

Associations of Social Isolation and Loneliness With Later Dementia

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Abstract

Background and Objectives

To investigate the independent associations of social isolation and loneliness with incident dementia and to explore the potential neurobiological mechanisms.

Methods

We utilized the UK Biobank cohort to establish Cox proportional hazard models with social isolation and loneliness as separate exposures. Demographic (sex, age, and ethnicity), socio-economic (education level, household income, and Townsend deprivation index), biological (body mass index, *APOE* genotype, diabetes, cancer, cardiovascular disease, and other), cognitive (speed of processing and visual memory), behavioral (current smoker, alcohol intake, and physical activity), and psychological (social isolation or loneliness, depressive symptoms, and neuroticism) factors measured at baseline were adjusted. Then, voxel-wise brainwide association analyses were used to identify gray matter volumes (GMVs) associated with social isolation and with loneliness. Partial least squares regression was performed to test the spatial correlation of GMV differences and gene expression using the Allen Human Brain Atlas.

Results

We included 462,619 participants (mean age at baseline 57.0 years [SD 8.1]). With a mean follow-up of 11.7 years (SD 1.7), 4,998 developed all-cause dementia. Social isolation was associated with a 1.26-fold increased risk of dementia (95% CI, 1.15–1.37) independently of various risk factors including loneliness and depression (i.e., full adjustment). However, the fully adjusted hazard ratio for dementia related to loneliness was 1.04 (95% CI, 0.94–1.16) and 75% of this relationship was attributable to depressive symptoms. Structural MRI data were obtained from 32,263 participants (mean age 63.5 years [SD 7.5]). Socially isolated individuals had lower GMVs in temporal, frontal, and other (e.g., hippocampal) regions. Mediation analysis showed that the identified GMVs partly mediated the association between social isolation at baseline and cognitive function at follow-up. Social isolation–related lower GMVs were related to underexpression of genes that are downregulated in Alzheimer disease and to genes that are involved in mitochondrial dysfunction and oxidative phosphorylation.

Discussion

Social isolation is a risk factor for dementia that is independent of loneliness and many other covariates. Social isolation–related brain structural differences coupled with different molecular functions also support the associations of social isolation with cognition and dementia. Social isolation may thus be an early indicator of an increased risk of dementia.

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Glossary

AD = Alzheimer disease; **BMI** = body mass index; **FDR** = false discovery rate; **GMV** = gray matter volume; **GO** = Gene Ontology; **HR** = hazard ratio; **ICD-10** = International Classification of Diseases–10; **KEGG** = Kyoto Encyclopedia of Genes and Genomes; **MNI** = Montreal Neurological Institute; **PERM** = percentage of excess risk mediated; **PLS** = partial least squares; **TIV** = total intracranial volume.

Social isolation (an objective measure of social relationships) and loneliness (subjectively perceived social isolation) are serious but underappreciated public health problems that are particularly associated with old age.¹ Dementia is a major cause of disability in the elderly, affecting more than 46 million people worldwide in 2015, and is estimated to increase to 131.5 million by 2050.² The influence of social isolation and loneliness on dementia remains unclear. Whereas in some studies social isolation but not loneliness was associated with an increased risk of dementia and cognitive decline,^{3,4} other studies found the opposite result.⁵ One possibility for this discrepancy is that the associations may be affected by risk factors that were not consistently considered in previous studies.

Moreover, little is known about the underlying neurobiological mechanisms. The social brain hypothesis posits that the evolution of the human brain is driven by increasingly complex social selection pressures.⁶ Only a paucity of studies has explored the neural underpinnings of social isolation and loneliness. Structural and functional changes in several brain regions including prefrontal, temporal, and parietal cortices, amygdala, hippocampus, striatum, and ventral tegmental area have been reported.^{7–10} Spreng et al.¹¹ reported that loneliness is associated with the default mode network. However, the findings are mixed, probably due to the heterogeneity of methods and study design.¹²

Gene expression may also be a factor. Social factors may play a significant role in regulating the transcriptional activity of the human genome.¹³ Previous gene expression studies in the postmortem nucleus accumbens and dorsolateral prefrontal cortex revealed that loneliness-related differentially expressed genes were associated with Alzheimer disease (AD) and immune dysfunction.^{14,15} One recent approach leveraged brain-wide gene expression atlases to link molecular function to macroscale brain organization,¹⁶ which was helpful to understand disease-related brain alterations, and has been useful for neurodegenerative diseases.¹⁷

With this background, we aimed to examine the separate associations of social isolation and loneliness with incident dementia after controlling for various confounders such as biological and psychological factors using an extremely large cohort of middle-aged and older adults. We investigated the neuroanatomical correlates of social isolation and of loneliness and tested whether the identified brain differences could explain the associations of social isolation and loneliness at

baseline with cognitive function at follow-up. We also analyzed gene expression to provide evidence about which biological processes or functional pathways were linked to social isolation– and loneliness-related brain differences. The associations between brain differences related to social isolation or to loneliness and AD-related genes were specifically examined.

Methods

Study Design and Participants

The workflow of this study is summarized in Figure 1. The UK Biobank is a prospective epidemiologic study that involves >500,000 individuals recruited in 22 centers across the United Kingdom between 2006 and 2010.¹⁸ The study has collected extensive questionnaire data, physical measurements, and biological samples. A subset of the cohort has been invited back to collect multimodal imaging data and repeat behavioral assessments since 2014. All participants are followed up for health conditions through linkage to national electronic health–related datasets. The health follow-up data used in the current study started at enrollment and ended on January 31, 2021. In this study, we restricted behavioral analyses to participants who had complete data on baseline social isolation, loneliness, and cognitive function, and incident dementia ($n = 462,619$). Neuroimaging analyses were performed in 32,263 participants with quality-controlled MRI data and complete behavioral measures. The average time interval between baseline and the imaging visit was 8.8 (SD 1.7) years.

