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Are loneliness and social isolation associated with cognitive decline? Evidence from a longitudinal population-based study

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CONFLICT OF INTEREST

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ABSTRACT

Objective: This study aimed to examine the association of loneliness and social isolation on cognition over a three-year follow-up period in middle- and older-aged adults.

Methods: Data from a Spanish nationally representative sample were analysed (n=1691; aged 50+ years). Loneliness, social isolation and cognition (immediate recall, delayed recall, verbal fluency, forward digit span, backward digit span and a composite cognitive score) was assessed both at baseline and at follow-up. Adjusted generalised estimating equations models were performed.

Results: Loneliness was significantly associated with lower scores in the composite cognitive score, immediate and delayed recall, verbal fluency and backward digit span (B=-0.14 to B=-3.16; $p<0.05$) and with a more rapid decline from baseline to follow-up in two out of six cognitive tests. Social isolation was associated with lower scores in composite cognitive score, verbal fluency and forward digit span (B=-0.06 to B=-0.85; $p<0.05$). The effect of loneliness and social isolation on cognition remained significant after the exclusion of individuals with depression.

Conclusions: Both loneliness and social isolation are associated with decreased cognitive function over a 3-year follow-up period. The development of interventions that include the enhancement of social participation and the maintenance of emotionally supportive relationships might contribute to cognitive decline prevention and risk reduction.

Keywords: cognitive function; loneliness; social isolation; population-based study, older adults

KEY POINTS

- Social determinants as potential risk factors for cognitive decline have gained increasing attention
- Loneliness is associated with decreased cognitive function over a follow-up period
- Social isolation is related to decreased cognitive function
- Social interventions might contribute to cognitive decline prevention and risk reduction

1. INTRODUCTION

Cognitive impairment constitutes a major determinant for middle- and older-aged adults' health, functionality, and well-being.[1,2] It is indeed a critical hallmark of neurocognitive disorders such as dementia. As a result, major efforts are being directed towards the identification of the factors that may contribute to cognitive decline prevention and risk reduction. One such factor is social relationships.

The lack of (satisfactory) interactions may refer to objective or subjective dimensions of social relationships, namely, social isolation and loneliness. Social isolation relates to structural aspects of the social network (e.g. low frequency of interactions, small size of the social network),[3] whereas loneliness refers to a distressing perceived discrepancy between one´s social desires and one´s actual interactions with others.[4]

Over the past decade, the study of loneliness and social isolation as potential risk factors for cognitive decline have gained increasing attention. Previous studies have suggested that being alone or never married, low frequency of interactions, small social network size or negative experiences of social support predict steeper cognitive decline.[5-8] Moreover, a recent meta-analysis of longitudinal population-based studies found evidence that loneliness is also associated with an increased risk of dementia.[9]

Although the correlation between loneliness and objective measures of social isolation appear small to moderate,[10] both concepts should be examined together in order to capture a more complete picture of individuals´ social context.[11,12] Earlier studies on social factors and cognitive decline in middle- and older-aged adults have commonly followed a single measurement approach.[13-15] Among the few ones in which researchers examined social isolation and loneliness simultaneously, the evidence have yielded mixed results.[10,16-20] For instance, findings from the English Longitudinal Study of Ageing revealed that social isolation was related to decreased episodic memory and verbal fluency after a 4-year follow-up period, whereas loneliness was found to be associated with poorer immediate and delayed recall over time.[17] By contrast, Wilson et al.[21] using data from a longitudinal cohort study of 823 older adults, reported that loneliness was linked to a more rapid decline in semantic memory rather than episodic memory. On the other hand, the focus of most studies on single cognitive screening tests[18,22-24] or aggregated results across diverse cognitive tasks,[19,25-27] might limit our potential to explore trajectories of different cognitive profiles.[28] Markers of fluid abilities (e.g. episodic memory), that are known to decline over the lifespan and to be impaired at the earlier stages of neurocognitive disorders,[29] might be more sensitive to the effects of loneliness and social isolation than those of crystallised abilities (e.g. verbal fluency). The underlying logic is related with the fact that objective and subjective social isolation lead to augmented stress reactivity that are linked to prolonged activation of the hypothalamic-pituitary-adrenal axis (HPA), the sympathoadrenal system and glucocorticoids resistance, assumed to have deleterious effects on the prefrontal cortex and the hippocampus, which are fundamental areas for learning and memory functions.[30,31]

