This compares to FUP1, where 93.10 % reported never smoking, and 5.15 % reported daily smoking, and at BA, where 60.28 % reported never smoking, and 6.67 % reported daily smoking (Table 1). Smoking has been closely associated with brain volume reduction and diminished memory performance, particularly in women compared to men (Gallinat et al., 2006; Lewis et al., 2021). Within the CLSA, the number of female participants exceeded male participants, with the proportion of females increasing slightly over time (BA= 52.14 %; FUP1= 52.66 %; FUP2= 54.35 %) (Table 1). These shifts in participants' demographic characteristics, coupled with attrition bias, may explain the broadening increases in memory scores over time.

On the other hand, the negative impact of being both isolated and lonely intensified over six years. Despite the attrition bias, we still observed a worsening of memory over time in those who started out in the 'both' group at BA. Had the attrition bias been smaller, the observed impact on memory of being isolated and lonely could well have been much greater. Thus, attrition biased our findings in the 'both' group toward the null. Notwithstanding the bias, our results show that experiencing both SI and LON has a more pronounced negative impact on memory than experiencing either factor alone, even in cognitively healthier samples.

Among the 12 articles included in Kang and Oremus's (2023) systematic review, only Fung et al. (2019) – a cross-sectional study of 497 adults aged $\geq$ 60 years – examined the combined impact of SI and LON, while the others treated each construct as an independent risk factor for memory. In contrast to our results, Fung et al. (2019) reported that SI (measured by the total size of one's social network) had no significant interaction effect with LON on memory (β= 0.083 [p = 0.062]), and the combined effect of SI and LON on memory was weaker than the individual effects of SI or LON. However, having large numbers of non-close family members in one's social network was associated with higher LON, compared to SI, and lower memory scores (β= 0.119 [p = 0.006]). This finding could be explained by the fact that Fung et al. (2019) focused on a single indicator of SI (i.e., social network size only) that did not include other crucial aspects of social isolation. Two other articles from Kang and Oremus's (2023) review also employed single-item measures of SI (Estrella et al., 2021; Kuiper et al., 2020), and none explored more than three indicators of SI. These measures overlook the multiplicity of different elements of SI; their incompleteness can lead to biased assessments of the true strength and direction of the association between SI and memory. Previous research in other areas of cognition (language, perceptual-motor skills, and executive function) (Jang et al., 2021; Luo et al., 2021; Power et al., 2019; Windsor et al., 2020) supports our finding of utmost vulnerability in the socially isolated and lonely group.

The second most vulnerable group in our study was the 'only LON' group, followed by the 'only SI' group. Here, the literature presents conflicting evidence on whether SI or LON has a greater impact on memory. For instance, Shankar et al. (2011) proposed that SI could be more harmful because socially isolated individuals have less opportunities for social learning and social bonding, which are crucial for strengthening neural connections that promote memory, compared to those who are lonely yet well connected. Conversely, other memory studies, including those by Estrella et al. (2021) and Fung et al. (2019), found that LON had a greater impact on memory than SI. Estrella et al. (2021) and Fung et al. (2019) reported positive regression coefficients for SI (β_{SI}= 0.126 [p = 0.005] and β_{LON}= −0.165 [p = 0.002], respectively) and inverse regression coefficients for LON (β_{SI}= 0.35 [95 % CI: 0.09, 0.60] and β_{LON}= -0.48 [95 % CI: -0.65, -0.32]). In addition, some studies showed that LON may be a stronger predictor of clinical outcomes involving a memory component. For example, Akhter-Khan et al. (2021), Holwerda et al. (2014), and Rafnsson et al. (2020) found that LON, rather than SI, predicted an elevated risk of Alzheimer's disease and all-cause dementia. These researchers believed that individuals with active social lives who still felt lonely might have faced greater psychological stress compared to those who found solace in solitude. Heightened psychological stress is strongly linked to hypercortisolism, reduced cognitive activity (e.g., hippocampal and prefrontal dendritic arborisation), and decreased neurotrophic factors, all of which contribute to impaired memory.

4.1. Strengths and limitations

The present study examined both the separate and combined impacts of SI and LON on memory, diverging from earlier memory studies (except Fung et al. (2019)) that kept these constructs apart and focused solely on their individual effects. Additionally, we utilized a 4-level exposure group for SI/LON to facilitate a more systematic method of identifying crucial differences in memory across combinations of SI and LON. Unlike most studies of SI, our research employed a multi-modal measure of SI, which provided a more accurate depiction of the association between social isolation and memory. Moreover, we utilized longitudinal data to explore changes in memory scores over a six-year follow-up period, which provided more time to observe changes in memory outcomes compared to cross-sectional or shorter longitudinal designs. Additionally, the six-year follow-up period gave us a deeper understanding of how memory scores change as individuals transition into more vulnerable SI and LON groups. Among the 12 published studies from Kang and Oremus's (2023) review, eight were either cross-sectional (Estrella et al., 2021; Fung et al., 2019; Gilmour, 2011; Gow et al., 2013) or had shorter follow-up times than our findings (Kuiper et al., 2020; Lara et al., 2019; Shankar et al., 2013; Yu et al., 2020).

Another notable strength of this study lies in the inclusion of both middle-aged and older adults, a departure from the predominantly exclusive focus on older adults in previous research. The inclusion of the middle-aged population allowed us to explore the association in a broader sample, which is important given that SI and LON tend to increase over time. Furthermore, our study accounted for a more comprehensive set of covariates compared to other similar research, thereby minimizing the potential for residual confounding. Other studies, on average, investigated seven covariates, with age, sex, education, and depressive symptoms being the most frequently adjusted variables (present in 8 out of 12 published memory studies).

The present study had some limitations. The participants might not represent an unbiased sample of the target population. CLSA participants at baseline were healthier, had higher incomes, and possessed greater education than the average Canadian in the 45- to 85-year age group (Rutter, 2019). In addition, the subgroup of CLSA participants who were older, depressed, had greater functional limitations, elevated SI/LON, and lower memory performance were more likely to drop out. Both factors led to an analytical sample that was cognitively healthy and experiencing low levels of SI/LON, which might have underestimated the true associations under investigation. Therefore, our findings are only applicable to persons who share similar characteristics with our analytical sample.