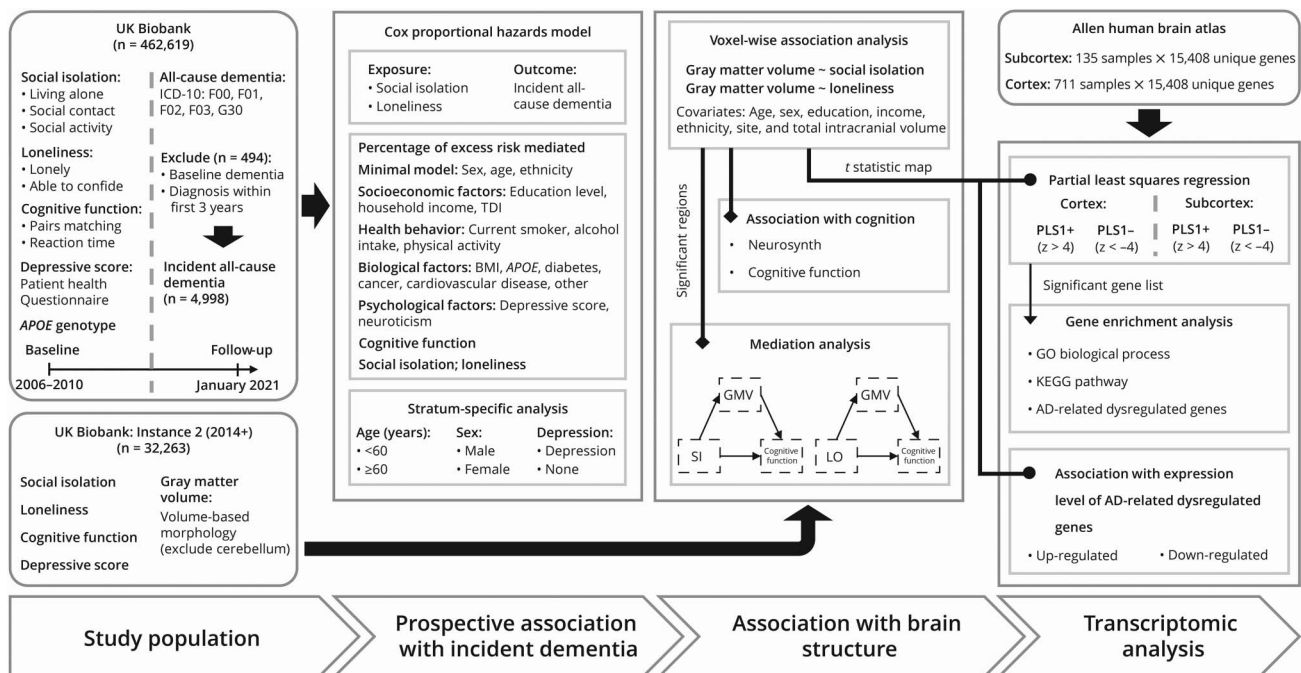
Standard Protocol Approvals, Registrations, and Patient Consents

All participants from the UK Biobank provided informed consent and the ethical approval was from the North West Multi-Centre Research Ethics Committee. The study was conducted under the UK Biobank application number 19542.

Defining Social Isolation and Loneliness

Social isolation was assessed with 3 dichotomous questions of living alone, social contact (1 = less than monthly), and participation in social activities (1 = less than weekly), as in a previous national survey.¹⁹ Loneliness was constructed from 2 questions that were similar to the questions in the revised UCLA loneliness scale²⁰: often feeling lonely (1 = yes) and frequency of confiding in close people (1 = less than once every few months). In the main analyses, social isolation and loneliness were classified into 2 categories, respectively. An individual was defined as socially isolated if he or she scored 2 or 3 and was defined as lonely if he or she scored 2.²¹ In

Figure 1 Study Flowchart



Overview of the study population and analyses conducted in this study. AD = Alzheimer disease; BMI = body mass index; GMV = gray matter volume; GO = Gene Ontology; KEGG = Kyoto Encyclopedia of Genes and Genomes; LO = loneliness; SI = social isolation; TDI = Townsend deprivation index.

addition, to test the potential dose-dependent associations of social factors with dementia risk and brain structure, sensitivity analyses were performed using 3-category variables (least isolated = 0, moderately isolated = 1, most isolated = 2 or 3; least lonely = 0, moderately lonely = 1, most lonely = 2).

Ascertainment of Dementia

All-cause dementia was identified as ICD-10 codes F00, F01, F02, F03, or G30 of the first occurrence data fields generated by the UK Biobank,²² which were ascertained by the combination of primary care, hospital inpatient, death register, and self-reported data. The date of diagnosis was set as the earliest date of dementia codes recorded regardless of source used. Prevalent dementia cases were defined as the date of diagnosis occurring within the first 3 years of follow-up or self-reported dementia, AD, or cognitive impairment at baseline, and these cases were excluded to avoid possible reverse-causation bias (n = 494). The sources of incident all-cause dementia cases are listed in eTable 1 (links.lww.com/WNL/C15).

Assessment of Cognitive Function

Pairs matching and reaction time tests were administered to ≈500,000 participants at baseline and to >40,000 participants at the imaging visit. In the first test, respondents were asked to identify matches from 6 pairs of cards after they had memorized their positions. The number of incorrect matches was recorded, with a greater number reflecting poorer visual memory. The card game Snap had participants press a button when 2 simultaneously presented cards matched, with shorter reaction time representing faster speed of processing. These 2

tests have been used in aging-related studies²³ and shown predictive value for dementia.²⁴ The raw scores were logarithmically transformed due to skewed distribution. As all cognitive tests in the UK Biobank loaded on a single factor²⁵ and in order to reduce measurement error, we standardized the separate scores and averaged them to yield a composite cognitive score to use in analyses, as in previous studies.²⁶

Structural MRI Data

Neuroimaging data were collected across 3 dedicated, identical imaging centers. The detailed MRI acquisition protocol has been described elsewhere.²⁷ All structural MRI data were preprocessed with the Statistical Parametric Mapping software version 12²⁸ using the CAT12 toolbox²⁹ with default settings, including the use of high-dimensional spatial normalization with an already integrated Dartel template in Montreal Neurologic Institute (MNI) space. All images were subjected to nonlinear modulations and corrected for each individual head size. Images were then smoothed with an 8-mm full width at half maximum Gaussian kernel with a resulting voxel size of 1.5 mm³. We focused our analyses on cortical and subcortical regions excluding the cerebellum.