Studies that provided cognitive domain-specific results are scarce and have not accounted for the correlation between repeated measures on the same individual over time.[10,17,32] Therefore, the aim of this study is to investigate the effect of loneliness and social

isolation on distinct cognitive domains over a 3-year follow-up period in a population-based sample of middle and older-aged adults. We hypothesize that the influence of the social factors will be stronger on cognitive measures that are predominantly diminished in both normal and pathological aging.

2. MATERIALS AND METHODS

2.1. Study design

Longitudinal data from "Edad con Salud", a nationally-representative household survey of the non-institutionalized adult population in Spain (aged ≥18 years), were analysed. The baseline survey (wave 1) was part of the Collaborative Research on Ageing in Europe (COURAGE in Europe) study [33] and was undertaken between July 2011 and May 2012. Potential participants were selected by a stratified multistage clustered design according to the Spanish regions and population size, with one individual being randomly selected from each household. Data on households were provided by the Spanish Statistical Office. The follow-up (wave 2) was conducted from December 2014 to June 2015.

Participants underwent face-to-face structured interviews with the use of Computer-Assisted Personal Interviewing (CAPI). The survey also included standardized physical examinations and a neuropsychological test battery assessment. If the respondent had a noticeable physical or cognitive impairment that precluded participation in the survey, a shorter version of the questionnaire was administered to a proxy respondent.

A total of 4753 individuals were initially interviewed at wave 1. The present study focused on participants aged 50 or older, which led to the exclusion of 962 individuals. Of the remaining 3791 individuals, those who participated in the survey via a proxy respondent (n=166) and those whose information on loneliness, social isolation or cognition was

incomplete or lacking (n=262) were further excluded, yielding a baseline sample of 3363 individuals. At follow-up, 157 (4.7%) participants deceased, 1351 (40.2%) were lost to follow-up, and 76 (4.1%) could not be interviewed due to limited cognitive function (i.e., Mini Mental State Examination (MMSE)[34] score <16 or identification of severe cognitive limitations by a family member or the interviewer). Finally, 88 (4.7%) subjects with missing information on loneliness, social isolation or cognition at follow-up were also excluded. Thus, the final analytical sample comprised 1691 respondents.

2.2. Ethics statement

Ethical approvals were obtained from the Ethics Review Committees of Parc Sanitari Sant Joan de Déu, Barcelona, and Hospital Universitario La Princesa, Madrid. Informed consent was obtained from all participants in both waves.

2.3. Measurements

2.3.1. Cognitive function

Cognitive function was assessed through the following five performance tests: word list immediate and delayed verbal recall from the Consortium to Establish a Registry for Alzheimer's Disease (CERAD);[35] digit span forward and backwards from the Wechsler Adult Intelligence Scale;[36] and the animal naming task.[35] Word list memory tasks assessed learning ability and episodic memory. Respondents were presented with 10 cards with unrelated items to remember. Word list memory and word list recall measured the ability to recall the 10 words given in the word list immediately and after 5 minutes respectively. Attention, working memory and executive function were evaluated through the forward and backward digit span. The participant was presented with a series of digits (e.g. 8, 5, 2) and was requested to repeat them in the same (forward digit span test) or reverse order (backward digit span test). If the respondent succeeded, a longer list was provided. The digit span was the greatest number of digits that the participant was able to repeat correctly. The animal naming task assessed

language, semantic memory and executive function. Participants were asked to name as many animals as possible within a 60-second period. A global composite cognitive score was also calculated by taking the average of the score of each test and later transforming it into a 0-100 scale. Higher scores indicate better cognitive function.

2.3.2. Loneliness

Loneliness was assessed by means of the Three-item UCLA Loneliness Scale.[37] It comprises the following items on a three-point scale: 1) "How often do you feel that you lack companionship?"; 2) "How often do you feel left out?"; and 3) "How often do you feel isolated from others?". Responses were added up to produce a loneliness score ranging from 3 to 9, with higher scores indicating higher level of loneliness. Two measures of loneliness were used in the current study. First, given the positively skewed nature of the loneliness score, a dichotomous loneliness variable (i.e. presence or absence of loneliness) was established using a cut off score of 6.[38] Second, the total loneliness score was transformed into a percentile scale and treated as a continuous variable.