Another limitation of this study is the use of a single-item measure for assessing LON, which can be vulnerable to recency/response biases (Dahlberg et al., 2022; Valtorta et al., 2016). Nonetheless, many researchers have used single-item measures of LON in their studies and still produced results comparable to those using valid and reliable multi-item instruments of LON, such as the De Jong-Gierveld Loneliness

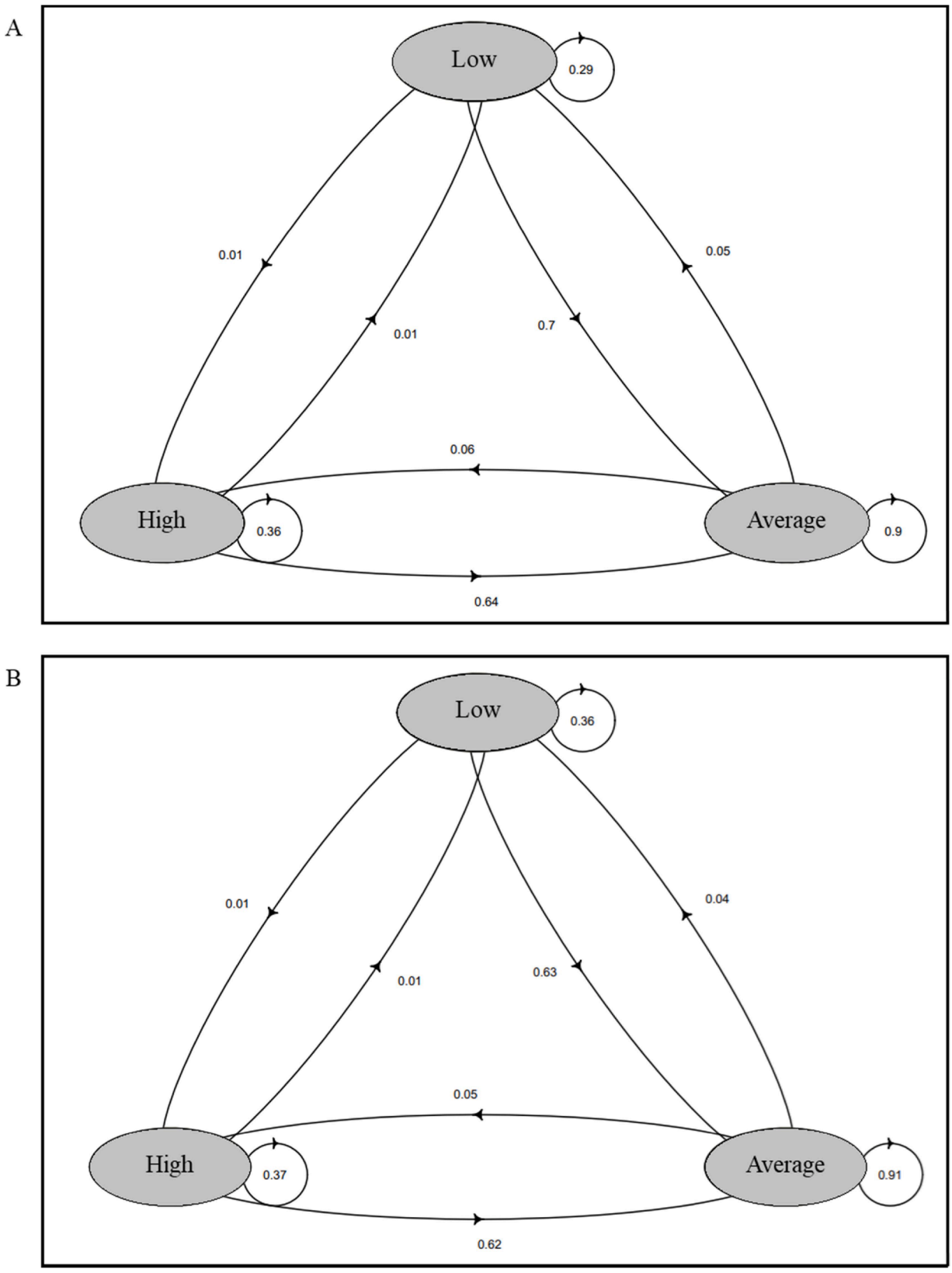


Fig. 2. State transition probabilities for combined memory groups across six years of follow-up
Notes.
A= Combined memory state transition probability: baseline to follow-up 1
B= Combined memory state transition probability: follow-up 1 to follow-up 2.

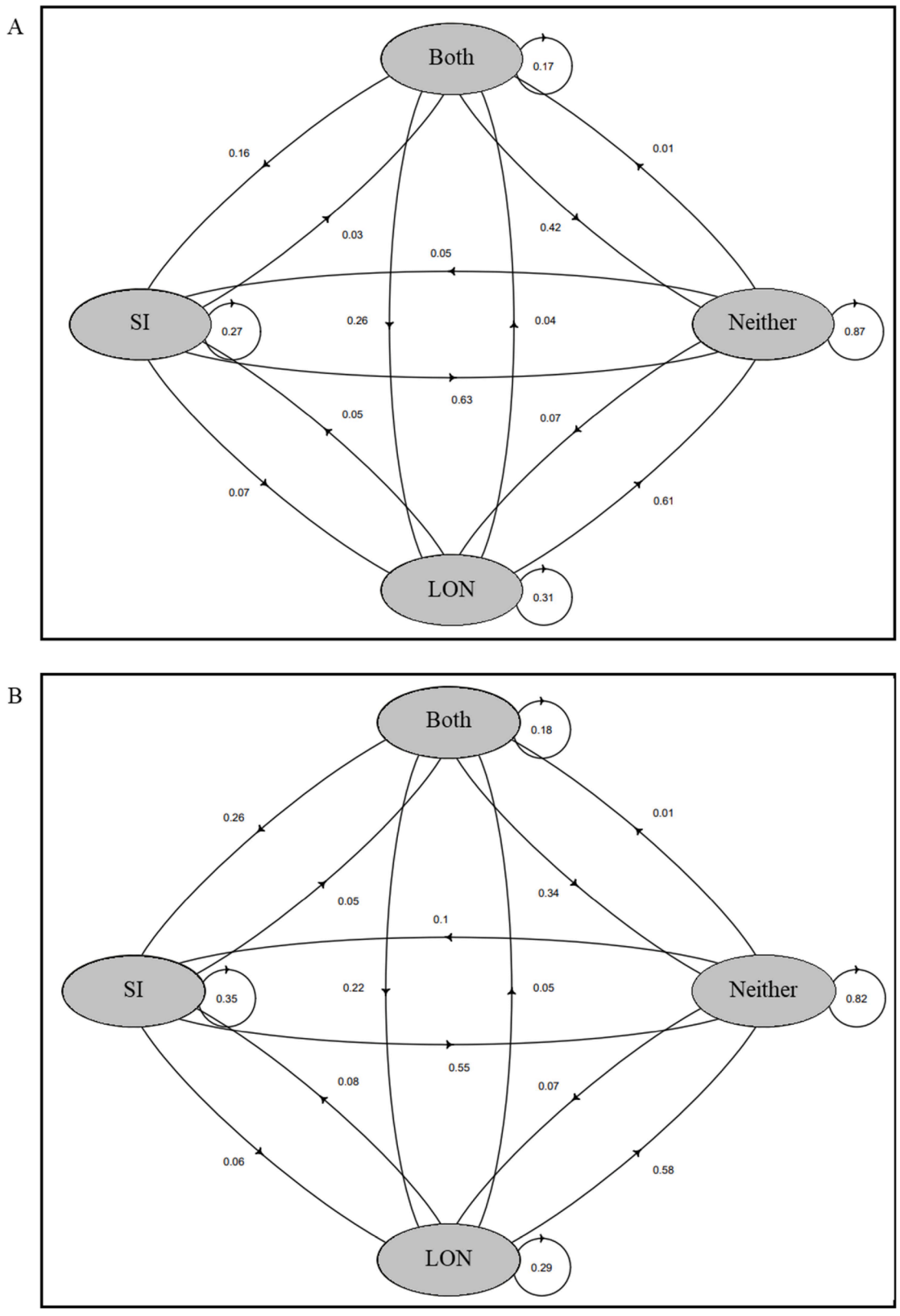


Fig. 3. State transition probabilities for social isolation/loneliness groups across six years of follow-up
Notes.
A= Social isolation/loneliness state transition probability: baseline to follow-up 1
B= Social isolation/loneliness state transition probability: follow-up 1 to follow-up 2
Abbreviations: SI= only socially isolated; LON= only lonely.

