Supplemental eMethods

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Acquisition Parameters
Imaging was performed with a Siemens Magnetom 1.0 Tesla field strength magnetic resonance machine using a double spin-echo coronal imaging sequence of 4 millimeter contiguous slices from nasion to occiput with repetition time of 2,420 msec, echo time (TE) of TE1 20/ TE2 90 msec; echo train length 8 msec; field of view 22 cm and a 182 × 256 acquisition matrix interpolated to a 256 × 256 with one excitation. Approximately 90% of scans were performed in Massachusetts; the remainder were performed out-of-state and used a 1.5T machine with identical scan protocol. Off-site scanners had test scans with verification that they were performed correctly according to the Framingham Study MRI scan protocol.

Image Analysis
MRI scan digital information was transferred after acquisition to the central laboratory directed by a co-author (CD) for processing and analysis. Analyses were all conducted blind to participant identifying information. Images were evaluated with semiautomatic segmentation analyses using operator-guided removal of non-brain elements by operator-guided tracing of the dura matter within the cranial vault. This included the middle cranial fossa and was above the posterior fossa and cerebellum. The cranial vault measure derived was defined as total cranial volume and was used as a head size estimate to correct for established sex differences in head size.

Total cerebral brain volume, hippocampal volume, and white-matter hyperintensities (WMH) were quantified using a multi-step process starting with image segmentation to define brain matter from cerebral spinal fluid (CSF). Subtraction of the second echo image from the first echo image yielded a difference image. Following image segmentation into brain matter and CSF, the operator returned to the image to measure lobar brain volumes. To preserve measurement precision, segmented brain-CSF images were rotated separately from the original image.

The image was transformed into anatomic standard space; the operator then returned to the image and identified brain lobar and regional CSF measures. Volumes were all calculated as the sum of the pixels within the identified region of interest multiplied by the pixel volume in milliliters. Repeat analysis of intra- and inter-rater reliabilities were consistently above 0.90.[38] Volume measures were corrected for head size using the ratio of each measure over total cranial volume, multiplied by 100. For hippocampal volume, analysis of central CSF spaces was divided into lateral ventricles subtracting temporal horns of the lateral ventricles and analyzed separately. For segmentation of WMH from brain matter, the first and second echo images were summed after excluding CSF and correcting image intensity non-uniformities. A repeat Gaussian distribution was fitted to the summed image data and a segmentation threshold for WMH was a priori determined as 3.5 SD in pixel intensity above the mean of the fitted distribution of brain parenchyma. Morphometric erosion of two exterior image pixels was applied to the image before modeling to remove effects of partial volume CSF pixels on WMH determination.[36]

Supplemental eTables

eTable 1. Cognitive Tasks and Standardization Used to Create the Global Cognitive Score[a]

Cognitive Task	Natural Log-Transformations	Standardizing Formula[b]	Component Loading[c]
Trails Making Test A	-log(score)	(score – 0.68) / 0.34	0.13
Trails Making Test B	-log(score)	(score + 0.22) / 0.45	0.18
Trails Making Test (B Minus A)	-log(2 + score)	(score + 1.03) / 0.22	0.16
Logical Memory – Immediate Recall		(score – 11.55) / 3.4	0.14
Logical Memory – Delayed Recall		(score – 10.61) / 3.59	0.15
Visual Reproductions – Immediate Recall		(score – 9.07) / 3.15	0.17
Visual Reproductions – Delayed Recall		(score – 8.2) / 3.36	0.18
Paired Associate Learning – Delayed Recall		(score – 8.3) / 1.46	0.13
Hooper Visual Organization Test	-log(31 – score)	(score + 1.65) / 0.52	0.14
Similarities Test		(score – 16.77) / 3.55	0.14

[a] Adapted from Pase et al. 2016.[30]

[b] Natural log transformed cognitive tasks were used to create the standardized variables where applicable.

[c] Global cognitive score calculated by summing the products of the standardizing formulas and the component loadings for each cognitive task.

eTable 2. Multivariable Models of Incident Dementia by Loneliness Status, Adjusted for Depressive Symptoms, Social Isolation, and Other Potential Confounders