Transcriptomic Data

We used transcriptomic data from 6 neurotypical adult brains in the Allen Human Brain Atlas. Tissue samples in the left hemisphere were used as right hemisphere data and were only available for 2 donors. Standard preprocessing steps included probe-to-gene reannotation, intensity-based data filtering, probe selection by mean, separating tissue samples into

subcortical and cortical regions, and within-donor normalization, as reported previously.³⁰ We obtained expression values for 15,408 unique genes at 711 cortical and 135 subcortical locations separately.

Covariates

Covariates were chosen based on the literature and availability at baseline. Socioeconomic factors included educational attainment (no secondary education, secondary education, university degree), annual household income (<£31,000, ≥£31,000) and Townsend deprivation index representing area-level deprivation (≥2.00, -2.00 to 1.99, <-2.00). Health behaviors were obtained by self-rated questions: current smoker, alcohol intake (<3, ≥3 times/week), and moderate/vigorous physical activity (<1, 1–3, ≥4 d/wk). Biological factors comprised body mass index (BMI) (<25, 25–30, ≥30), APOE genotype (ε4 noncarrier, carrier, homozygous; eMethods 1, links.lww.com/WNL/C15), diabetes, cancer, cardiovascular disease (e.g., heart attack, angina, stroke, high blood pressure) and any other serious medical conditions diagnosed by a doctor. Depressive symptoms over the past 2 weeks were measured by 4 items from the Patient Health Questionnaire³¹: depressed mood, uninterest/absence of enthusiasm, tenseness/restlessness, and tiredness/lethargy. Neuroticism was assessed by 11 out of 12 available items (excluding loneliness) from the brief Eysenck Personality Inventory Neuroticism scale.³²

Data Availability

Data from the UK Biobank are available to eligible researchers on the website (www.ukbiobank.ac.uk). Data from the Allen Human Brain Atlas are publicly available (<https://human.brain-map.org/static/download>).

Statistical Analysis

Cox Proportional Hazard Model

Associations of social isolation and loneliness with dementia incidence were investigated using Cox proportional hazard models with age as a timescale. The results are presented as hazard ratios (HRs) and 95% CIs. The proportional hazard assumptions were checked using Schoenfeld residuals and no major violations were observed. All the models were adjusted for age, sex, and ethnicity. To assess the extent to which baseline covariates explained the associations of social isolation and loneliness with incident dementia, the percentage of excess risk mediated (PERM)³³ was estimated by $[\text{HR}_{(\text{age, sex, and ethnicity adjusted})} - \text{HR}_{(\text{age, sex, ethnicity, and risk factor adjusted})}] / [\text{HR}_{(\text{age, sex, and ethnicity adjusted})} - 1] \times 100$ for the following 6 groups of explanatory variables: (1) socioeconomic (education level, household income, and Townsend deprivation index); (2) health behavioral (current smoker, alcohol intake, and physical activity); (3) biological (BMI, APOE genotype, diabetes, cancer, cardiovascular disease, and any other); (4) psychological factors (depressive symptoms and neuroticism); (5) cognitive function; and (6) loneliness (for social isolation as the exposure) or social isolation (for loneliness as the exposure). A full adjustment model including all covariates was conducted. Covariates were treated as

categorical variables with missing values as a separate category. Collinearity diagnostic tests were performed to check that collinearity was not present and that variable inflation factors were <2.5. We performed subgroup analyses to assess potential modification effects by sex (men or women) and age (<60 or ≥60 years) and a sensitivity analysis using complete cases to test the robustness. In order to further examine the effect of depression, we also conducted a subgroup analysis separately for participants with and without a diagnosis of depression at baseline. Antidepressant medication was also adjusted in the depressive group (eMethods 2, links.lww.com/WNL/C15).

Whole-Brain and Voxel-wise Analysis

Linear regression models were used to investigate the cross-sectional associations of social isolation and loneliness with gray matter volume (GMV). Age, education, and income at the imaging visit, sex, ethnicity, site, and total intracranial volume (TIV) were used as covariates of no interest. Multiple comparison correction was performed at the voxel level with a $P^{\text{FDR}} < 0.05$. A significant cluster was defined on the basis of an 18-connectivity criterion³⁴ and having more than 217 voxels falling into the 90% CI of the smoothing kernel voxels.³⁰ Three sensitivity analyses were performed: (1) excluding participants with dementia at any time ($n = 29$); (2) also controlling for loneliness or social isolation; (3) also controlling for depressive symptoms. The significant GMVs were decoded for cognitive functions using the Neurosynth meta-analysis toolbox³⁵ and visualized on a word-cloud plot (eMethods 3, links.lww.com/WNL/C15). We also examined the cross-sectional associations between the significant GMVs and cognitive function in the UK Biobank by partial correlation analysis controlling for the same covariates as in the whole-brain analysis. Finally, the mediation effect of the significant GMVs on the association between social isolation/loneliness at baseline and cognitive function at the imaging visit was examined. Age, education, and income at baseline, time interval between baseline and the imaging visit, sex, ethnicity, site, and TIV were adjusted. The significance of the mediation was estimated by 10,000 bias-corrected bootstrapping.

Transcriptomic Analysis

If significant GMVs associated with social isolation and with loneliness were identified, partial least squares (PLS) regression was used to relate the unthresholded t statistic brain map (the response variable) to the gene expression data (predictor variable). The response variable was calculated by the average t value of a spherical region with a radius of 4 mm centered by the MNI coordinates of each gene expression sampling site.³⁰ PLS was performed for cortical and subcortical regions separately. The first PLS component (PLS1) was the linear combination of gene expression values maximizing the covariance between the expression profile and GMV differences. The significance of the variance explained by PLS1 was assessed by permutation (5,000 times), in which PLS was recomputed using null t statistic maps obtained by label shuffling for social isolation or loneliness (denoted as P_{perm}).

