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CLINICAL INVESTIGATION

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The effect of anxiety on all-cause dementia: A longitudinal analysis from the Hunter Community Study

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Abstract

Background: Anxiety is common, however, the effect of chronicity of anxiety on dementia has not been explored. This study aims to assess the longitudinal relationship between chronic versus resolved versus new onset anxiety, and all-cause dementia risk.

Methods: A total of 2132 participants with mean age 76 years from the Hunter Community Study were recruited. Anxiety was measured using Kessler Psychological Distress Scale (K10). Dementia was defined as per International Classification of Disease—10 codes. The Fine–Gray subdistribution hazard model was computed to assess dementia risk, while adjusting for the competing risk of death.

Results: Chronic anxiety and new onset anxiety at follow-up were associated with all-cause dementia risk (HR 2.80, 95% CI 1.35–5.72 and HR 3.20, 95% CI 1.40–7.45 respectively) with an average time to dementia diagnosis of 10 years (SD = 1.7) whereas resolved anxiety was not. In subgroup analyses, these results were driven particularly by chronic and new anxiety among participants below the age of 70 years (HR 4.58, 95% CI 01.12–18.81 and HR 7.21, 95%CI 1.86–28.02 respectively). Sensitivity analyses imputing missing data and addressing reverse causation gave very similar results.

Conclusion: Chronic and new anxiety were associated with increased risk of all-cause dementia, and this association was significant in those 70 years and younger. However, the resolved anxiety at follow-up reduced the risk, similar to that of the non-exposed group. These results suggest that timely management of anxiety may be a viable strategy in reducing the risk of dementia.

KEYWORDS

anxiety, chronic anxiety, dementia, dementia risk, longitudinal study

See related Editorial by Karp and Lenze.

INTRODUCTION

Globally, there were over 55 million people living with dementia in 2020, and this number is estimated to increase to 78 million by 2030 and 139 million by 2050.[1] The global cost of dementia was estimated to be US$ 1.3 trillion in 2019 and is projected to rise to US$ 2.8 trillion by 2050.[1] Dementia was the seventh leading cause of death globally and the second leading cause of death in high-income countries in 2020.[2] With the increasing social and economic burden of dementia in the community, the focus has been directed toward prevention, targeting possible modifiable risk factors including anxiety.

Previous studies reporting the relationship between anxiety and dementia have largely measured anxiety at one time point (baseline),[12–16,22,30,31] with inconclusive results. This could be due to significant heterogeneity in the measurement of anxiety and dementia, the follow-up period, and the characteristics of participants, such as age. Moreover, these studies did not address the persistence of anxiety (chronic vs. resolved vs. new onset) on dementia risk, which could also contribute to the inconclusive results. Occasional anxiety is a normal response to stress or fear, and is usually transient,[25] whereas chronic anxiety is associated with cardiovascular disease,[3] neuronal apoptosis, and neuronal atrophy,[17–19] all of which are well-known risk factors for dementia.

Huang et al. suggested that the risk of cardiovascular disease in older adults with anxiety was lower when compared with a control population of the same age without anxiety, whereas the risk is higher in young adults,[20] suggesting that the age of exposure to anxiety might also play a role in dementia risk. However, this has not been explored previously.

We hypothesized that the chronicity of anxiety could have an impact on dementia risk and the age of exposure might also have an effect. Therefore, this study aimed to explore (i) the effect of chronic versus resolved versus new onset anxiety and (ii) the effect of timing of exposure of anxiety on all-cause dementia risk in an existing, longitudinal cohort of community-dwelling older Australians.

Key points

- Chronic and new onset anxiety are associated with increased risk of dementia.
- Resolved anxiety cases have similar risk of dementia compared to participants without anxiety.
- Successful management of anxiety may play a role in reducing dementia risk.

Why does this paper matter?

To our knowledge, this is the first study assessing the effect of persistence of anxiety (chronic vs. resolved vs. new anxiety) and the timing of exposure to anxiety on dementia risk. This study found that both chronic and new anxiety at follow-up were associated with increased risk of all-cause dementia, and the association was stronger in participants exposed to anxiety below the age of 70 years. However, where anxiety had been resolved, there was no association with dementia risk. These results suggest the possibility of anxiety as a modifiable risk factor for dementia and the timely management of anxiety helps to reduce the risk of dementia.