Table 3
Regression analysis results - comparisons of social isolation/loneliness groups for combined memory.

Least squares means for combined memory scores							
SI/LON groups		**Model 0**	**Model 1**	**Model 2**	**Model 3**	**Model 4**	**Model 5**
Neither socially isolated nor lonely		-0.26 (-0.63, 0.12)	-0.31 (-0.68, 0.07)	**-0.51 (-0.89, -0.13)**	-0.27 (-0.65, 0.12)	**-0.44 (-0.82, -0.05)**	**-0.65 (-1.05, -0.25)**
Only socially isolated		-0.31 (-0.69, 0.07)	-0.35 (-0.73, 0.03)	**-0.56 (-0.94, -0.17)**	-0.31 (-0.70, 0.07)	**-0.49 (-0.88, -0.10)**	**-0.69 (-1.09, -0.29)**
Only lonely		**-0.41 (-0.79, -0.03)**	**-0.43 (-0.81, -0.05)**	**-0.65 (-1.03, -0.27)**	**-0.41 (-0.80, -0.02)**	**-0.55 (-0.94, -0.17)**	**-0.73 (-1.13, -0.34)**
Both socially isolated and lonely		**-0.51 (-0.91, -0.11)**	**-0.51 (-0.91, -0.11)**	**-0.74 (-1.15, -0.34)**	**-0.50 (-0.91, -0.09)**	**-0.64 (-1.05, -0.23)**	**-0.80 (-1.22, -0.39)**
Differences of Least Squares Means (for Combined Memory Scores)							
SI/LON groups	**Benjamini-Hochberg Critical Value ((k/m) α)**	**Model 0**	**Model 1**	**Model 2**	**Model 3**	**Model 4**	**Model 5**
Neither socially isolated nor lonely vs. only socially isolated	5/6 × 0.05 = 0.04	-0.05 (0.08)	-0.05 (0.14)	-0.05 (0.11)	-0.05 (0.12)	-0.05 (0.11)	-0.04 (0.26)
Neither socially isolated nor lonely vs. only lonely	1/6 × 0.05 = 0.01	**-0.15 (0.00)**	**-0.12 (0.00)**	**-0.14 (0.00)**	**-0.15 (0.00)**	**-0.12 (0.00)**	**-0.09 (0.00)**
Neither socially isolated nor lonely vs. socially isolated and lonely	2/6 × 0.05 = 0.02	**-0.25 (0.00)**	**-0.20 (0.00)**	**-0.23 (0.00)**	**-0.24 (0.00)**	**-0.21 (0.00)**	-0.16 (0.03)
Only socially isolated vs. only lonely	4/6 × 0.05 = 0.03	**0.10 (0.02)**	0.08 (0.07)	**0.09 (0.03)**	**0.10 (0.02)**	0.07 (0.11)	0.05 (0.24)
Only socially isolated vs. socially isolated and lonely	3/6 × 0.05 = 0.03	**0.20 (0.01)**	0.16 (0.04)	**0.18 (0.02)**	**0.19 (0.01)**	0.16 (0.04)	0.12 (0.12)
Only lonely vs. socially isolated and lonely	6/6 × 0.05 = 0.05	0.10 (0.20)	0.08 (0.28)	0.09 (0.22)	0.09 (0.23)	0.09 (0.24)	0.07 (0.35)

Note. Least squares means estimates are shown, with their 95 % confidence intervals in brackets. For differences of least squares means, p-values are presented instead of 95 % confidence intervals to facilitate comparisons with the Benjamini-Hochberg (BH) critical values. BH method sorts the p-values from all conducted tests in ascending order (i.e., from the smallest to the largest values) and then computes the BH critical value using the formula: $\frac{k}{m}(\alpha)$, where k= rank of each p-value, m= total number of tests, and α= significance level. The subsequent step identifies the highest k rank for which the sorted p-value is less than the corresponding BH critical value, and all p-values up to this k rank are deemed statistically significant.
Model 0= controls for age, sex, education, province, follow-up time, and SI/LON*time interaction. Model 1= Model 0+ area of residence+ annual household income. Model 2= Model 0+ basic and instrumental activities of daily living. Model 3= Model 0+ alcohol consumption+ smoking status. Model 4= Model 0+ clinical depression+ other chronic conditions. Model 5= Model 0+ all other sociodemographic, functional ability, lifestyle, and health-related covariates.
Statistically significant values are bolded ($p < 0.05$ or $p <$ BH critical value).

Scale (Gierveld & Tilburg, 2006) and the University of California, Los Angeles (UCLA) Loneliness Scale (Russell, 1996) (Goldberg et al., 2021; Kuiper et al., 2020; Lara et al., 2019; Shankar et al., 2013; Yu et al., 2020). Pinquart (2001) even posited that single-item measures are most commonly used in research examining LON, and attributed their popularity to their simplicity and strong face validity. Mund et al. (2019) discussed how single-item direct and indirect measures (i.e., asking about the availability of confiding relationships rather than directly questioning about LON) demonstrate convergent validity, particularly at the extreme levels of LON. Victor et al. (2005) conducted a direct comparison between single-item and multidimensional measures of LON, and noted the similarity in estimates. This stands in contrast to SI, which inherently comprises numerous objective elements of social relationships, and measures of SI must be careful not to overlook certain types of structural support. Therefore, using a single-item measure may pose greater concerns for SI than for LON.

Most single-item measures of LON typically assess the frequency of feeling lonely within a timeframe of 7 days, usually using four response choices (Dahlberg et al., 2022; Newall & Menec, 2019; Yu et al., 2020), similar to the CES-D question (Andresen et al., 1994) used for the CLSA baseline data. Among these single-item measures, the CES-D has been a popular choice of instrument in many studies as it is proven to be a valid and reliable instrument in middle-aged and older populations from multiple ethnicities (Dahlberg et al., 2022; Newall & Menec, 2019; Yu et al., 2020). In Kang and Oremus's (2023) review, 11 of 12 studies assessed LON using either the De Jong-Gierveld Loneliness Scale, UCLA Loneliness Scale, or CES-D Scale, and all of these studies produced validated results. Only Gow et al.'s (2013) assessment of LON, which inquired about participants' current feelings of LON at the present moment, was considered to be unreliable.