2.3.3. Social isolation

A social isolation index, based on the one proposed by Shankar et al. [39] was computed with respondents given a point if they: a) were not married/not cohabiting with a partner; b) had less than monthly contact with children; c) had less than monthly contact with other immediate family; d) had less than monthly contact with friends; and e) did not participate in any organizations, religious groups, or committees. Scores ranged from 0 to 5, with higher scores representing greater social isolation.

2.3.4. Covariates

Demographic confounders included age (in years), sex, and educational level (in years). Level of physical activity was assessed by means of the Global Physical Activity Questionnaire (GPAQ) version 2.[40] It comprises 16 items on the duration and frequency of vigorous and

moderate intensity activities in three settings and an additional question on sedentary behavior. The physical activity levels were classified as low, moderate or high following the GPAQ guidelines.[41] Alcohol consumption was categorized as: lifetime abstainers; occasional drinkers (no consumption in past month); non-heavy drinkers (consumed alcohol in past month and in past 7 days); and heavy drinkers (consumed alcohol ≥1-2 days per week, with 5 or more standard drinks in past 7 days for men and 4 or more for women).[42] Disability was assessed by a set of self-reported difficulties with basic activities of daily living (ADL) in the previous 30 days.[43] Disability was considered to be present if individuals reported severe or extreme/cannot do difficulties at least on one item. Finally, three chronic conditions were measured. Depression in the previous 12-months was assessed with an adapted version of the Composite International Diagnostic Interview (CIDI 3.0).[44] An algorithm based on the DSM-IV was used for the endorsement of one or more major depressive episodes.[45] A diagnosis of stroke was made based on self-reported diagnosis and/or self-reported symptoms. Specific questions were: "Have you ever suffered from sudden onset of paralysis or weakness in your arms or legs on one side of your body for more than 24 hours?" and "Have you ever had, for more than 24 hours, sudden onset of loss of feeling on one side of your body, without anything having happened to you immediately before?" Individuals who answered affirmatively to both questions were considered to have had a stroke. Diabetes was based solely on self-reported lifetime diagnosis.

2.4. Statistical analysis

Descriptive analyses on the baseline sociodemographic and clinical characteristics of the sample were conducted. These analyses included proportions, means, and standard deviations (SD). Percentages and mean estimates for loneliness, social isolation and all the cognitive tests were calculated in both waves. Significance tests to evaluate changes in these estimates during

the follow-up were performed using McNemar's test and paired *t*-tests for categorical and continuous variables respectively.

The association of loneliness and social isolation (exposure variables) with all the individual and composite cognitive scores (outcomes) was evaluated using generalised estimating equations models (GEE).[46] This method can be viewed as an extension to the generalized linear models (GLM) for clustered data.[47] It allows for the correlation between repeated measures on the same individual over time, evaluating within and between-subjects' relationships.[48] Models were constructed using a Gaussian family function and the exchangeable correlation structure with robust estimation of the standard errors. Step-by-step linear GEE models were separately constructed for loneliness and social isolation. First, loneliness and social isolation were included as predictors adjusting for time. Time was added as a continuous variable coded as months, assuming a linear relationship with time (model 1). Second, sociodemographic variables (i.e. age, sex and education) were included to the models (model 2). In a third step, GEE models were further adjusted for level of physical activity, alcohol consumption, ADL limitations, stroke, diabetes, depression, and mutually adjusted for loneliness or social isolation (model 3). Finally, an adjusted model was constructed for all the aforementioned variables simultaneously in addition to two separate interaction terms (i.e. loneliness x time and social isolation x time) to evaluate whether the rate of cognitive decline varied as a function of the exposure variables. For significant loneliness x time interactions, marginal effects were then computed to plot the predicted estimate for the specific outcome according to loneliness status over a 3-year follow-up period while keeping all other covariates at their means. In order to evaluate whether differences on these predicted estimates were statistically significant, we further performed pairwise multiple comparisons with *Bonferroni* correction. A series of sensitivity analyses were conducted to explore whether the main results

remained unchanged after: a) excluding individuals with depression; and b) using loneliness as a continuous variable.