METHODS

Study design and participants

For this study, longitudinal data from the Hunter Community Study (HCS)[4] was used, with approval from the University of Newcastle Human Research Ethics Committee. Informed consent to participate in the study and to linkage with administrative health data was obtained from the participants. Participants aged between 55 to 85 who resided in Newcastle, New South Wales, Australia were randomly selected from the NSW state electoral roll and recruited between December 2004 and December 2007. Persons who did not speak English or who were residents of an aged care facility were excluded. HCS includes three waves of contact (wave 1 to 3), 5 years apart. Demographics and health related data were measured at wave 1. For this analysis, we excluded persons with dementia at baseline, that is, self-reported dementia, Alzheimer's dementia, or cognitive impairment at baseline ($n = 1$), missing data for age ($n = 16$), missing data for Kessler Psychological Distress Scale (K10)[7] at wave 1 ($n = 138$), and missing data for K10 at wave 2 ($n = 1031$). The final sample of the present study included 2132 participants (Figure 1).

Measures

Demographics and health data

Participants' demographics data (age, gender, and highest level of education: primary school, high school,

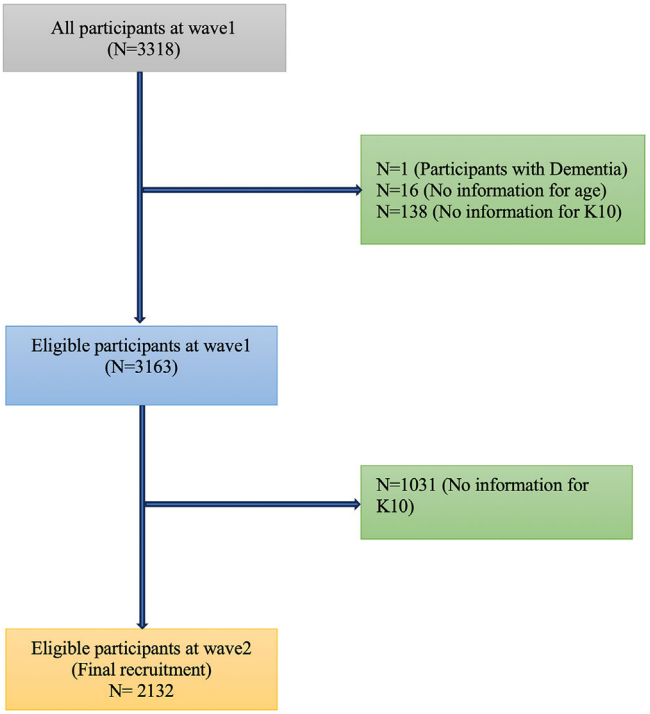

FIGURE 1 Participants recruitment process.

University degree, Postgraduate degree) and health related data (tobacco smoking, alcohol intake, hypertension, diabetes mellitus, hypercholesterolemia, cardiovascular disease, cerebrovascular disease) were collected using self-administered questionnaires at baseline. Health related data were dichotomous (yes/no) except for tobacco smoking and alcohol intake which were categorical. Depression was measured with the Center for Epidemiologic Studies Depression Scale (CES-D score).[5] The score was calculated from the sum of 20 items (ranges from 0 to 60) with a total score of 16 and above indicating depression, coded as a dichotomous variable.

Anxiety symptoms

Anxiety symptoms were assessed using the Kessler Psychological Distress Scale (K10).[7] K10 is a 10-item questionnaire with two main subscale scores: Anxiety (items 2, 3, 5, 6) and Depression (items 1, 4, 7, 8, 9, 10). Each item is scored one to five points, giving a total score ranging from 10 to 50. Anxiety was defined as present if K10 total score was 16 or above and anxiety items were positive (two points or above). The sensitivity and specificity of K10 in identifying anxiety disorder meeting criteria of the DSM-IV or ICD-10 is 0.90 and 0.72 respectively for K10 score of ≥15.[28] Anxiety was measured at baseline (wave 1) and first follow-up (wave 2). The length of time between wave 1 and wave 2 was 5 years. The temporal differences in anxiety were further subdivided into the following subgroups.

1. Chronic: anxiety at both wave 1 and wave 2.
2. Resolved: anxiety only at wave 1.
3. New anxiety: anxiety only at wave 2.