Finally, despite the many benefits of dichotomizing the SI and LON measures in our study, this approach may not have fully captured the subtleties of the ordinal scale. While introducing bias through dichotomization is more of a concern for continuous variables than for ordinal ones (Altman & Royston, 2006), it is still crucial to conduct further research to verify that this method does not result in a biased interpretation of SI and LON.

4.2. *Future implications and conclusions*

The findings of this research underscore the critical need for targeted interventions, particularly for the combined SI and LON group, which faces the highest risk of memory impairment. Despite representing a smaller proportion of the population, this group's high prevalence of health issues and low income (Table 1) suggests the existence of structural barriers to social engagement that should demand attention. Addressing these barriers may involve making affordable transportation options available and implementing social programs designed to promote memory (e.g., group-based arts and craft projects, group-based social outings such as visits to museums or public parks) (Cohen-Mansfield & Perach, 2015; Menec et al., 2020; Poscia et al., 2018). These social engagement programs can be tailored for various memory levels within specific SI/LON groups.

The 'only LON' group emerges as the next priority. Given that

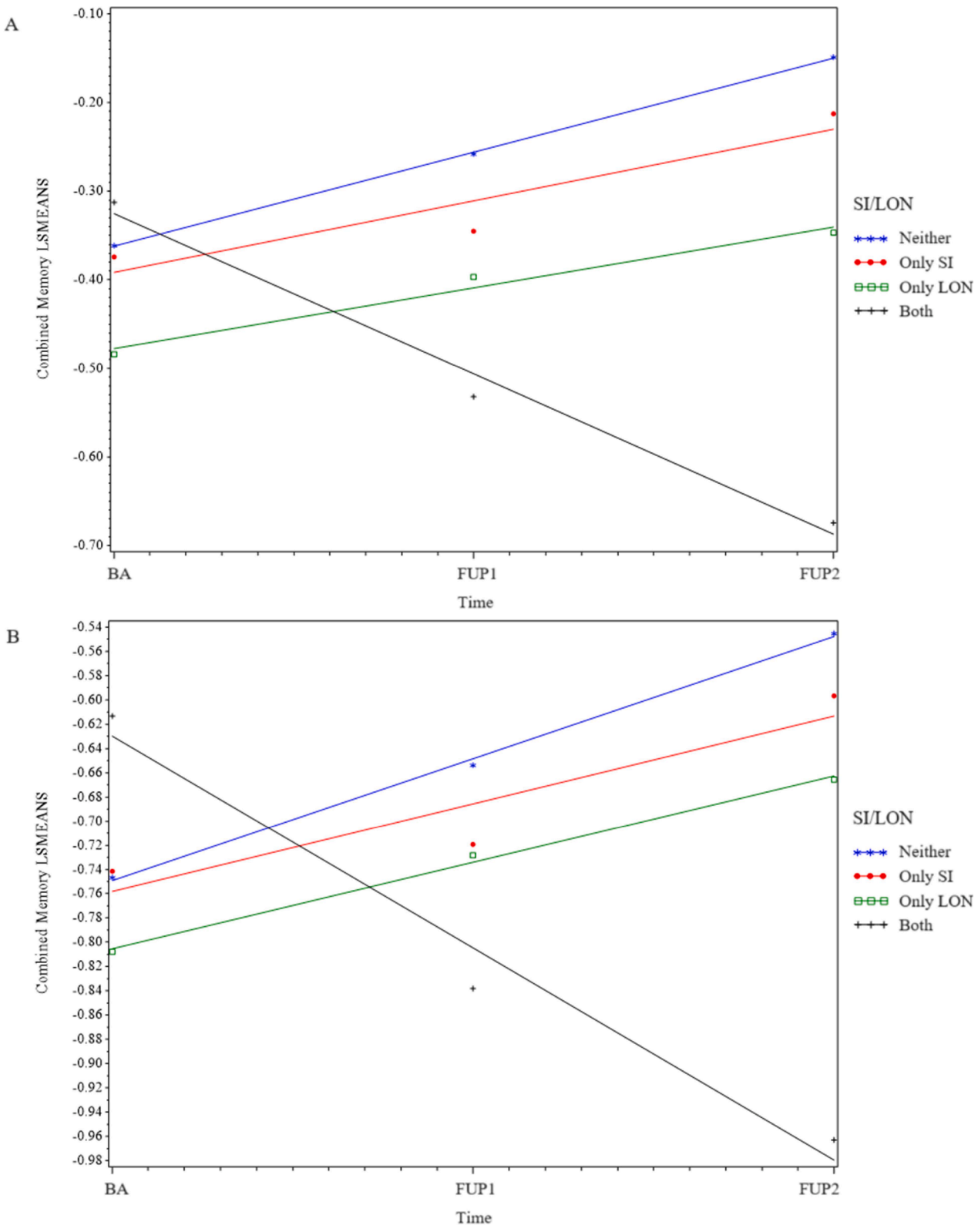


Fig. 4. Multivariable, mixed effects regression analyses between combined memory and social isolation/loneliness groups