Results from all GEE models are presented as unstandardized regression coefficients (*B*) with its corresponding 95% confidence intervals (CIs), standard errors (SE), test statistics (Z) and *p* values. The level of statistical significance was set at $p<0.05$. Data analyses were performed using Stata 14.2 (Stata Corp LP, College Station, Texas).

3. RESULTS

3.1. Sample characteristics

A total of 1691 respondents aged ≥50 years were included in the analysis. Each participant underwent between 2.7 and 3.7 (mean=3.3; SD=0.2) years of follow-up. **Table 1** provides a summary of the baseline sociodemographic and clinical characteristics of the study sample. Overall, the mean age was 64.5 years (SD=9.8) and there were more women than men (52.8% vs. 47.2%). **Table 2** shows percentages and mean estimates (SD) of loneliness, social isolation and cognitive tests at baseline and follow-up. The proportion of participants reporting feelings of loneliness was similar at each assessment. Likewise, the level of social isolation remained unchanged at follow-up. Scores on most of the cognitive tests significantly differ between wave 1 and wave 2, with the exception of immediate recall ($p=0.153$).

Supplementary table 1 illustrates differences between respondents who were included in the analysis (n=1691) to those who were eligible for our analyses from wave 1 but did not have a follow-up assessment or whose information on loneliness, isolation or cognitive function at wave 2 was incomplete or lacking (n=1672). Excluded individuals were significantly older, had lower years of education and higher disability, reported lower alcohol consumption, higher feelings of loneliness and social isolation and scored lower on all of the cognitive tests.

3.2. The association of loneliness and social isolation with cognitive function

The results of the GEE analysis assessing the association of loneliness and social isolation with cognitive function are presented in **Table 3**. After full adjustment for the covariates (model 3), loneliness was found to be associated with lower performance in composite cognitive score (B=-3.16; 95% CI=-4.95, -1.37), immediate recall (B=-0.83; 95% CI=-1.29, -0.36), delayed recall (B=-0.25; 95% CI=-0.46, -0.03), verbal fluency (B=-0.98; 95% CI=-1.61, -0.34) and backward digit span (B=-0.14; 95% CI=-0.24, -0.04). Higher social isolation was also significantly related to decreased scores on composite cognitive score (B=-0.85; 95% CI=-1.55, -0.14), verbal fluency (B=-0.34; 95% CI=-0.57, -0.11) and forward digit span (B=-0.06; 95% CI=-0.11, -0.02) in fully covariate-adjusted models (model 3). However, no effect of social isolation on the remaining cognitive tests was found. A significant loneliness x time effect was found in the composite cognitive score, delayed recall, forward and backward digit span, indicating that the rate of cognitive decline varied as a function of loneliness (B=-0.01 to B=-0.11; $p<0.05$). **Figure 1** depicts the predicted values for these cognitive outcomes in lonely vs non-lonely individuals over time. Both groups showed a decreased cognitive function over the time. However, individuals who reported feelings of loneliness experienced a more rapid rate of cognitive decline when compared to those respondents without loneliness in the composite cognitive score and backward digit span ($p<0.03$ for the composite cognitive score, and $p<0.04$ for backward digit span), but this effect was no significant across other cognitive domains. The social isolation x time interaction did not reach statistical significance for any of the cognitive domains, suggesting that individuals with higher levels of social isolation did not show a faster rate of decline as compared with those less socially isolated.

The association between loneliness and social isolation with cognitive function after excluding of individuals with depression let to substantively similar results (**Supplementary table 2**). Feelings of loneliness were also significantly related to decreased cognitive function over time in composite cognitive score, delayed recall, and forward digit span, whereas higher

levels of social isolation were not found in association with a faster rate of cognitive decline (data not shown). In sensitivity analyses using loneliness as a continuous variable, each additional unit increase in the UCLA loneliness scale was significantly associated with lower scores in the composite cognition score, immediate recall and verbal fluency in the fully covariate-adjusted model (**Supplementary table 3**). Significant interactions effects were also observed for the composite cognitive score and backward digit span (data not shown).