Ascertainment of dementia

The primary outcome, incident all-cause dementia, during the follow-up period (maximum 13 years after the baseline) was identified using International Classification of Disease—10 (ICD 10) codes F00, F01, F02, F03, or G30[8] which were ascertained through linked data from Hunter Area Disease Registers, Hunter New England Area Health Service Medical Records, and the national death index (death register)[4]; and using Anatomical Therapeutic and Chemical codes (ATC)[26] for drugs for dementia from pharmaceutical benefits data provided by the Australian Department of Health and Aged Care.[4] The date of diagnosis was the earliest date of recorded dementia codes regardless of the source of the data.

Statistical analysis

The baseline characteristic of participants who developed dementia and who remained cognitively normal at the last follow-up were computed using Student's *t*-test for continuous data and Chi square test for categorical data.

The confounder variables were selected as per a directed acyclic graph (DAG) (based on current literature on the topic) using online software DAGitty v3.1[6,23] (Supplementary Figure S1). DAGs rigorously map variables and the direction of causal relations among them and provide information about the conditional independencies of the variables using graphical criteria,[23,29] thereby identifying the covariates which are the potential sources of confounding and removing the confounding bias through adjustment.[23,29]

To estimate the probability of incident dementia, the subdistribution hazard of the effect of anxiety groups on the cumulative incidence function (CIF) with death as the competing event over time was analyzed using the Fine and Gray regression model.[9,10] Hazard ratios (HRs) with 95% confidence intervals (CIs) were used to present the results and $p < 0.05$ was considered significant. Three models were built: Model 1—accounting for social demographic data (age and gender), Model 2—adjusted model controlling all variables suggested by the DAG, and Model 3—a sensitivity analysis where dementia and deaths identified within the first 5 years from baseline were excluded

to eliminate the possibility of reverse causation, while still adjusting for all variables in Model 2.

Time to event (in years) was calculated from the date of first entry to the study (wave 1) to the date of first dementia diagnosis or death, with censoring at the last available date (March 31, 2017).

To test the effect of age of exposure of anxiety on dementia risk, the participants were subdivided into three groups based on their baseline age (Group 1: Age 60–70, Group 2: Age 71–80, Group 3: Age 81+). We did not include the participants aged between 55 and 60 in the analysis due to their very low risk of dementia with estimated prevalence at 0.1%.[11] The cumulative incidence functions for each age group were modeled with death as the competing event and the subdistribution hazard was estimated using the Fine and Gray regression model.

We performed two further sensitivity analyses. Firstly, there is the possibility of bias due to missing data, therefore, we analyzed the competing risk analysis of baseline anxiety and dementia with (i) observed cases ($N = 2123$) and (ii) multiple imputations ($N = 3163$) (Supplementary Text S1). Secondly, we assessed the effect of the dose of exposure (the severity of anxiety) on dementia (Supplementary Text S2).

We used SAS software (version 9·4) to perform the statistical analysis.

RESULTS

Figure 1 describes the recruitment process from the Hunter Community Study. A total of 3318 participants took part in wave 1. After excluding participants with dementia at baseline, and those without information for age and K10, there were 3163 eligible participants at wave 1, from which 1031 participants did not have data for K10 at wave 2, leaving 2132 participants (female 53% and male 47%) in this study. The mean age of participants was 76 years with standard deviation (SD) 7 years, of whom 449/2132 (21%) had anxiety at baseline (wave1). Sixty-four participants (3%) developed dementia and 151 (7%) participants died over the mean follow-up of 10 years (SD 1.6). The average onset of dementia was 10 years (SD = 1.7). The baseline characteristics of participants are shown in Table 1; those of missing participants are shown in Supplementary Table S1. Missing participants had lower level of education and higher rate of smoking, alcohol drinking, hypertension, diabetes, cardiovascular and cerebrovascular disease, depression, and baseline anxiety.

Main analysis

Chronic anxiety was associated with an increased risk of all-cause dementia in both Model 1 (HR 2.57, 95% CI 1.27–5.20, p 0.01) and Model 2 (HR 2.80, 95% CI 1.35–5.72, p 0.01) (Table 2). Higher risk of all-cause dementia was found in new anxiety cases at wave 2 (Model 1 – HR 3.20, 95% CI 1.37–7.43, p 0.01 and Model 2 – HR 3.20, 95% CI 1.40–7.45, p 0.01) (Table 2). There was no significant risk of dementia in Resolved cases (Model 1 – HR 1.02, 95% CI 0.41–2.55, p 1.06 and Model 2 – HR 1.06, 95% CI 0.40–2.81, p 0.90) (Table 2). The results of adjusted model (Model 2) of anxiety groups are shown in Figure 2.