	Lonely vs Not Lonely[a]							
	Model 2		Model 3		Model 4		Model 5	
Dementia Incidence	No. of Cases /No. at risk	Hazard Ratio (95% CI)	No. of Cases /No. at risk	Hazard Ratio (95% CI)	No. of Cases /No. at risk	Hazard Ratio (95% CI)	No. of Cases /No. at risk	Hazard Ratio (95% CI)
Overall	327/ 2265	1.23 (0.79-1.91)	299/ 2150	1.18 (0.74-1.87)	297/ 2147	1.16 (0.73-1.86)	251/ 1957	1.20 (0.69-2.08)
Age ≥80	197/ 551	0.77 (0.41–1.43)	180/ 512	0.73 (0.38–1.41)	179/ 510	0.70 (0.36-1.38)	141/ 403	0.73 (0.31-1.71)
Age 60-79[b]	130/ 1714	2.44 (1.29–4.61)	119/ 1638	2.34 (1.18–4.61)	118/ 1637	2.16 (1.10-4.24)	110/ 1554	1.94 (0.91-4.12)
Age 60-79 by APOE ε4 status[c]								
At least one APOE ε4 allele	40/ 341	1.20 (0.25–5.80)	37/ 324	0.74 (0.14–3.80)	36/ 323	0.75 (0.15-3.88)	34/ 306	0.37 (0.04-3.75)
No APOE ε4 alleles	83/ 1292	2.87 (1.36–6.05)	75/ 1239	2.69 (1.20–6.04)	75/ 123	2.24 (1.09-5.37)	70/ 1179	2.49 (1.05-5.93)

[a]Predictor: Lonely (3+ days/week) versus not lonely (<3 days/week).

Model 2 adjusts for age, sex, and educational level and additionally adjusts for depressive symptoms (logarithm of modified Center for Epidemiologic Studies Depression Scale without loneliness item).

Model 3 adjusts for age, sex, educational level, depressive symptoms, and additionally adjusts for social isolation (Berkman-Syme Social Network Index, <2 points).

Model 4 adjusts for age, sex, educational level, depressive symptoms, social isolation, and additionally adjusts for antidepressant medication use. Participants were asked to bring all current medications in their original pill bottles to follow-up clinic visits where FS staff would record all label information, including names of medications used regularly (>2 weeks), dose, and duration of use to determine initiation of treatment for diagnosed or potential depressive symptoms. Medications classified as antidepressants included selective serotonin reuptake inhibitors, monoamine oxidase inhibitors, tricyclics, and modified cyclic agents. Although these medications can be prescribed to treat other psychiatric conditions that can co-occur with depression, such as generalized anxiety, or other conditions such as migraine, these medications are often prescribed to treat depressive symptoms which may include reports of loneliness.

Model 5 adjusts for age, sex, educational level, depressive symptoms, social isolation, antidepressant medication use, and additionally adjusts for the following vascular risk factors which may influence risk of vascular dementia: prevalent cardiovascular disease (includes coronary heart disease, congestive heart failure, peripheral vascular disease, ischemic cardiomyopathy, stroke, and transient ischemic attack), prevalent hypertension (Stage 1 or higher Joint National Commission-VII hypertension, or antihypertensive medication use), prevalent smoker, and prevalent obesity (body mass index ≥30 kg/m^2).

[b] The dementia analytic sample excluded participants age<60.

[c] Among all participants in the dementia analytic sample, 1635 had any genotypic information. For participants below age 80, a significant interaction between loneliness status and APOE ε4 allele carrier status was present.

eTable 3. Multivariable Models of Cognitive and Neuroanatomical Measures as a Function of Loneliness Status, Adjusted for Depression and Social Isolation: Participants Age 40-79 Without an APOE ε4 Allele

	Lonely vs Not Lonely[a]					
	Model 2			Model 3		
Outcome	No. of participants	Estimate (SE)	*P* value	No. of participants	Estimate (SE)	*P* value
Cognitive function						
Global	1839	-0.08 (0.10)	0.40	1765	-0.02 (0.10)	0.83
Logical memory delayed recall	1870	0.12 (0.11)	0.27	1793	0.19 (0.12)	0.10
Trails making test B minus A[b]	1852	-0.14 (0.11)	0.19	1778	-0.14 (0.11)	0.22
Brain atrophy and injury[c]						
Total cerebral volume, % of TCV	1610	-0.21 (0.10)	0.04	1558	-0.18 (0.10)	0.08
Hippocampal volume, % of TCV	1610	0.03 (0.13)	0.80	1558	0.07 (0.14)	0.59
White matter hyperintensity volume, % of TCV[b]	1588	0.28 (0.12)	0.02	1537	0.26 (0.12)	0.03

Abbreviation: TCV, total cranial volume.

[a] Predictor: Lonely (3+ days/week) versus not lonely (<3 days/week).

Data are presented as beta estimate in standard deviation units and standard error (SE).

Models used participants in the cognition analytic sample (n=1875, which includes participants age 40-79 without an APOE ε4 allele.

Model 2 adjusts for age, age^2, sex, educational level, time interval from collection of loneliness measure to when cognitive function or brain MRI were measured, and additionally adjusts for depressive symptoms (logarithm of modified Center for Epidemiologic Studies Depression Scale without loneliness item).