Bootstrapping (5,000 times) was used to estimate the variability of each gene's PLS1 weight and the ratio of the weight to its bootstrapped standard error was used to calculate the z score.³⁰

Genes with PLS1 weights $z > 4$ (PLS1+) or $z < -4$ (PLS1−) (all $p_{\text{FDR}} < 0.001$) were used to calculate enrichments in both Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways and Gene Ontology (GO) terms of biological processes (eMethods 4, links.lww.com/WNL/C15). False discovery rate (FDR) correction for KEGG and GO terms simultaneously was used to determine the significance ($p_{\text{FDR}} < 0.05$). We examined whether AD-related dysregulated genes, including 2,444 upregulated and 2,978 downregulated genes, reported by a recent systematic integrated analysis,³⁶ were expressed most in regions that were morphometrically correlated with social isolation (eMethods 5). We also investigated the relationship of GMV differences with the average expression level of up- and downregulated AD-related genes by Spearman correlation, respectively. The significance was tested by permutation, in which the null distribution was defined by 5,000 random t statistic maps described above.

Results

Demographics

The characteristics of 462,619 participants are shown in Table 1. At baseline, 41,886 (9%) individuals reported being socially isolated and 29,036 (6%) of individuals felt lonely. Compared with controls, both isolated ($t[342,868] = 9.55$, Cohen $d = 0.04$, $p < 0.001$) and lonely individuals ($t[342,868] = 4.76$, Cohen $d = 0.06$, $p < 0.001$) had worse cognitive function after controlling for age, sex, ethnicity, education, and income. Depressive symptoms were significantly associated with cognitive function ($r_p[318,891] = 0.04$, $p < 0.001$) after controlling for the same covariates. During a mean follow-up of 11.7 (SD 1.7) years, 4,998 participants developed dementia. At the imaging visit, 32,263 individuals (mean [SD] age 63.5 [7.5] years, 52% female) were included, in which 2,371 (7%) were socially isolated and 1,503 (5%) were lonely (eTable 2, links.lww.com/WNL/C15).

Social Isolation but Not Loneliness Is Associated With All-Cause Dementia

After adjustment (i.e., removal as covariates of no interest) for age, sex, and ethnicity, the HR for the incidence of all-cause dementia was 1.64 (95% CI, 1.51–1.78) for social isolation compared with no social isolation. Further adjustment for different risk factors attenuated the association (PERM 5%–30%). The overall attenuation after adjustment for all covariates was 59% to 1.26 (95% CI, 1.15–1.37; Figure 2). In contrast, the minimally adjusted HR for loneliness was 1.55 (95% CI, 1.40–1.71), but reduced to nonsignificance when all risk factors were included ($p = 0.44$). Adjustment for depressive symptoms had the greatest effect on the association between loneliness and dementia, which was decreased by 75% (Figure 2).

Consistent findings were found in the complete cases (social isolation: fully adjusted HR 1.20 [95% CI, 1.02–1.42], loneliness: fully adjusted HR 1.07 [95% CI, 0.88–1.31]; eFigure 1, links.lww.com/WNL/C15). Subgroup analyses found that the association between social isolation and dementia was consistent across sex (in women: fully adjusted HR 1.24 [95% CI, 1.09–1.40]; in men: fully adjusted HR 1.26 [95% CI, 1.12–1.42]; eFigure 2). However, the association was only significant in the elderly group (mean [SD] 64.6 [2.9] years, 43% of the sample; fully adjusted HR 1.28 [95% CI, 1.16–1.40]; eFigure 3). Furthermore, the association was only significant in the group without depression (fully adjusted HR 1.27 [95% CI, 1.15–1.41]; eFigure 4). In the sensitivity analysis using 3-category variables, the risk of all-cause dementia was significantly higher in the most isolated group than in the least isolated group, which was robust in the full adjustment model (HR 1.27 [95% CI, 1.16–1.39]) and in complete cases (HR 1.22 [95% CI, 1.03–1.45]; eFigure 5).

Social Isolation–Related Brain Structures and the Association With Cognition

Whole-brain analyses revealed that the volumes of brain structures including the medial temporal lobe, hippocampus, middle temporal gyrus, fusiform gyrus, angular gyrus, and ventromedial prefrontal cortex (e.g., gyrus rectus), and subcortical regions such as the amygdala and thalamus, were negatively associated with social isolation (Figure 3A and eTable 3, links.lww.com/WNL/C15). The total volumes of the identified regions were significantly lower in socially isolated individuals ($t[32,253] = -7.92$, Cohen $d = 0.17$, $p < 0.001$). Similar regions were found when the most isolated individuals were compared with the least isolated ones (eFigure 6). The findings were robust if patients with dementia were excluded (eFigure 7) and similar brain regions were found when further adjusted for loneliness (eFigure 8) or depressive symptoms (eFigure 9).

Using Neurosynth, we found that the significant regions where GMV was smaller in socially isolated individuals than controls tend to be involved in memory and learning tasks (Figure 3B and eTable 4). In the UK Biobank, the total GMV of the significant brain regions was associated with cognitive function at the imaging visit ($r_p[30,469] = -0.04$, $p < 0.001$; Figure 3C), and significantly mediated the association between social isolation at baseline and cognitive function at the imaging visit (path ab : $\beta = 0.003$, 4% of the total effect size, $p < 0.001$; Figure 4).

Gene Expression Profiles in the Brain Are Related to the Volume Differences in the Brain That Are Related to Social Isolation

In cortical regions, the PLS1 was significant (i.e., explained 15% of the variance of social isolation–related structural changes; $p_{\text{perm}} < 0.05$). The PLS1 in subcortical regions was not significant ($p_{\text{perm}} = 0.46$). Therefore, we focused on the PLS1 weights in cortical regions in further analyses. Based on the normalized PLS1 weights, there were 2,029 genes in the PLS1+ gene set ($z > 4$) and 1,048 genes in the PLS1− gene set