4. DISCUSSION

4.1. Summary of results and significance of findings

Longitudinal data from a cohort study were used to examine the relationship of loneliness and social isolation with decline in specific cognitive domains, by adjusting for multiple confounding variables. Our findings revealed that loneliness is related to lower scores in the composite cognitive score, immediate and delayed recall, verbal fluency and backward digit span and with a more rapid decline from baseline to follow-up in the composite cognition score and backward digit span. Furthermore, social isolation was found in association with lower scores in composite cognitive score, verbal fluency and forward digit span but not with a faster rate of decline at three-year follow-up. Sensitivity analyses further showed that the effect of loneliness and social isolation on cognition remained unchanged after the exclusion of individuals with depression, supporting the notion that loneliness and social isolation are not merely makers from depressive symptoms.[49,50] On the other hand, loneliness as a continuous variable was associated with lower scores for composite cognition score, immediate recall and verbal fluency and predicted changes in two out of six cognitive tests. One possible explanation is that loneliness may negatively impact on cognitive processes only when participants exhibited loneliness in a moderate or severe intensity. The current analysis suggests that both social factors are important for cognitive outcomes, as indicated by its distinguishable effects on multiple cognitive domains, and even when these constructs are considered simultaneously.

However, loneliness predicted various outcomes beyond what was predicted by social isolation.

These results are consistent with some but not other previous research.[5,7,12,16-19,21,27,51-54] For instance, Griffin et al.[19] found that loneliness correlated with lower cognitive function whereas social isolation was longitudinally associated with worse cognitive performance in older Americans (n=6654). By contrast, two meta-analysis on loneliness and cognitive function/dementia did found evidence for such longitudinal association.[49,51] Furthermore, our finding that verbal fluency was not associated with loneliness and social isolation over time is supported by some[10] but not all[17,54] prior literature. The fact that few studies reported findings for loneliness and social isolation simultaneously together with the high variability across studies in terms of conceptual and measurement approaches, may account for the observed heterogeneity. In addition, some of our non-significant results could be explained by the short follow-up period. Nevertheless, convincing evidence, including the present study, highlighted the association between social factors and markers of fluid intelligence.

Several hypotheses may be offered in attempt to explain the association of social factors and cognitive function. Loneliness and social isolation may represent a risk factor for cognitive decline. Variations in social networks and support appear likely at older ages due to transition from full-time employment to retirement and emotional losses.[55] Thus, older individuals may be at greater risk of social isolation and loneliness.[56] In this regard, prolonged activation of the hypothalamic pituitary adrenal axis and the sympathoadrenal system, glucocorticoids resistance and over-expression of pro-inflammatory genes, among others, have been suggested to compromise neural responses that may directly influence the development of neurodegenerative conditions.[57-59] At the same time, this resulting disrupted brain response might contribute to the development of certain cardiovascular events (e.g. atherosclerosis, elevated blood pressure) and other common chronic diseases,[57,59,60] such as diabetes, which

are well-known risk factors for cognitive decline.[61] There may be other factors (mediators) through which loneliness and social isolation increase cognitive decline. For instance, individuals reporting feelings of loneliness or social isolation might engage to a greater extent in unhealthy behaviours (e.g. physical inactivity or poor dietary choices),[62] which in turn are associated with increased odds of developing cardiovascular diseases and cognitive impairment.[60] Alternatively, loneliness and social isolation might appear as a response of the cognitive impairment or as a result of an underlying neuropathology leading to dementia.[21,63] Consistently with this hypothesis, various longitudinal studies showed that global cognitive function and discrete cognitive domains predicted changes in perceived social isolation over time.[23,64,65] Findings of previous studies also indicated that social withdrawal or misperception of the social contacts are common among individuals with young onset dementia caused by behavioural alterations that lead to maladjustment to the social environment.[66]