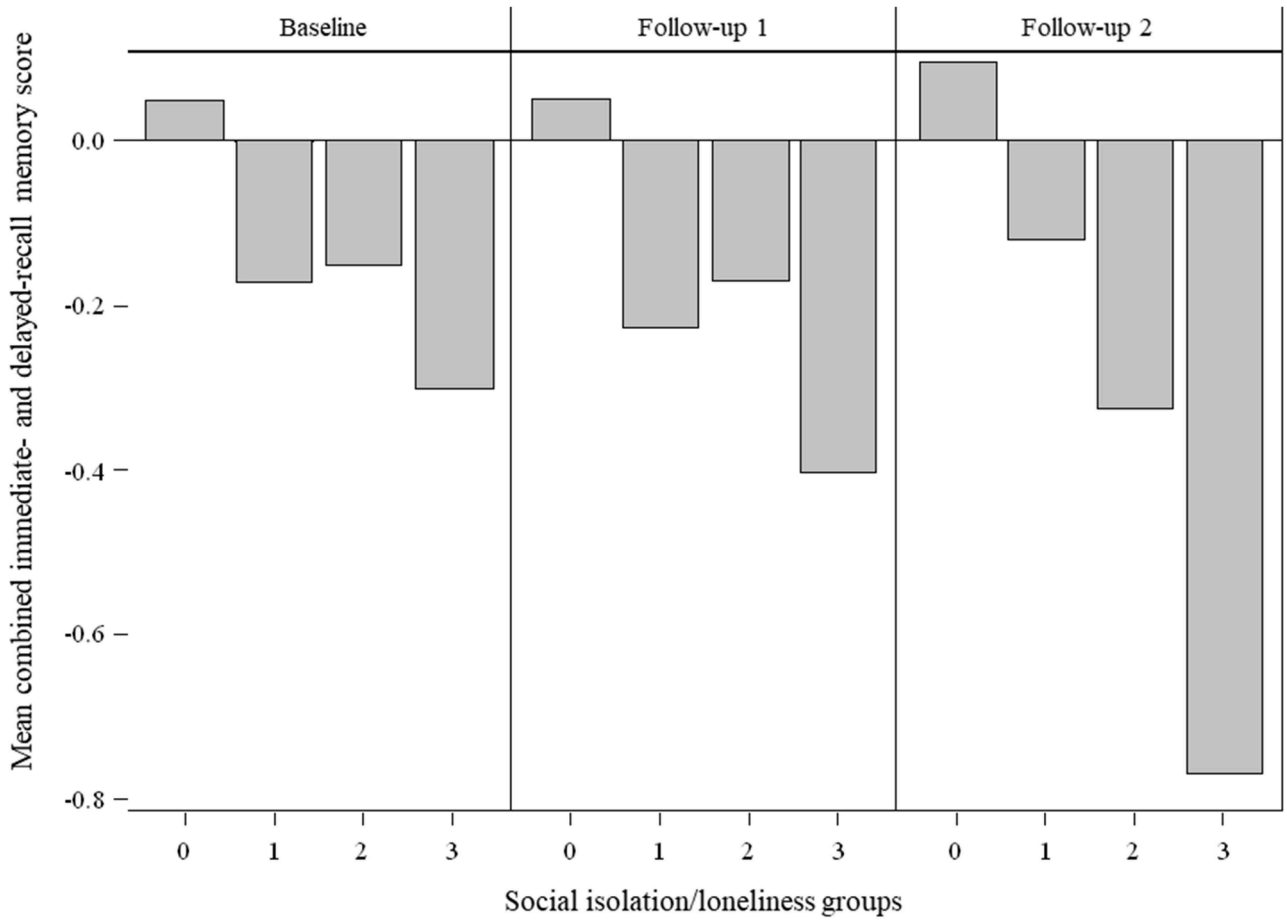
Notes.

A= This graph represents the base model, adjusted for age, sex, education, and province.

B= This graph represents the full model, adjusted for age, sex, education, province, area of residence, annual household income, 14 basic and instrumental activities of daily living, alcohol consumption, smoking status, clinical depression, and 37 other chronic conditions.

Parameter estimates are derived from least squares regression of the combined memory scores.

Abbreviations: SI= social isolation; LON= loneliness; BA= baseline; FUP1= follow-up 1; FUP2= follow-up 2.



N	10023	953	964	149	10477	840	1141	159	8422	1037	932	187
Mean	0.048	-0.17	-0.15	-0.30	0.050	-0.23	-0.17	-0.40	0.09	-0.14	-0.31	-0.74
Std Dev	1.89	1.87	1.84	2.16	1.88	1.96	1.89	2.13	1.88	1.94	1.89	1.89

Fig. 5. Mean memory score by social isolation/loneliness groups at baseline, Follow-up 1, and Follow-up 2
Notes.
Social isolation/loneliness group 0= neither isolated nor lonely; group 1= only socially isolated; group 2= only lonely; group 3= both isolated and lonely.
Abbreviations: N= number of subjects; Std Dev= standard deviation.

individuals in this category, despite possibly having large social networks, struggle with unmet social needs, traditional social/group interventions solely focused on increasing the frequency of social interactions may not yield optimal benefits for them. Instead, interventions focused on conducting needs assessment (i.e., collaborating with social workers or other professionals to identify individual goals, needs, and challenges) and providing counseling to navigate existing relationships may prove effective (Hoang et al., 2022; Kiecolt-Glaser & Wilson, 2017). For instance, despite having a spouse, individuals in this category might experience strained marital relationships, significantly impacting their well-being. Indeed, addressing the negative perceptions individuals may hold about their social relationships (e.g., how others perceive them, how supportive their relationships are, or how they fit into their social circles) could be crucial for the 'only LON' group.

The 'only SI' group poses a slight risk of memory impairment, showing no significant difference from the 'neither' group, especially after adjusting for covariates. Considering that these individuals may find contentment in isolation and do not want more social interaction, reaching out to them for interventions promoting social participation might be challenging. For this group, an effective intervention may involve providing practical strategies for coping with memory changes, coupled with education on the cognitive health risks of social isolation (Newall & Menec, 2019). Moreover, it is important to recognize the potential for these individuals to experience LON as they age and encounter more functional limitations, chronic conditions, or income decline (Newall & Menec, 2019). Therefore, monitoring their transitions into other SI/LON categories is crucial for identifying factors contributing to experiencing both SI and LON.

In conclusion, this research emphasized the importance of SI and LON in understanding memory outcomes in middle-aged and older adults over a six-year period. The study found that LON had a more pronounced impact on memory than SI. Furthermore, experiencing both SI and LON together had a more severe impact on memory than experiencing either SI or LON alone. These associations remained after adjusting for various covariates, including sociodemographic factors, functional limitations, lifestyle variables, and health comorbidities.

Study funding and data access

The funders had no role in study design, data collection, data analyses, data interpretation or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit the manuscript for publication. Further, the corresponding author had the right to publish all data, separate and apart from the guidance of the sponsor. The corresponding author takes full responsibility for the data, the analyses and

interpretation, and the conduct of the research.

Data availability statement

Data are available from the Canadian Longitudinal Study on Aging (www.clsa-elcv.ca) for researchers who meet the criteria for access to de-identified CLSA data.

CRediT authorship contribution statement

Ji Won Kang: Writing – original draft, Visualization, Investigation, Data curation, Conceptualization. **Mark Oremus:** Writing – review & editing, Visualization, Validation, Supervision. **Joel Dubin:** Writing – review & editing, Validation, Formal analysis. **Suzanne L. Tyas:** Writing – review & editing, Validation. **Charity Oga-Omenka:** Writing – review & editing, Visualization. **Meira Golberg:** Writing – review & editing, Methodology.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

This research was made possible using the data/biospecimens collected by the Canadian Longitudinal Study on Aging (CLSA). Funding for the Canadian Longitudinal Study on Aging (CLSA) is provided by the Government of Canada through the Canadian Institutes of Health Research (CIHR) under grant reference: LSA 94473 and the Canada Foundation for Innovation, as well as the following provinces, Newfoundland, Nova Scotia, Quebec, Ontario, Manitoba, Alberta, and British Columbia. This research has been conducted using the CLSA Baseline Tracking Dataset v4.0, Follow-up 1 Tracking Dataset v3.1, and Follow-up 2 Tracking Dataset v1.1, under Application Number 2209001. The CLSA is led by Drs. Parminder Raina, Christina Wolfson, and Susan Kirkland.

The opinions expressed in this manuscript are the author's own and do not reflect the views of the Canadian Longitudinal Study on Aging.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.archger.2024.105483.