Table 1 Characteristics of Study Population at Baseline in the UK Biobank

	All (n = 462,619)	Social isolation at baseline		Loneliness at baseline		Dementia status during follow-up	
		Not isolated (n = 420,733)	Socially isolated (n = 41,886)	Not lonely (n = 433,583)	Lonely (n = 29,036)	No dementia (n = 457,621)	Dementia (n = 4,998)
Age at baseline, y	57.0 (8.1)	57.0 (8.1)	57.1 (7.8)	57.0 (8.1)	56.4 (7.9)	56.9 (8.1)	65.0 (4.5)
Men	209,975 (45.4)	189,783 (45.1)	20,192 (48.2)	196,126 (45.2)	13,849 (47.7)	207,318 (45.3)	2,657 (53.2)
White	440,872 (95.3)	401,773 (95.5)	39,099 (93.3)	413,891 (95.5)	26,981 (92.9)	436,068 (95.3)	4,804 (96.1)
College or university degree	153,040 (33.1)	140,452 (33.4)	12,588 (30.1)	145,773 (33.6)	7,267 (25.0)	152,019 (33.2)	1,021 (20.4)
Annual household income \geq £31,000	212,029 (45.8)	200,133 (47.6)	11,896 (28.4)	202,766 (46.8)	9,263 (31.9)	211,114 (46.1)	915 (18.3)
Townsend deprivation index \geq 2.00	71,365 (15.4)	59,144 (14.1)	12,221 (29.2)	64,166 (14.8)	7,199 (24.8)	70,408 (15.4)	957 (19.1)
Diabetes	23,264 (5.0)	20,084 (4.8)	3,180 (7.6)	20,954 (4.8)	2,310 (8.0)	22,545 (4.9)	719 (14.4)
Cardiovascular disease	136,026 (29.4)	121,661 (29.9)	14,365 (34.3)	125,767 (29.0)	10,259 (35.3)	133,520 (29.2)	2,506 (50.1)
Cancer	35,753 (7.7)	32,298 (7.7)	3,455 (8.2)	33,618 (7.8)	2,135 (7.4)	35,230 (7.7)	523 (10.5)
Other	92,340 (20.0)	82,054 (19.5)	10,286 (24.6)	85,103 (19.6)	7,237 (24.9)	90,672 (19.8)	1,668 (33.4)
Current smoker	47,969 (10.4)	40,137 (9.5)	7,832 (18.7)	42,957 (9.9)	5,012 (17.3)	47,441 (10.4)	528 (10.6)
Alcohol consumption \geq 3 times/week	204,221 (44.1)	190,651 (45.3)	13,570 (32.4)	193,944 (44.7)	10,277 (35.4)	202,255 (44.2)	1,966 (39.3)
Obesity (BMI \geq 30 kg/m ²)	111,803 (24.2)	99,707 (23.7)	12,096 (28.9)	102,659 (23.7)	9,144 (31.5)	110,438 (24.1)	1,365 (27.3)
Moderate/vigorous physical activity <1 d/wk	77,954 (16.9)	66,681 (15.8)	11,273 (26.9)	71,333 (16.5)	6,621 (22.8)	77,028 (16.8)	926 (18.5)
High neuroticism (\geq 8)	58,824 (12.7)	51,572 (12.3)	7,252 (17.3)	48,795 (11.3)	10,029 (34.5)	58,226 (12.7)	598 (12.0)
Depressed mood	21,448 (4.6)	17,371 (4.1)	4,077 (9.7)	15,767 (3.7)	5,681 (19.5)	21,137 (4.6)	311 (6.3)
Uninterest/unenthusiasm	21,451 (4.6)	17,359 (4.2)	4,092 (9.7)	16,350 (3.8)	5,101 (17.6)	21,132 (4.6)	319 (6.3)
Tenseness/restlessness	20,087 (4.3)	16,652 (3.9)	3,435 (8.2)	15,527 (3.6)	4,560 (15.7)	19,796 (4.4)	291 (5.8)
Tiredness/lethargy	55,728 (12.0)	47,381 (11.3)	8,347 (20.0)	47,001 (10.9)	8,727 (30.1)	54,995 (12.1)	733 (14.7)
Depression diagnosis	82,977 (17.9)	73,078 (17.4)	9,899 (23.6)	74,152 (17.1)	8,825 (30.4)	81,993 (17.9)	984 (19.7)
Antidepressant medication	33,564 (7.3)	28,867 (6.9)	4,697 (11.2)	29,231 (6.8)	4,243 (14.6)	32,850 (7.2)	714 (14.3)
Cognitive function ^a	0.0 (0.8)	-0.01 (0.8)	0.1 (0.8)	0.0 (0.8)	0.04 (0.8)	0.0 (0.8)	0.4 (0.8)
APOE ϵ 4 carrier ^b	115,395 (24.9)	105,462 (25.1)	9,933 (23.7)	108,419 (25.0)	6,976 (24.1)	112,927 (24.7)	2,424 (48.5)

Abbreviation: BMI = body mass index.

Values are mean (SD) or n (%).

^a The composite score of pairs matching and reaction time tests.^b APOE ϵ 2/4, ϵ 3/4, and ϵ 4/4 were collated as ϵ 4 carrier here.

($z < -4$) (all $p_{\text{FDR}} < 0.001$; eFigure 10). After FDR correction, the PLS1+ gene set was enriched in 38 biological processes, such as mitochondrion organization and oxidative phosphorylation, and 6 KEGG pathways, such as Parkinson disease and Alzheimer disease (Figure 5A and eTable 5, links.lww.com/WNL/C15). No significant enrichment results were found for the PLS1- gene set.