4.2. Strengths and limitations

The strengths of the study include the use of a large nationally-representative sample that allows for the simultaneous examination of multiple factors. Furthermore, we used a set of cognitive tests assessing diverse core aspects of cognition, whereas other studies only included a brief screening cognitive instrument. The loneliness variable was based on a validated questionnaire with both satisfactory reliability and validity[37] whereas previous research on similar topics has used definitions of loneliness that are based on single-item questions. Finally, our analyses included individuals aged 50+ years in order to capture the potential prodromal phase of neurocognitive disorders. These study results should also be interpreted in the light of its shortcomings. First, our study is limited by a short follow-up period, which reduces the power to evaluate the impact of persistent loneliness and social isolation on cognitive function. However, our statistical approach allowed us to simultaneously explore predictors and outcomes at different time-points. Second, we acknowledge that the artificial dichotomization

of loneliness may result in some biased estimates. However, a small percentage of individuals scored high on the UCLA loneliness scale questionnaire, suggesting that this variable may falls into two groups. Moreover, we conducted sensitivity analysis using continuous scores of loneliness, which lead to comparable but not equivalent results to those of main analyses. Third, meaningful grouping was used to create a composite variable on social isolation with equal weights assigned to all index components.[39] This may have affected our results on the association of social isolation with cognition, as some aspects of the social network may have more importance than others. Fourth, a potential reverse causal direction cannot be ruled out. In this regard, it is possible that some individuals with abnormal cognitive decline or even dementia may have been included in our study during the baseline or the follow-up assessments. Nevertheless, we made use of family-reported dementia diagnosis and interviewers were trained to identify participants with severe cognitive function that precluded participation in the survey. Fifth, attrition bias may exist, which might have led to an underestimation of the true association of loneliness and social isolation with cognitive function.

4.3. Conclusions

Loneliness and social isolation were associated with lower cognitive function over a 3-year follow-up period in middle- and older-aged older adults. These results may have some implications for health care providers. Increasing awareness about the importance of screening for (perceived) social isolation in daily practice may help to identify people who may be at high risk of cognitive decline. Indeed, previous studies have demonstrated that individuals with unmet social needs are more likely to be frequent users of health care services.[67] The development of tailored interventions that include the enhancement of social participation and the maintenance of emotionally supportive relationships, might contribute to cognitive decline

prevention and risk reduction. Further research is needed toward a more comprehensive understanding of the impact of social factors on cognitive function.

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TABLE 1. Baseline sociodemographic and clinical characteristics of the study sample.

Characteristic		n=1691
Age in years (mean, SD)		64.5 (9.8)
Sex		
	Male	47.2
	Female	52.8
Years of education (mean, SD)		10.5 (6.4)
Physical activity		
	High	29.4
	Moderate	39.9
	Low	30.7
Alcohol consumption		
	Lifetime abstainers	28.0
	Occasional drinkers	29.5
	Non heavy drinkers	40.2
	Heavy drinkers	2.3
Disability		27.7
Comorbidities		
	Depression	11.5
	Diabetes	16.3
	Stroke	4.4

Note. Values are percentages for each category unless otherwise indicated.
Some percentages are based on an incomplete sample because of missing data (less than 1%).
Abbreviations: SD=Standard Deviation.

TABLE 2. Percentages and mean estimates (SD) on loneliness, social isolation and cognitive tests at baseline and follow-up (n=1691).

	Baseline	Follow-up	*p*-value*
Loneliness (%)	12.5	12.4	<0.899
Social isolation (0-5)	1.9 (1)	1.9 (1)	0.033
Immediate recall (0-30)	15.4 (5.2)	15.2 (5.2)	0.153
Delayed recall (0-10)	4.5 (2.3)	4.4 (2.3)	0.010
Verbal fluency (0+)	18.1 (7.2)	17.1 (6.9)	<0.001
Forward digit span (0-9)	5.5 (1.4)	5.4 (1.3)	<0.001
Backward digit span (0-8)	3.7 (1.2)	3.5 (1.2)	<0.001
Composite cognitive score (0-100)	49.5 (22.6)	44.2 (23.9)	<0.001

Note. Values are mean estimates (SD) unless otherwise indicated. Abbreviations: SD=Standard Deviation.
*The difference between baseline and follow-up values was tested by McNemar's test and paired Student t tests for categorical and continuous variables, respectively.

TABLE 3. Multiple linear regression models with GEE method for the association of loneliness and social isolation (exposures) with cognitive function (outcome).