References

Adam, E. K., Hawkley, L. C., Kudielka, B. M., & Cacioppo, J. T. (2006). Day-to-day dynamics of experience – cortisol associations in a population-based sample of older adults. *Proceedings of the National Academy of Sciences, 103*(45), 17058–17063. https://doi.org/10.1073/pnas.0605053103

Akhter-Khan, S. C., Tao, Q., Ang, T. F. A., Itchapurapu, I. S., Alosco, M. L., Mez, J., Piers, R. J., Steffens, D. C., Au, R., & Qiu, W. Q. (2021). Associations of loneliness with risk of Alzheimer's disease dementia in the Framingham Heart Study. *Alzheimer's & Dementia, 17*(10), 1619–1627. https://doi.org/10.1002/alz.12327

Altman, D. G., & Royston, P. (2006). The cost of dichotomising continuous variables. *BMJ (Clinical research ed.), 332*(7549). https://doi.org/10.1136/bmj.332.7549.1080, 1080–1080.

Andresen, E. M., Malmgren, J. A., Carter, W. B., & Patrick, D. L. (1994). Screening for depression in well older adults: Evaluation of a short form of the CES-D (Center for Epidemiologic Studies Depression Scale). *American Journal of Preventive Medicine, 10*(2), 77–84. https://doi.org/10.1016/S07493797(18)30622-6

Barnes, T. L., MacLeod, S., Tkatch, R., Ahuja, M., Albright, L., Schaeffer, J. A., & Yeh, C. S. (2022). Cumulative effect of loneliness and social isolation on health outcomes among older adults. *Aging & Mental Health, 26*(7), 1327–1334. https://doi.org/10.1080/13607863.2021.1940096

Benjamini, Y., & Hochberg, Y. (1995). Controlling the false discovery rate: A practical and powerful approach to multiple testing. *Journal of the Royal Statistical Society. Series B, Methodological, 57*(1), 289–300. https://doi.org/10.1111/j.2517-6161.1995.tb02031.x

Berkman, L. F., & Syme, S. L. (1979). Social networks, host resistance, and mortality: A nine-year follow-up study of Alameda County residents. *American Journal of Epidemiology, 109*(2), 186–204. https://doi.org/10.1093/oxfordjournals.aje.a112674

Boss, L., Kang, D.-H., & Branson, S. (2015). Loneliness and cognitive function in the older adult: A systematic review. *International Psychogeriatrics, 27*(4), 541–553. https://doi.org/10.1017/S1041610214002749

Brunier, A., & Muchnik, A. (2021). World failing to address dementia challenge. *World Health Organization*. https://www.who.int/news/item/02-09-2021-world-failing-to-address-dementia-challenge.

Cacioppo, S., Capitanio, J. P., & Cacioppo, J. T. (2014). Toward a neurology of loneliness. *Psychological Bulletin, 140*(6), 1464–1504. https://doi.org/10.1037/a0037618

Canadian Longitudinal Study on Aging (CLSA). (2014). *Cognition (COG) – in-home visit*. Available at: https://www.clsa-elcv.ca/doc/2292 Accessed on: 7 May 2024.

Cimarolli, V., & Boerner, K. (2005). Social support and well-being in adults who are visually impaired. *Journal of Vision Impairment and Blindness, 99*(9), 521–534. https://doi.org/10.1177/0145482×0509900904

CLSA. (2019). *Tracking and Comprehensive cognition measurements (baseline) portal dataset overview v1.1*. Aavailable at: https://www.clsa-elcv.ca/doc/3457 Accessed on: 7 May 2024.

CLSA. (2023). *Technical document (v2.0) sampling and computation of response rates and sample weights for the Tracking (telephone interview) participants and Comprehensive participants*. Available at: https://www.clsa-elcv.ca/doc/5130 Accessed on: 7 May 2024.

Cohen-Mansfield, J., & Perach, R. (2015). Interventions for alleviating loneliness among older persons: A critical review. *American Journal of Health Promotion, 29*(3), e109–e125. https://doi.org/10.4278/ajhp.130418-LIT-182

Craik, F. I. M., & Rose, N. S. (2012). Memory encoding and aging: A neurocognitive perspective. *Neuroscience and Biobehavioral Reviews, 36*(7), 1729–1739. https://doi.org/10.1016/j.neubiorev.2011.11.007

Dahlberg, L., McKee, K. J., Frank, A., & Naseer, M. (2022). A systematic review of longitudinal risk factors for loneliness in older adults. *Aging & Mental Health, 26*(2), 225–249. https://doi.org/10.1080/13607863.2021.1876638

Donovan, N. J., & Blazer, D. (2020). Social isolation and loneliness in older adults: Review and commentary of a national academies report. *The American Journal of Geriatric Psychiatry, 28*(12), 1233–1244. https://doi.org/10.1016/j.jagp.2020.08.005

Estrella, M. L., Durazo-Arvizu, R. A., Gallo, L. C., Tarraf, W., Isasi, C. R., Perreira, K. M., Zeng, D., Marquine, M. J., Lipton, R. B., González, H. M., Daviglus, M. L., & Lamar, M. (2021). Psychosocial factors associated with cognitive function among middle-aged and older Hispanics/Latinos: The Hispanic Community Health Study/Study of Latinos and its sociocultural ancillary study. *Journal of Alzheimer's Disease, 79*(1), 433–449. https://doi.org/10.3233/JAD-200612

Evans, I. E. M., Martyr, A., Collins, R., Brayne, C., & Clare, L. (2019). Social isolation and cognitive function in later life: A systematic review and meta-analysis. *Journal of Alzheimer's Disease, 70*(s1), S119–S144. https://doi.org/10.3233/JAD-180501

Fung, A. W. T., Lee, A. T. C., Cheng, S.-T., & Lam, L. C. W. (2019). Loneliness interacts with family relationship in relation to cognitive function in Chinese older adults. *International Psychogeriatrics, 31*(4), 467–475. https://doi.org/10.1017/S1041610218001333

Gallinat, J., Meisenzahl, E., Jacobsen, L. K., Kalus, P., Bierbrauer, J., Kienast, T., Witthaus, H., Leopold, K., Seifert, F., Schubert, F., & Staedtgen, M. (2006). Smoking and structural brain deficits: A volumetric MR investigation. *The European Journal of Neuroscience, 24*(6), 1744–1750. https://doi.org/10.1111/j.1460-9568.2006.05050.x

Gierveld, J. D. J., & Tilburg, T. V. (2006). A 6-Item scale for overall, emotional, and social loneliness: Confirmatory tests on survey data. *Research on Aging, 28*(5), 582–598. https://doi.org/10.1177/0164027506289723

Gilmour, H. (2011). Cognitive performance of Canadian seniors. *Health Reports, 22*(2), 27–31.