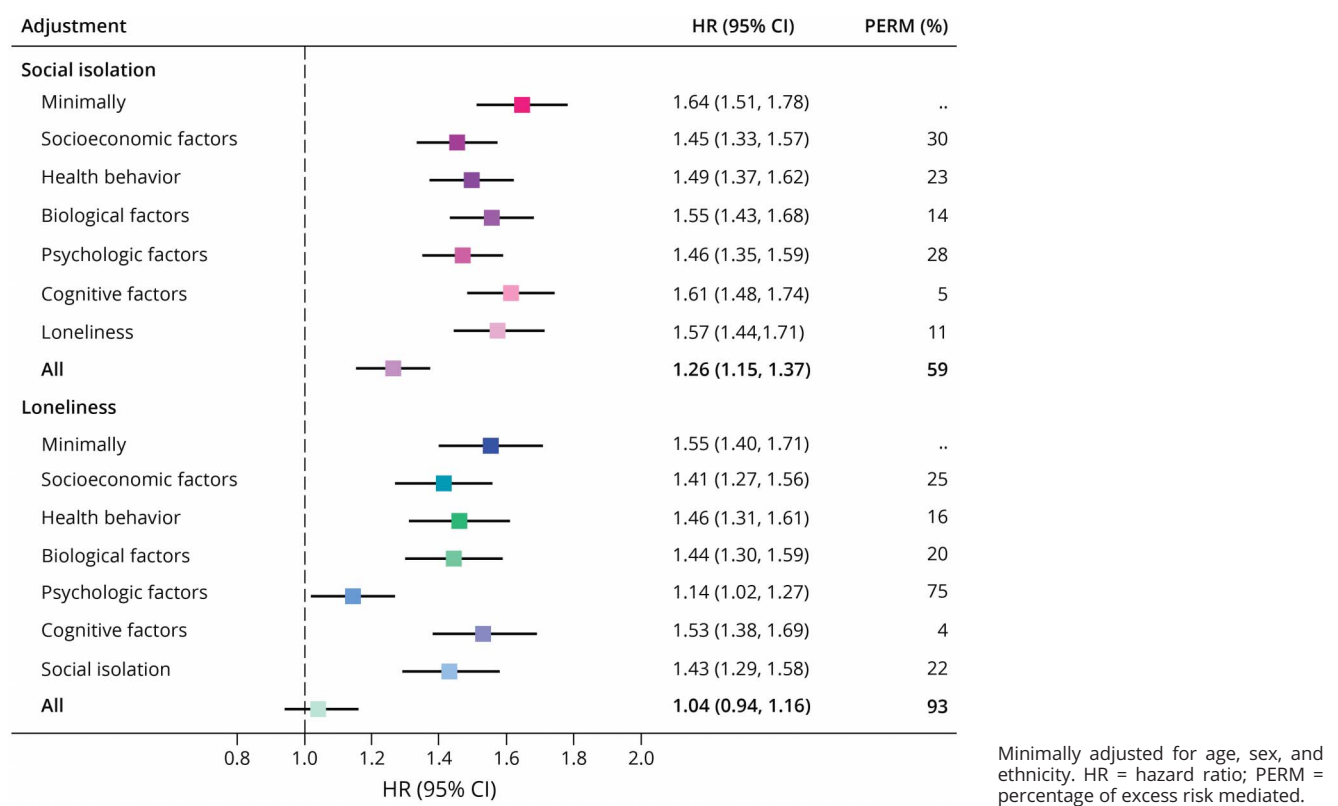
Moreover, the PLS1+ gene set was highly enriched among genes that were recently reported as underexpressed in post-mortem brain tissue from patients with AD ($p_{\text{FDR}} < 0.001$; eTable 6, links.lww.com/WNL/C15). Social isolation-related

differences in regional GMVs were positively associated with cortical gene expression of downregulated AD-related genes ($r_{\text{s}}[711] = 0.13$, $p_{\text{perm}} = 0.02$; Figure 5B) (i.e., genes that are downregulated in AD are underexpressed in regions with higher levels of differences related to social isolation). No significant spatial correlation with upregulated AD-related genes was found ($p_{\text{perm}} = 0.28$; Figure 5C).

Discussion

This study provides evidence that social isolation but not loneliness is associated with an elevated risk of all-cause

Figure 2 Associations of Social Isolation and Loneliness With Incident All-Cause Dementia and Proportions Attributable to Different Risk Factors (n = 462,619)



dementia. Socially isolated individuals were found to have lower GMVs of brain regions involved in memory and learning, which partly mediated the relationship between social isolation and cognitive function. Transcriptomic analyses found that social isolation-related brain differences were related to genes that were downregulated in AD and to genes that were involved in mitochondrial dysfunction and oxidative phosphorylation. The findings highlight the potential threat of social isolation to cognitive function and risk of dementia, especially in the elderly.

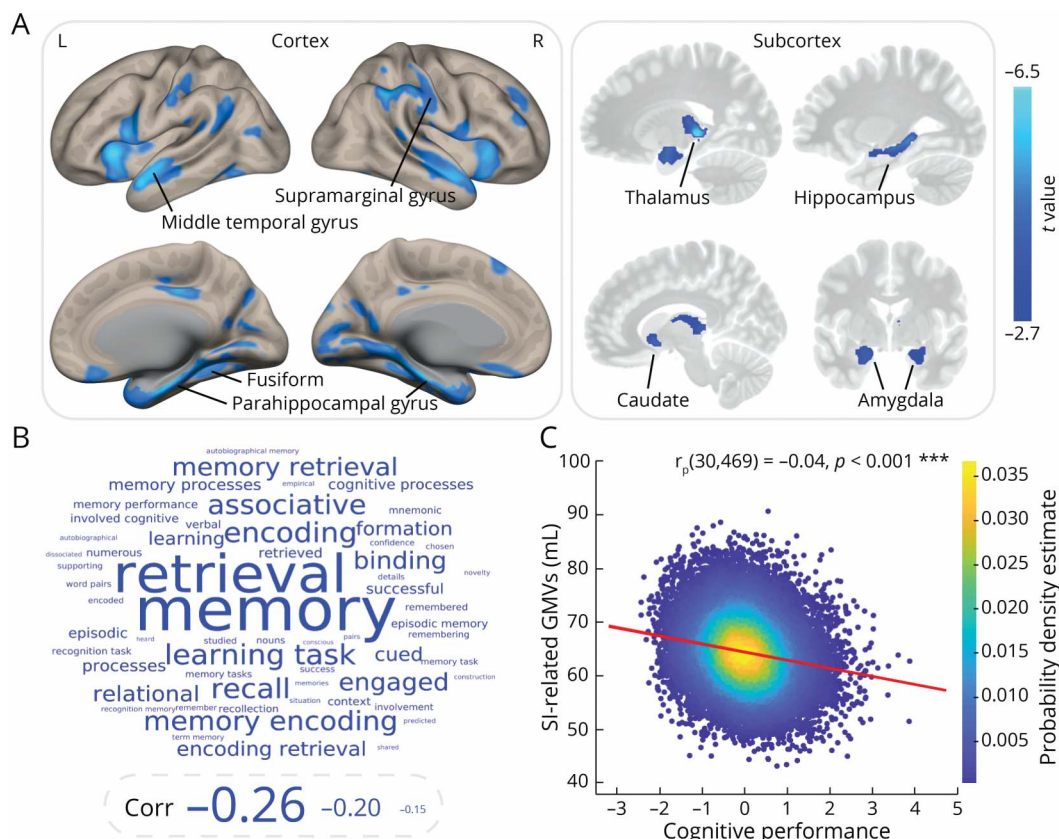
To our knowledge, this is the first large-scale study controlling for various risk factors and quantifying their contributions to the associations of social isolation and loneliness with dementia. Consistent with previous longitudinal studies,³⁷ we found that social isolation was associated with a 1.26-fold increased risk of developing dementia, which was independent of loneliness and other risk factors. Loneliness was not related to the incidence of dementia after removal of all covariates including social isolation, and 75% of the relationship was attributable to depressive symptoms. Social isolation and loneliness are often weakly correlated³⁸ and our results also suggest that these 2 are related but distinct constructs.