	Composite cognitive score				Immediate recall				Delayed recall				Verbal fluency				Forward digit span				Backward digit span			
Loneliness	B (95% CI)	SE	Z	p	B (95% CI)	SE	Z	p	B (95% CI)	SE	Z	p	B (95% CI)	SE	Z	p	B (95% CI)	SE	Z	p	B (95% CI)	SE	Z	p
Model 1†	**-4.20 (-6.06, -2.33)**	**0.95**	**-4.42**	**0.000**	**-1.10 (-1.56, -0.63)**	**0.24**	**-4.62**	**0.000**	**-0.37 (-0.59, -0.15)**	**0.11**	**-3.27**	**0.001**	**-1.56 (-2.21, -0.90)**	**0.34**	**-4.63**	**0.000**	**-0.18 (-0.30, -0.05)**	**0.06**	**-2.85**	**0.004**	**-0.23 (-0.34, -0.13)**	**0.05**	**-4.45**	**0.000**
Model 2‡	**-4.04 (-5.82, -2.26)**	**0.91**	**-4.45**	**0.000**	**-1.00 (-1.45, -0.54)**	**0.23**	**-4.32**	**0.000**	**-0.34 (-0.55, -0.12)**	**0.11**	**-3.12**	**0.002**	**-1.26 (-1.89, -0.63)**	**0.33**	**-3.90**	**0.000**	**-0.13 (-0.24, -0.01)**	**0.06**	**-2.11**	**0.035**	**-0.18 (-0.28, -0.09)**	**0.05**	**-3.68**	**0.000**
Model 3§	**-3.16 (-4.95, -1.37)**	**0.91**	**-3.46**	**0.001**	**-0.83 (-1.29, -0.36)**	**0.24**	**-3.50**	**0.000**	**-0.25 (-0.46, -0.03)**	**0.11**	**-2.26**	**0.024**	**-0.98 (-1.61, -0.34)**	**0.33**	**-3.02**	**0.003**	0.06 (-0.18, 0.06)	0.06	0.99	0.324	**-0.14 (-0.24, -0.04)**	**0.05**	**-2.73**	**0.006**
Social isolation	B (95% CI)	SE	Z	p	B (95% CI)	SE	Z	p	B (95% CI)	SE	Z	p	B (95% CI)	SE	Z	p	B (95% CI)	SE	Z	p	B (95% CI)	SE	Z	p
Model 1†	**-2.20 (-3.00, -1.41)**	**0.41**	**-5.43**	**0.000**	**-0.50 (-0.70, -0.30)**	**0.10**	**-4.99**	**0.000**	**-0.15 (-0.24, -0.07)**	**0.04**	**-3.51**	**0.000**	**-0.81 (-1.06, -0.55)**	**0.13**	**-6.23**	**0.000**	**-0.14 (-0.19, -0.09)**	**0.03**	**-5.27**	**0.000**	**-0.10 (-0.15, -0.05)**	**0.02**	**-4.20**	**0.000**
Model 2‡	**-1.30 (-2.08, -0.59)**	**0.37**	**-3.57**	**0.000**	**-0.25 (0.43, -0.06)**	**0.09**	**-2.63**	**0.009**	-0.04 (-0.12, 0.04)	0.04	-1.08	0.281	**-0.51 (-0.74, -0.28)**	**0.12**	**-4.32**	**0.000**	**-0.08 (-0.13, -0.03)**	**0.02**	**-3.43**	**0.001**	**-0.48 (-0.09, -0.01)**	**0.02**	**-2.23**	**0.026**
Model 3§	**-0.85 (-1.55**	**0.36**	**-2.35**	**0.019**	-0.12 (-0.31	0.09	-1.32	0.187	-0.01 (-0.08	0.04	-0.17	0.868	**-0.34 (-0.57**	**0.12**	**-2.93**	**0.003**	**-0.06 (-0.11**	**0.02**	**-2.62**	**0.009**	**-0.03 (-0.07**	**0.02**	-1.27	0.203

, -0.14)	, 0.06)	, 0.07)	**, -0.11)**	**, -0.02)**	**, 0.02)**

Note. Time was introduced in the models as months. Abbreviations: CI=Confidence Interval; GEE= Generalized Estimating Equation; SE=Standard Error. In bold, statistically significant values.