Model 3 adjusts for age, age^2, sex, educational level, time interval from collection of loneliness measure to when cognitive function or brain MRI were measured, depressive symptoms, and additionally adjusts for social isolation (Berkman-Syme Social Network Index, <2 points).

[b] Log transformed to decrease skewness of distribution.

[c] Among participants in the cognition sample, 1611/1875 (86%) were included in the MRI analytic subsample.

eTable 4. Adjusted 10-Year Risk of Incident Dementia By Loneliness Severity

	<1 Day	1-2 Days	3-7 Days
Dementia Incidence[a]	**Hazard Ratio (95% CI)**	**Hazard Ratio (95% CI)**	**Hazard Ratio (95% CI)**
Overall	1 [Reference]	1.29 (0.97, 1.71)	1.63 (1.11, 2.37)
Age ≥80	1 [Reference]	1.41 (1.01, 1.99)	1.26 (0.74, 2.13)
Age 60-79[b]	1 [Reference]	1.15 (0.69, 1.93)	2.32 (1.34, 4.01)
Age 60-79 by APOE ε4 status[c]			
At least one APOE ε4 allele	1 [Reference]	1.50 (0.65, 3.44)	0.99 (0.23, 4.18)
No APOE ε4 alleles	1 [Reference]	1.09 (0.56, 2.15)	3.07 (1.64, 5.74)

[a]Predictor: Self-reported loneliness severity as number of days the respondent felt lonely in the past week. All models adjust for age, sex, and educational level.

[b] The dementia analytic sample excluded participants age<60.

[c] Among all participants in the dementia analytic sample, 1635 had any genotypic information. For participants age 60-79, a significant interaction between loneliness status and APOE ε4 allele carrier status was present.

eTable 5. Multivariable-Adjusted Models of Cognitive and Neuroanatomical Measures as a Function of Loneliness Severity: Participants Age 40-79 Without an APOE ε4 Allele

	<1 Day		1-2 Days		3-7 Days	
Outcome[a]	**Estimate (SE)**	***P* value**	**Estimate (SE)**	***P* value**	**Estimate (SE)**	***P* value**
Cognitive Function						
Global	1 [Reference]	NA	0.04 (0.05)	.51	-0.16 (0.09)	.09
Logical memory delayed recall	1 [Reference]	NA	0.06 (0.06)	.35	0.08 (0.11)	.48
Trails making test B minus A[b]	1 [Reference]	NA	-0.02 (0.06)	.74	-0.23 (0.11)	.03
Brain atrophy and injury[c]						
Total cerebral volume, % of TCV	1 [Reference]	NA	-0.07 (0.05)	.19	-0.26 (0.10)	.008
Hippocampal volume, % of TCV	1 [Reference]	NA	-0.02 (0.07)	.78	0.05 (0.13)	.72
White matter hyperintensity volume, % of TCV[b]	1 [Reference]	NA	-0.05 (0.06)	.41	0.27 (0.11)	.02

Abbreviations: NA, not applicable; TCV, total cranial volume.

[a] Predictor: Self-reported loneliness severity as number of days the respondent felt lonely in the past week.

Data are presented as beta estimate in standard deviation units and standard error (SE).

Models used participants in the cognition analytic sample (n=1875, which includes participants age 40-79 without an APOE ε4 allele.

All models adjust for age, age^2 sex, educational level, time interval between from collection of loneliness measure to when cognitive function or brain MRI were measured.

[b] Log transformed to decrease skewness of distribution.

[c] Among participants in the cognition sample, 1611/1875 (86%) were included in the MRI analytic subsample.

eTable 6. Adjusted 10-Year Risk of Incident Dementia Subtypes By Loneliness Status: Participants Age 60-79 Without an APOE ε4 Allele

			Lonely vs Not Lonely
Dementia Subtype Incidence[a]	**No. at Risk**	**No. of Cases**	**Hazard Ratio (95% CI)**
Alzheimer's Disease[b]	1294	54	2.60 (1.16-5.79)
Vascular Dementia[c]	1294	22	3.01 (0.87-10.41)

[a] Predictor: Lonely (3+ days/week) versus not lonely (<3 days/week). All models adjust for age, sex, and educational level.

[b] Participants diagnosed with possible, probable, or definite Alzheimer's Disease, regardless of whether there is concomitant possible or probable vascular dementia, based on criteria from the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Association,[29] and the Alzheimer's Disease Diagnostic and Treatment Centers.[30]

[c] Participants diagnosed with possible or probable vascular dementia, regardless of whether a participant also has a diagnosis of possible or probable Alzheimer's disease in the setting of mixed vascular and Alzheimer's etiology for dementia.