We identified multiple brain regions associated with social isolation in the largest sample to date, but found no significant

association with loneliness. In the UK Biobank, socially isolated individuals had the most severely low GMVs in hippocampus, parahippocampus, thalamus, amygdala, and temporal cortex, which was not confounded by loneliness and depressive symptoms. The effect of social stressors on hippocampal morphology has been well documented.³⁹ The amygdala is involved in emotional processing and is relevant to social network size.^{8,9} Temporal cortical areas such as the fusiform gyrus and superior and middle temporal gyrus are important for social perception.⁴⁰ Experimental manipulation of group size in macaques resulted in variation in the volume of the cortex in the midsuperior temporal sulcus and amygdala.⁴¹

Cognitive annotation of the significant brain map demonstrated that impaired regions related to social isolation were involved in cognitive processes, especially memory and learning. Indeed, we found that the volumes of these regions were positively associated with cognitive function and partly mediated the association between social isolation at baseline and cognitive function at follow-up, which was on average 8.8 years later. Previous epidemiologic studies have revealed that social isolation is associated with cognitive function in later life,⁴ but evidence on the potential mechanism is sparse. Animal studies suggest that isolation affects cognition by altering the excitatory and inhibitory synaptic density in the

Figure 3 Neuroanatomical Correlates of Social Isolation at the Imaging Visit



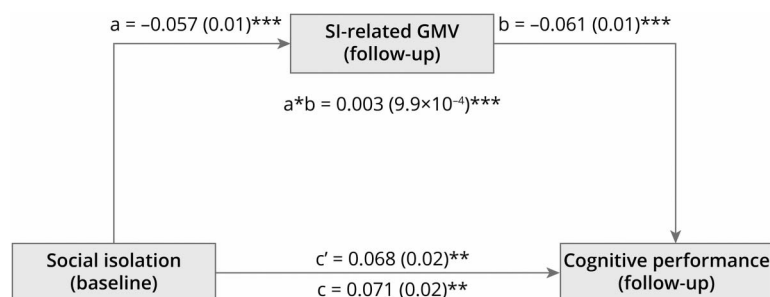
(A) Results of whole-brain voxel-wise analysis of social isolation ($n = 32,263$). Significant gray matter volumes (GMVs) in cortical and subcortical regions are presented separately. The color bar presents t value. (B) Word cloud of cognitive terms associated with social isolation-related GMVs. The size of cognitive terms corresponds to the Spearman correlation of corresponding meta-analytic maps in Neurosynth with the significant social isolation t statistic map. (C) Cross-sectional association between social isolation-related GMVs and cognitive function in the UK Biobank ($n = 30,480$). Cognitive function was assessed by the composite score of pairs matching and reaction time tests. The color bar presents the estimated probability density.

hippocampus⁴² and social interaction reversed the memory deficit by increasing hippocampal neurogenesis.⁴³ For AD, the largest form of dementia, the neuropathologic changes are suggested to start in the hippocampus and related areas and are associated with early cognitive impairments in learning and memory.⁴⁴

The gene expression profile of the social isolation-related cortical changes was enriched in biological processes and

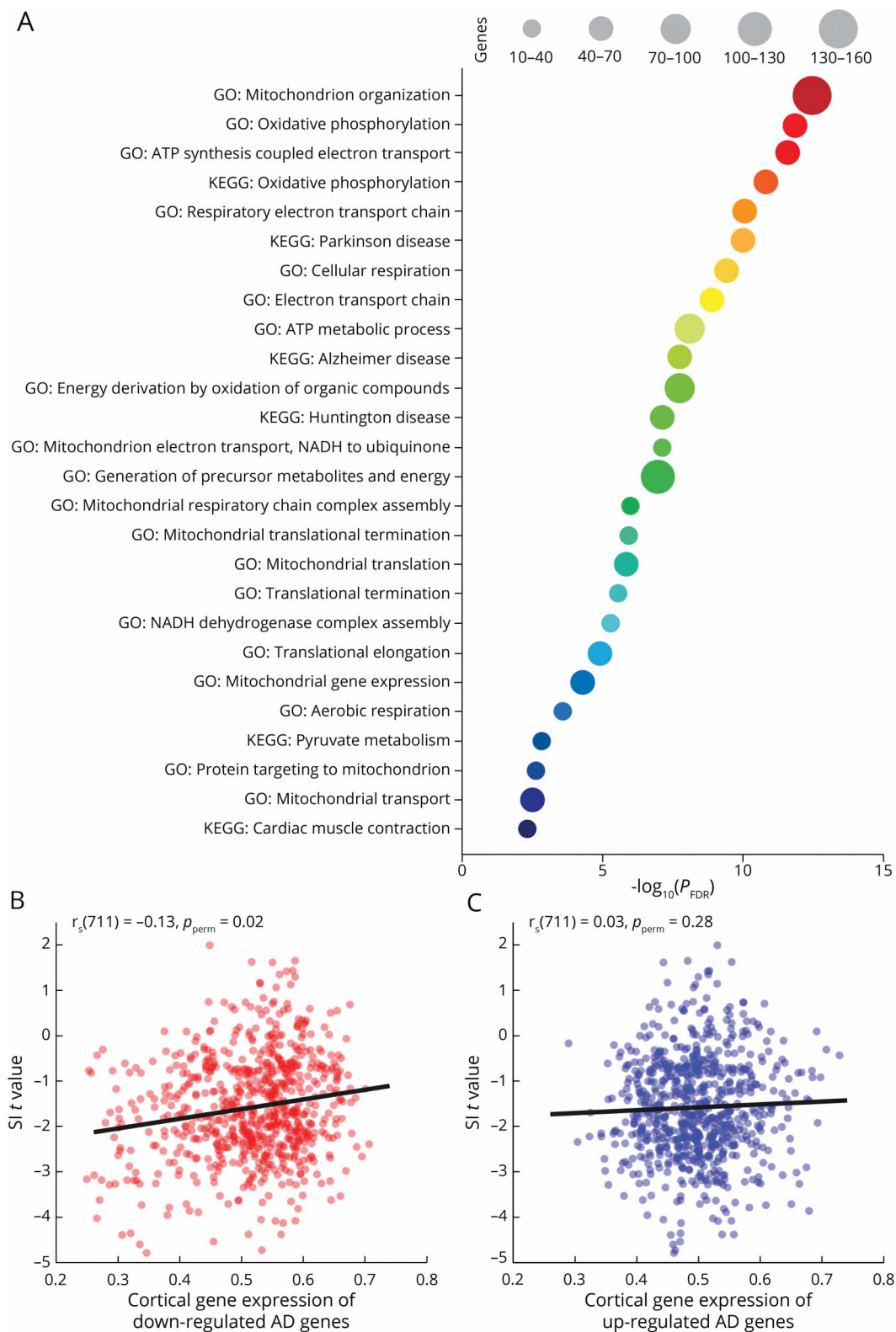
KEGG pathways closely linked to dementia. It is well established that mitochondrial dysfunction and oxidative damage is critical in aging and neurodegenerative diseases.⁴⁵ Animal research shows that impairments of mitochondrial function⁴⁶ and oxidative phosphorylation⁴⁷ precede the development of AD-like pathology. We found more genes that are down-regulated in AD in the list of positively weighted genes with differences in cortical GMVs. Furthermore, the expression