† Model 1 adjusted for time.

‡ Model 2 adjusted for time, gender, age and years of education.

§ Model 3 adjusted for time, gender, age, years of education, stroke, diabetes, physical activity, disability, alcohol consumption, and loneliness or social isolation as appropriate.

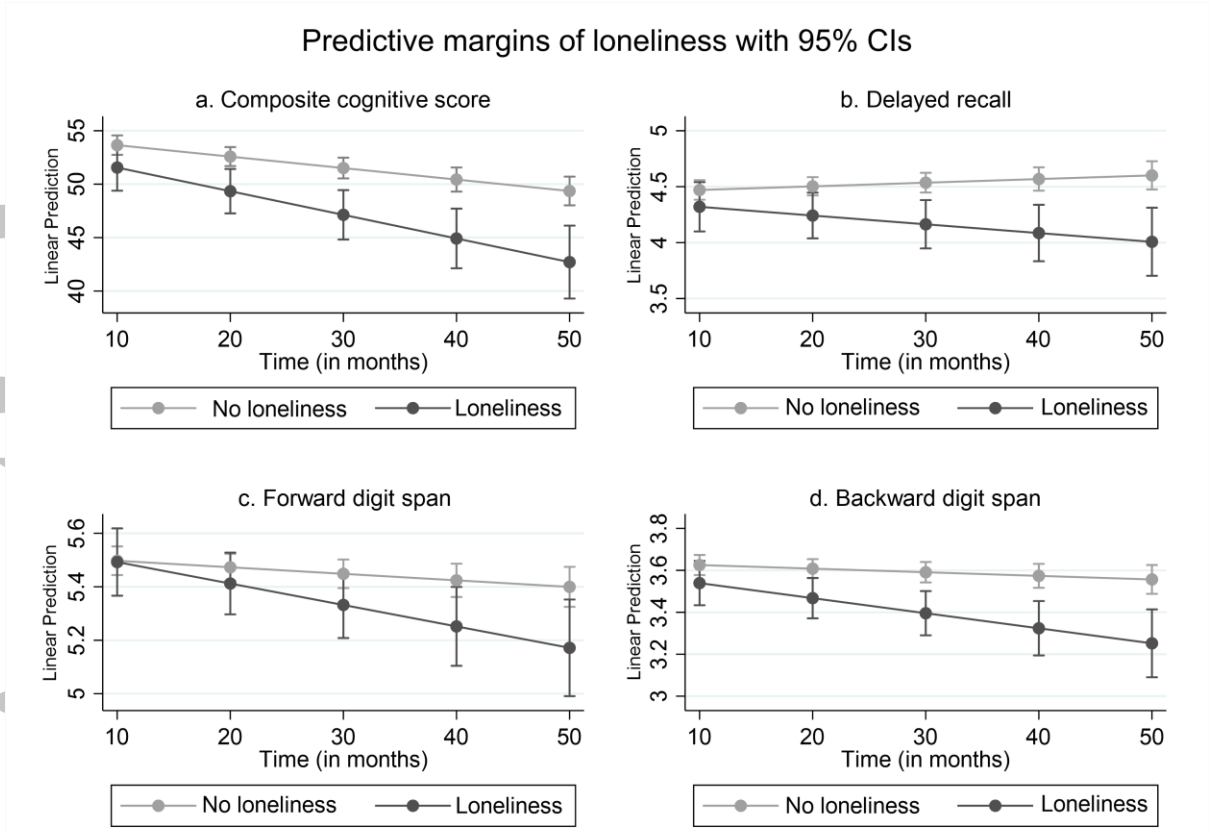

FIGURE 1. Predictive estimates and 95% CI for cognitive outcomes over time according to loneliness status.
Notes. Abbreviation= CI: Confidence Interval. Margins were computed from the fully-adjusted GEE model (including interactions) when fixing covariates at their means. Pairwise comparisons using *Bonferroni* correction led to significant differences on predicted estimates between loneliness (vs no loneliness) and time in the composite cognitive score (p=0.025, p=0.002, and p=0.001 at 30, 40, and 50 months respectively) and backward digit span (p=0.039 and p=0.037 at 40, and 50 months respectively).