Considering age, the age group younger than 70 years old who had chronic anxiety had higher risk of dementia (HR 4.58, 95% CI 01.12–18.81, $p = 0.03$). Similar effects were seen for those younger than 70 years who had anxiety only at follow-up (HR 7.21, 95%CI 1.86–28.02, p 0.004) (Table 3). Anxiety did not have a significant association with dementia risk in the other age groups (Table 3).

Sensitivity analyses

After excluding the participants censored within the first 5 years from baseline (Model 3), a similar increased risk of all-cause dementia was found in both participants with chronic anxiety and new onset anxiety at wave 2 (HR 2.94, 95% CI 1.42–6.11, $p = 0.004$ and HR 2.80, 95% CI 1.16–6.78, $p = 0.02$ respectively) whereas those with anxiety only at baseline did not have significantly increased risk (HR 1.10, 95% CI 0.41–2.92, p 0.85) (Table 2).

In the sensitivity analysis for missing data, both multiple imputations and observed case analysis which tested the association between baseline anxiety (measured at only one time point) and the risk of all-cause dementia revealed similar but attenuated effect sizes (HR 1.24, 95% CI 0.83–1.86, $p = 0.29$ and HR 1.23, 95%CI 0.65–2.36, $p = 0.52$ respectively) (Supplementary Table S4).

There was a graded association with severity of anxiety; participants with anxiety and K10 score 16 to 30 had HR of 1.24 (95% CI 0.61 to 2.54, $p = 0.55$) and those with anxiety and K10 score >30 had HR of 2.62 (95% CI 0.58–11.79, $p = 0.21$) (Supplementary Table S2), although these estimates were not statistically significantly different.

DISCUSSION

To our knowledge, this is the first longitudinal study addressing the association between the temporal difference of anxiety (chronic vs. resolved vs. new onset anxiety) and all-cause dementia risk. Among 2132 cognitively healthy participants, 64 developed dementia and

TABLE 1 Baseline characteristics of participants.

Characteristics	Participants without dementia ($N = 2068$) (97%)	Participants who developed dementia ($N = 64$) (3%)	*p*-value
Age	75 (7)	83 (7)	<0.001
Female	1096 (53%)	30 (47%)	0.33
Highest level of education			0.02
Primary schooling only	31 (1.5%)	4 (7%)	
Secondary schooling completed	513 (25%)	9 (15%)	
Secondary schooling not completed	382 (19%)	14 (23%)	
Trade qualification or TAFE	619 (31%)	19 (32%)	
University or other tertiary study	473 (23%)	14 (23%)	
Tobacco smoking			0.06
Current smokers	137 (7%)	1 (2%)	
Former smokers	897 (44%)	31 (52%)	
Alcohol intake (standard drinks/week)			0.25
0	327 (18%)	8 (15%)	
1–4	1147 (62%)	40 (75%)	
5–7	162 (9%)	3 (6%)	
8–14	120 (6%)	1 (2%)	
>15	105 (6%)	1 (2%)	
Hypertension	902 (45%)	38 (63%)	0.01
Diabetes mellitus	189 (9%)	8 (13%)	0.32
Hypercholesterolemia	807 (40%)	34 (57%)	0.01
Cardiovascular disease	210 (10%)	14 (22%)	0.003
Cerebrovascular disease	59 (3%)	5 (8%)	0.02
Depression	229 (11%)	10 (16%)	0.26
Chronic anxiety	211 (10%)	10 (16%)	
Resolved anxiety	318 (15%)	10 (16%)	
New anxiety at follow-up	108 (5%)	9 (14%)	

Abbreviation: TAFE, technical and further education.

TABLE 2 Association between anxiety groups and incidence all-cause dementia.