Figure 4 Associations of Social Isolation, Gray Matter Volume, and Cognitive Function



Mediation analysis implemented by significant gray matter volumes (GMVs) (mediator) from social isolation (SI) at baseline (predictor) on cognitive function at the imaging visit (dependent variable). Path a measures the association between the predictor and the mediator; path b represents the effect of the mediator on the dependent variable while controlling for the predictor; path c measures the total relationship between the predictor and the dependent variable; path c' measures the direct effect; the mediation effect is the product of path a and path b ($a \times b$). $n = 30,612$; $**p < 0.01$, $***p < 0.001$.

Figure 5 Relationship Between Social Isolation–Related Brain Differences and Gene Expression



(A) Functional enrichment results of PLS1– genes in cortical regions. Gene Ontology (GO) biological processes and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways with a $p_{FDR} < 0.005$ are presented. The size of the circle represents the number of genes involved in a given GO term. (B) Association between social isolation *t* value and the average expression level of downregulated Alzheimer disease (AD)–related genes in cortical regions. (C) Association between social isolation *t* value and the average expression level of upregulated AD-related genes in cortical regions. The significance was tested by 5,000 times permutation, in which the null distribution was defined by 5,000 random *t* statistic maps obtained by label shuffling for social isolation.

level of downregulated genes was significantly associated with cortical differences. These results suggest that genes with reduced brain postmortem transcription in AD are underexpressed in cortical regions with higher levels of differences related to social isolation. We also found that the expression of immune-related genes like LCP2 ($z = 7.4$) was significantly associated with social isolation–related cortical differences, consistent with previous studies.¹⁴

The following issues should be taken into account when considering our findings. Participants in the UK Biobank had fewer self-reported health conditions and were less likely to live alone than the general population.⁴⁸ Although it has been reported that the generalizability of the exposure–mortality relationship seems to be little limited by the lack of representativeness,⁴⁹ the extent to which a selection bias would influence the associations of social isolation and loneliness with dementia risk is unknown. Second, the method we used to identify dementia cases might be insufficient due to the increasing prevalence of dementia within care settings.⁵⁰ However, for all-cause dementia, the positive predictive value in combination with primary care, hospital admissions, and mortality data in the UK Biobank was relatively high (i.e., 82.5%).⁵¹ The participants used in neuroimaging analyses were population-based (only 29 with dementia). Thus, lower GMVs associated with social isolation found in the present study were not related to dementia directly, although there may be more individuals who will develop dementia during longer follow-up. Finally, cultural factors might moderate the social relationship–health association.⁵² For instance, in individualistic societies, living alone might be the consequence of a quest for socioeconomic independence. Although social isolation was defined by multiple items and socioeconomic factors were controlled in the analyses, the findings should be interpreted in a specific cultural context.

We used simple measures to assess multilayered social factors. Although we found consistent results and a potential dose-dependent association of social isolation with incident dementia and brain volumes using 3-category variables, validation of our findings using well-designed scales is needed. Another point to note is that three-quarters of the loneliness–dementia relationship could be attributable to depressive symptoms. However, we found bidirectional associations between social factors and depressive symptoms but the effect was stronger for depression as the initial symptom using longitudinal data in the UK Biobank (eFigure 11, links.lww.com/WNL/C15). Therefore, it is possible that depressive symptoms might be a mediator rather than a simple confounder. Future studies should also pay attention to the trajectories of social isolation and loneliness. Akhter-Khan et al.⁵³ found that persistent loneliness was a risk factor for dementia, while transient loneliness was beneficial. In practice, it is impossible to test the hypothesis due to few individuals developing incident dementia when individuals are classified into 4 trajectories in the UK Biobank. The cognitive tests used in the current study are brief, whereas cognitive impairments in aging

are heterogeneous. In the future, it will be important to include episodic memory tests, which have been shown to be valid, sensitive tests for the early detection of amnesic mild cognitive impairment and the early stage of AD.

We revealed that social isolation was associated with an increased incidence of dementia independent of loneliness and many potential risk factors. Integrating the neuroimaging and transcriptomic data, we showed that social isolation was related to lower GMVs coupled with different molecular functions, and these structural differences partly mediated the association between social isolation and cognitive function. In the context of the COVID-19 pandemic, which critically exacerbates social isolation, these findings have implications for social relationship interventions.

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Disclosure

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Continued

Appendix (continued)

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