Goldberg, T. E., Choi, J., Lee, S., Gurland, B., & Devanand, D. P. (2021). Effects of restriction of activities and social isolation on risk of dementia in the community. *International Psychogeriatrics, 33*(11), 1207–1215. https://doi.org/10.1017/S1041610221000776

Gorelick, P. B. (2010). Role of inflammation in cognitive impairment: Results of observational epidemiological studies and clinical trials. *Annals of the New York Academy of Sciences, 1207*(1), 155–162. https://doi.org/10.1111/j.1749-6632.2010.05726.x

Gow, A. J., Corley, J., Starr, J. M., & Deary, I. J. (2013). Which social network or support factors are associated with cognitive abilities in old age? *Gerontology, 59*(5), 454–463. https://doi.org/10.1159/000351265

Higgins, J. P. T, Li, T., & Deeks, J. J. (2022). Chapter 6: Choosing effect measures and computing estimates of effect. In J. P. T. Higgins, J. Thomas, J. Chandler, M. Cumpston, T. Li, M. J. Page, & V. A. Welch (Eds.), *Cochrane handbook for systematic reviews of interventions version 6.3*. Cochrane.

Hoang, P., King, J. A., Moore, S., Moore, K., Reich, K., Sidhu, H., Tan, C. V., Whaley, C., & McMillan, J. (2022). Interventions associated with reduced loneliness and social isolation in older adults: A systematic review and meta-analysis. *JAMA Network Open, 5*(10), Article e2236676. https://doi.org/10.1001/jamanetworkopen.2022.36676

Holwerda, T. J., Deeg, D. J. H., Beekman, A. T. F., Tilburg, T. G., Stek, M. L., Jonker, C., & Schoevers, R. A (2014). Feelings of loneliness, but not social isolation, predict dementia onset: Results from the Amsterdam Study of the Elderly (AMSTEL). *Journal of Neurology, Neurosurgery & Psychiatry, 85*(2), 135–142. https://doi.org/10.1136/jnnp-2012-302755

Hultsch, D. F., Hertzog, C., Small, B. J., & Dixon, R. A. (1999). Use it or lose it: Engaged lifestyle as a buffer of cognitive decline in aging? *Psychology and Aging, 14*(2), 245–263. https://doi.org/10.1037/0882-7974.14.2.245

Hülür, G. (2022). Structural and functional aspects of social relationships and episodic memory: Between-person and within-person associations in middle-aged and older adults. *Gerontology, 68*(1), 86–97. https://doi.org/10.1159/000514949

Hülür, G., Elayoubi, J., Nelson, M. E., & Haley, W. E. (2022). Change in episodic memory with spousal loss: The role of social relationships. *The Journals of Gerontology: Series B, 77*(4), 683–694. https://doi.org/10.1093/geronb/gbab231

Jang, Y., Park, N. S., & Chiriboga, D. A. (2021). Cognitive health risks posed by social isolation and loneliness in older Korean Americans. *Alzheimer's & Dementia, 17*(S7), Article e049804. https://doi.org/10.1002/alz.049804

Kaldenberg, J. (2019). Low vision rehabilitation services: Perceived barriers and facilitators to access for older adults with visual impairment. *British Journal of Occupational Therapy, 82*(8), 466–474. https://doi.org/10.1177/0308022618821591

Kang, J. W., & Oremus, M. (2023). Examining the combined effects of social isolation and loneliness on memory: A systematic review. *Archives of Gerontology and Geriatrics, 104*, Article 104801. https://doi.org/10.1016/j.archger.2022.104801

Kiecolt-Glaser, J. K., & Wilson, S. J. (2017). Lovesick: How couples' relationships influence health. *Annual Review of Clinical Psychology, 13*, 421–443. https://doi.org/10.1146/annurev-clinpsy-032816-045111

Kiernan, K., Tobias, R., Gibbs, P., & Tao, J. (2011). *CONTRAST and ESTIMATE statements made easy: The LSMESTIMATE statement*.

Kuiper, J. S., Smidt, N., Zuidema, S. U., Comijs, H. C., Oude Voshaar, R. C, & Zuidersma, M. (2020). A longitudinal study of the impact of social network size and loneliness on cognitive performance in depressed older adults. *Aging & Mental Health, 24*(6), 889–897. https://doi.org/10.1080/13607863.2019.1571012

Lara, E., Caballero, F. F., Rico-Uribe, L. A., Olaya, B., Haro, J. M., Ayuso-Mateos, J. L., & Miret, M. (2019). Are loneliness and social isolation associated with cognitive decline? *International Journal of Geriatric Psychiatry, 34*(11), 1613–1622. https://doi.org/10.1002/gps.5174

Lewis, C. R., Talboom, J. S., De Both, M. D., Schmidt, A. M., Naymik, M. A., Håberg, A. K., Rundek, T., Levin, B. E., Hoscheidt, S., Bolla, Y., Brinton, R. D., Hay, M., Barnes, C. A., Glisky, E., Ryan, L., & Huentelman, M. J. (2021). Smoking is associated with impaired verbal learning and memory performance in women more than men. *Scientific Reports, 11*(1). https://doi.org/10.1038/s41598-021-88923-z, 10248–13.

Luo, M., Edelsbrunner, P. A., Siebert, J. S., Martin, M., & Aschwanden, D. (2021). Longitudinal within-person associations between quality of social relations, structure of social relations, and cognitive functioning in older age. *The Journals of Gerontology: Series B, 76*(10), 1960–1971. https://doi.org/10.1093/geronb/gbab001

Menec, V. H., Newall, N. E., Mackenzie, C. S., Shooshtari, S., Nowicki, S., & Reppermund, S. (2020). Examining social isolation and loneliness in combination in relation to social support and psychological distress using Canadian Longitudinal Study of Aging (CLSA) data. *PloS one, 15*(3). https://doi.org/10.1371/journal.pone.0230673. e0230673–e0230673.

Nakagawa, S., & Cuthill, I. C. (2007). Effect size, confidence interval and statistical significance: A practical guide for biologists. *Biological Reviews of the Cambridge Philosophical Society, 82*(4), 591–605.

Newall, N. E. G., & Menec, V. H. (2019). Loneliness and social isolation of older adults: Why it is important to examine these social aspects together. *Journal of Social and Personal Relationships, 36*(3), 925–939. https://doi.org/10.1177/0265407517749045

Newall, N. E. G., & Menec, V. H. (2020). A comparison of different definitions of social isolation using Canadian Longitudinal Study on Aging (CLSA) data. *Ageing and Society, 40*(12), 2671–2694. https://doi.org/10.1017/S0144686×19000801

Papadopoulos, K., Papakonstantinou, D., Montgomery, A., & Solomou, A. (2014). Social support and depression of adults with visual impairments. *Research in Developmental Disabilities, 35*(7), 1734–1741. https://doi.org/10.1016/j.ridd.2014.02.019

Park, D. C., & Festini, S. B. (2017). Theories of memory and aging: A look at the past and a glimpse of the future. *The Journals of Gerontology: Series B, 72*(1), 82–90. https://doi.org/10.1093/geronb/gbw066