	Model 1			Model 2			Model 3		
	HR	95% CI	*p*-value	HR	95% CI	p-value	HR	95% CI	*p*-value
No anxiety ($N = 1418$)	1			1			1		
Chronic anxiety ($N = 202$)	2.57	1.27–5.20	0.01	2.80	1.35–5.72	0.01	2.94	1.42–6.11	0.004
Resolved anxiety ($N = 247$)	1.02	0.41–2.55	0.96	1.06	0.40–2.81	0.90	1.10	0.41–2.92	0.85
New anxiety at follow-up ($N = 85$)	3.20	1.37–7.43	0.01	3.20	1.40–7.45	0.01	2.80	1.16–6.78	0.02

Note: Model 1—adjusted age, gender. Model 2—adjusted Model 1+ depression. Model 3—excluded participant developed dementia within 5 years from baseline, adjusted Model 2 variables.

151 participants died; as expected in a group of this age, death was a powerful competing event for dementia.

Our results indicated that chronic anxiety and new anxiety at follow-up were associated with increased risk of all-cause dementia, with a mean time to diagnosis of 10 years. Our results were somewhat similar to those of Santabárbara and colleagues which showed that anxiety increased the risk of dementia with death as an

important competing risk factor,[12] although their study tested only baseline anxiety and dementia risk, as did most of the other previous studies.[13–16,22,30,31] Our findings are also in line with Brieler et al.[24] who suggested that anxiety disorder was associated with greater risk of dementia. In our study, the risk of dementia among resolved cases were similar to those without anxiety.

Anxiety is linked to vascular disease and dementia pathology via pathways such as neuronal inflammation, cellular apoptosis, brain and hippocampal atrophy, beta amyloid formation and deposition, and cardiovascular disease.[3,17–19] People with anxiety are more likely to engage in unhealthy lifestyle behaviors including unhealthy diet, physical inactivity, and smoking, which in turn can lead to cardiovascular disease,[3] which is strongly associated with dementia. Therefore, these are plausible direct and indirect mechanisms by which anxiety can increase the risk of dementia.

Although some previous studies revealed the link between anxiety and dementia risk, other previous studies found contradictory results. Two studies reported that baseline anxiety was not associated with the risk of dementia or cognitive decline at a later time point[15,30] and one study found that anxiety did not increase the risk of Alzheimer's dementia among people with mild cognitive impairment.[31] Given that previous studies used anxiety measured at a single time point, we suggested that this misclassification was biased toward the null; indeed in an analysis of our data that used only baseline anxiety, our effect sizes were dramatically attenuated toward the null. This might explain the previous conflicting results where some studies found an association,[12–14,16,22] while others did not.[15,30,31] Moreover, there is a substantial variation in recruited population, anxiety measurements, identifying dementia and/or cognitive impairment, and follow-up periods which might also modify the association between anxiety and dementia risk.

We found that being anxious (either chronic or new onset) below the age of 70 years increased the risk of dementia, compared to those aged 70 and above. This was somewhat in agreement with the previous studies showing that being anxious at younger ages was associated with increased risk of cardiovascular disease,[20] and anxiety at middle age was related to all-cause and cardiovascular death.[21] Our cohort did not include people younger than 60, so we were unable to compare our results for the younger range of middle age.

Anxiety is very common in older adults and people with dementia, and therefore, it can be argued that anxiety could be a prodromal symptom of dementia, that is, early or subclinical dementia could cause anxiety. However, the sensitivity analysis in our study excluding both dementia and deaths within the first 5 years from baseline provided nearly identical results of the association, indicating the association between anxiety and dementia may not be explained by reverse causality.

A causal association between anxiety and dementia is also supported by the point estimates that show a dose-response curve, that is, the greater the degree of anxiety, the greater the risk of dementia. We acknowledge that the confidence intervals on these estimates were wide, and that the estimates were therefore not statistically significant, so this requires further confirmation.

Our study has five major strengths. Firstly, our study tested the effect of persistence of anxiety (chronic vs. resolved vs. new onset) on all-cause dementia risk. Secondly, our study used a recognized measure of anxiety (K10, including its anxiety subscale). The co-occurrence

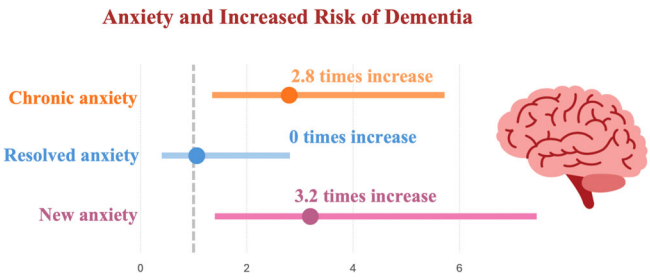

FIGURE 2 Anxiety and increased risk of dementia.