Pollard, T. L., Simpson, J. A., Lamoureux, E. L., & Keeffe, J. E. (2003). Barriers to accessing low vision services. *Ophthalmic and Physiological Optics, 23*(4), 321–327. https://doi.org/10.1046/j.1475-1313.2003.00123.x

Poscia, A., Stojanovic, J., La Milia, D. I., Duplaga, M., Grysztar, M., Moscato, U., Onder, G., Collamati, A., Ricciardi, W., & Magnavita, N. (2018). Interventions targeting loneliness and social isolation among the older people: An update systematic review. *Experimental Gerontology, 102*, 133–144. https://doi.org/10.1016/j.exger.2017.11.017

Power, J. E. M., Sjöberg, L., Kee, F., Kenny, R. A., & Lawlor, B. (2019). Comparisons of the discrepancy between loneliness and social isolation across Ireland and Sweden: Findings from TILDA and SNAC-K. *Social Psychiatry and Psychiatric Epidemiology, 54*(9), 1079–1088. https://doi.org/10.1007/s00127-019-01679-w

Pugh, E., De Vito, A., Divers, R., Robinson, A., Weitzner, D. S., & Calamia, M. (2021). Social factors that predict cognitive decline in older African American adults. *International Journal of Geriatric Psychiatry, 36*(3), 403–410. https://doi.org/10.1002/gps.5435

Rafnsson, S. B., Orrell, M., d'Orsi, E., Hogervorst, E., & Steptoe, A. (2020). Loneliness, social integration, and incident dementia over 6 years: Prospective findings from the English Longitudinal Study of Ageing. *The Journals of Gerontology. Series B, Psychological Sciences and Social Sciences, 75*(1), 114–124. https://doi.org/10.1093/geronb/gbx087

Raina, P., Wolfson, C., Kirkland, S., Griffith, L. E., Balion, C., Cossette, B., Dionne, I., Hofer, S., Hogan, D., van den Heuvel, E. R., Liu-Ambrose, T., Menec, V., Mugford, G., Patterson, C., Payette, H., Richards, B., Shannon, H., Sheets, D., Taler, V., … Young, L. (2019). Cohort profile: The Canadian Longitudinal Study on Aging (CLSA). *International Journal of Epidemiology, 48*(6), 1752–1753j. https://doi.org/10.1093/ije/dyz173

Raina, P., Wolfson, C., & Krikland, S. (2009). Canadian Longitudinal Study on Aging (CLSA) combined protocol v3.0. *Canadian Longitudinal Study on Aging*. https://clsa-elcv.ca/doc/511.

Read, S., Comas-Herrera, A., & Grundy, E. (2020). Social isolation and memory decline in later-life. *The Journals of Gerontology: Series B, 75*(2), 367–376. https://doi.org/10.1093/geronb/gbz152

Reinhardt, J. P. (2001). Effects of positive and negative support received and provided on adaptation to chronic visual impairment. *Applied Developmental Science, 5*(2), 76–85. https://doi.org/10.1207/S1532480XADS0502_3

Rubin, D. B. (1987). *Multiple imputation for nonresponse in surveys*. New York: John Wiley and Sons.

Russell, D. W. (1996). UCLA Loneliness Scale (version 3): Reliability, validity, and factor structure. *Journal of Personality Assessment, 66*(1), 20–40. https://doi.org/10.1207/s15327752jpa6601_2

Rutter, E. C. (2019). *The association between social support availability and executive function in the canadian longitudinal study on aging*. [Master Thesis, University of Waterloo]. https://uwspace.uwaterloo.ca/handle/10012/14772.

Shankar, A., Hamer, M., McMunn, A., & Steptoe, A. (2013). Social isolation and loneliness: Relationships with cognitive function during 4 years of follow-up in the English Longitudinal Study of Ageing. *Psychosomatic Medicine, 75*(2), 161–170. https://doi.org/10.1097/PSY.0b013e31827f09cd

Shankar, A., McMunn, A., Banks, J., & Steptoe, A. (2011). Loneliness, social isolation, and behavioral and biological health indicators in older adults. *Health Psychology, 30*(4), 377–385. https://doi.org/10.1037/a0022826

Smith, K. J., & Victor, C. (2019). Typologies of loneliness, living alone and social isolation, and their associations with physical and mental health—ProQuest. *Ageing and Society, 39*(8), 1709–1730. https://doi.org/10.1017/S0144686×18000132

Statistics Canada, S.C. (2008). , March 26) *Canadian community health survey – healthy aging (CCHS)* https://www23.statcan.gc.ca/imdb/p2SV.pl?Function=getSurvey&SDDS=5146.

Steptoe, A., Shankar, A., Demakakos, P., & Wardle, J. (2013). Social isolation, loneliness, and all-cause mortality in older men and women. *Proceedings of the National Academy of Sciences - PNAS, 110*(15), 5797–5801. https://doi.org/10.1073/pnas.1219686110

Tuokko, H., Griffith, L. E., Simard, M., & Taler, V. (2017). Cognitive measures in the Canadian Longitudinal Study on Aging. *Clinical Neuropsychologist, 31*(1), 233–250. https://doi.org/10.1080/13854046.2016.1254279

Valtorta, N. K., Kanaan, M., Gilbody, S., & Hanratty, B. (2016). Loneliness, social isolation and social relationships: What are we measuring? A novel framework for classifying and comparing tools. *BMJ Open, 6*(4). https://doi.org/10.1136/bmjopen-2015-010799

Victor, C., Grenade, L., & Boldy, D. (2005). Measuring loneliness in later life: A comparison of differing measures. *Reviews in Clinical Gerontology, 15*(1), 63–70. https://doi.org/10.1017/S0959259805001723

von Elm, E., Altman, D. G., Egger, M., Pocock, S. J., Gøtzsche, P. C., & Vandenbroucke, J. P. (2007). The strengthening the reporting of observational studies in epidemiology (STROBE) statement: Guidelines for reporting observational studies. *Epidemiology (Cambridge, Mass), 18*(6), 800–804. https://doi.org/10.1097/EDE.0b013e3181577654

Windsor, T. D., Ghisletta, P., & Gerstorf, D. (2020). Social resources as compensatory cognitive reserve? Interactions of social resources with education in predicting late-life cognition. *The Journals of Gerontology: Series B, 75*(7), 1451–1461. https://doi.org/10.1093/geronb/gby143

Yoo, S. S., Tyas, S. L., Maxwell, C. J., & Oremus, M. (2023). The association between functional social support and memory in middle-aged and older adults: A prospective analysis of the Canadian Longitudinal Study on Aging's Comprehensive cohort. *Archives of Gerontology and Geriatrics, 114*, Article 105076. https://doi.org/10.1016/j.archger.2023.105076

Yu, B., Steptoe, A., Chen, Y., & Jia, X. (2021). Social isolation, rather than loneliness, is associated with cognitive decline in older adults: The China Health and Retirement Longitudinal Study. *Psychological Medicine, 51*(14), 2414–2421. https://doi.org/10.1017/S0033291720001014