TABLE 3 Association between anxiety groups of different age groups and incidence all-cause dementia.

	Model 2 Chronic anxiety			Model 2 Resolved anxiety			Model 2 New anxiety		
Within group comparison	**HR**	**95% CI**	***p*-value**	**HR**	**95% CI**	***p*-value**	**HR**	**95% CI**	***p*-value**
Age 60–70 years $N = 925$	4.58	1.12–18.81	0.03	0.92	0.11–7.67	0.94	7.21	1.86–28.02	0.004
Age 71–80 years $N = 447$	2.42	0.90–7.25	0.08	1.03	0.22–4.88	0.97	0.98	0.13–7.16	1.0
Age 80+ $N = 91$	0.84	0.24–2.94	0.80	0.56	0.10–5.24	0.61	2.52	0.52–12.32	0.25

Note: Model 1—adjusted age, gender. Model 2—adjusted Model 1+ depression.

of anxiety and depression is very common and therefore, it is sometimes difficult to tease out anxiety from depression. Using the anxiety subscale of K10 together with the total K10 score helped to identify anxiety symptoms effectively. Thirdly, using competing risks analysis accounted for the fact that those who die (especially in an aging cohort) cannot develop dementia and this will bias results. Fourthly, our study tested the effect of anxiety exposure at different stages of life on dementia risk. Finally, we used causal inference methods applying DAG[6,23] to determine the optimal set of confounders to adjust for in our models.

However, there are a few limitations in our study. Most people with dementia were identified through linked data. Therefore, there is a chance of missing cases or dating cases later than when they actually happened; this however would bias toward the null. Secondly, anxiety was identified using K10 score which assessed the anxiety symptoms experienced in the most recent 4 weeks, therefore, its precision over the entire observed period may be questioned. However, a nationally representative longitudinal survey of the Australian population showed that repeated measures of K10 scores did not change substantially over an 8 years follow-up period, suggesting single assessments as useful proxies in the absence of repeated measures.[27] Thirdly, despite the fact that we predicated our exposure on a combination of total K10 score and the anxiety subscale, this may not completely disentangle the co-occurrence of anxiety and depression. Therefore, there is a possibility of residual confounding of depression on the outcome of interest. Fourthly, we did not have information regarding how the anxiety was resolved at the follow-up wave 2. Finally, we lost about 33% of participants at follow-up who had higher rate of anxiety at baseline, which could result in missing participants with dementia and consequently could affect the effect estimate. However, the sensitivity analyses using multiple imputations and observed cases revealed similar results indicating that the loss may not have significant impact on the estimation.

In conclusion, both chronic anxiety and new anxiety at follow-up were associated with increased risk of all-cause dementia especially in those 70 years and younger even after considering mortality as a competing risk and controlling for depression as a confounder. The risk of dementia among resolved anxiety cases was similar to those who had no anxiety. Therefore, these findings support anxiety as a potential modifiable risk factor for dementia and point to the possible role of managing anxiety in middle aged and "young" older adults to reduce the risk of dementia in later life.

AUTHOR CONTRIBUTIONS

All authors participated in conceptualization. KK had the original idea of the study. BN, JB, JA, and XD supervised the project. JA contributed to data curation. KK and XD analyzed the data. KK, BN, JB, JA, and XD participated in data interpretation. KK prepared the draft manuscript. KK, BN, JB, JA, and XD reviewed and edited the manuscript. All authors approved the final manuscript. All authors had access to study data. KK, BN, JB, JA made final decision to publish.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

SPONSOR'S ROLE

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

Supplementary Figure S1. DAG—Variables for adjustment.
Supplementary Table S1. Baseline characteristics of missing participants and recruited participants.
Supplementary Table S2. Association between severity of anxiety and incidence 30 dementia.
Supplementary Table S3. Missing data patterns.
Supplementary Table S4. Sensitivity analysis for missing data (The association between the baseline loneliness and dementia risk).
Supplementary Text S1. Analysis to deal with missing data.
Supplementary Text S2. Analysis to assess the severity of anxiety on all-cause dementia.

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