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Association of Higher Cortical Amyloid Burden With Loneliness in Cognitively Normal Older Adults

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Abstract

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IMPORTANCE—Emotional and behavioral symptoms in cognitively normal older people may be direct manifestations of Alzheimer disease (AD) pathophysiology at the preclinical stage, prior to the onset of mild cognitive impairment. Loneliness is a perceived state of social and emotional isolation that has been associated with cognitive and functional decline and an increased risk of incident AD dementia. We hypothesized that loneliness might occur in association with elevated cortical amyloid burden, an in vivo research biomarker of AD.

OBJECTIVE—To determine whether cortical amyloid burden is associated with greater loneliness in cognitively normal older adults.

DESIGN, SETTING, AND PARTICIPANTS—Cross-sectional analyses using data from the Harvard Aging Brain Study of 79 cognitively normal, community-dwelling participants. A continuous, aggregate measure of cortical amyloid burden, determined by Pittsburgh Compound B–positron emission tomography (PiB-PET), was examined in association with loneliness in linear regression models adjusting for age, sex, apolipoprotein E ε4 (APOEε4), socioeconomic status, depression, anxiety, and social network (without and with the interaction of amyloid and APOEε4). We also quantified the association of high amyloid burden (amyloid-positive group) to loneliness (lonely group) using logistic regression, controlling for the same covariates, with the amyloid-positive group and the lonely group, each composing 32%of the sample (n = 25).

MAIN OUTCOMES AND MEASURES—Loneliness, as determined by the 3-item UCLA Loneliness Scale (possible range, 3–12, with higher score indicating greater loneliness).

RESULTS—The 79 participants included 43 women and 36 men with a mean (SD) age of 76.4 (6.2) years. Mean (SD) cortical amyloid burden via PiB-PET was 1.230 (0.209), and the mean (SD) UCLA-3 loneliness score was 5.3 (1.8). Twenty-two (28%) had positive APOEε4 carrier status, and 25 (32%) were in the amyloid-positive group with cortical PiB distribution volume ratio greater than 1.2. Controlling for age, sex, APOEε4, socioeconomic status, depression, anxiety, and social network, we found that higher amyloid burden was significantly associated with greater loneliness: compared with individuals in the amyloid-negative group, those in the amyloid-positive group were 7.5-fold (95%CI, 1.7-fold to 34.0-fold) more likely to be classified as lonely than nonlonely (β = 3.3, partial $r = 0.4$, $P = .002$). Furthermore, the association of high amyloid burden and loneliness was stronger in APOEε4 carriers than in noncarriers.

CONCLUSIONS AND RELEVANCE—We report a novel association of loneliness with cortical amyloid burden in cognitively normal older adults, suggesting that loneliness is a neuropsychiatric symptom relevant to preclinical AD. This work will inform new research into the neural underpinnings and disease mechanisms involved in loneliness and may enhance early detection and intervention research in AD.

Alzheimer disease (AD) is a pathophysiological process encompassing preclinical, mild cognitive impairment and dementia stages that leads to progressive neuropsychiatric, cognitive, and functional declines.[1,2] Concerted research has focused on characterizing sensitive biological and neuropsychological markers of AD at the preclinical stage, prior to the onset of mild cognitive impairment, to identify high-risk individuals for secondary prevention trials.[1,3,4] At the same time, there has been less attention to late-life emotional and behavioral changes (known as neuropsychiatric symptoms) in preclinical AD and their association with AD biomarkers in at-risk, cognitively normal older people. Although

neuropsychiatric symptoms such as depression, anxiety, and irritability are known to predict progression from normal cognition to prodromal AD,[2,5] their pathological correlates are not yet defined. Furthermore, relatively little is known of the range of emotional and behavioral changes that are part of the natural history of preclinical AD.

Loneliness is a perceived state of social and emotional isolation that has been associated with cognitive[6–10] and functional[11] decline and an increased risk of incident AD dementia.[6] As such, loneliness may be a sensitive clinical marker of pathological brain changes in older people. Importantly, loneliness is a specific construct that can be reliably measured and distinguished from depression, anxiety, and objective social isolation through the use of well-established instruments.[12,13] In community-dwelling elderly persons, loneliness has been prospectively associated with declines in delayed recall, adjusting for sociodemographic factors, depression, and social isolation over 4 years,[9] with worsening memory performance over 12 years, independent of demographics, medical burden, social network, and baseline depression,[10] and with increased progression to AD dementia over 4 years in models adjusting for demographics, premorbid intelligence, depression, social network, vascular health, and levels of social, cognitive, and physical activity.[6] Thus, while loneliness may accompany depression,[14] interpersonal loss,[15] or objective isolation,[16] we hypothesized that late-life loneliness might also have a distinct role as a prototypical symptom of AD-related molecular pathologies beginning in preclinical AD.

The current research model of preclinical AD describes a pathological process that begins with a prolonged stage of cerebral amyloidosis, detectable with established positron emission tomography (PET) imaging techniques,[17] followed by a neurodegenerative stage defined by tau aggregation and propagation as well as progressive amyloidoisis.[3,18,19] Early neuropsychiatric symptoms in the form of subtle alterations in socioemotional perception or regulation, such as loneliness, may be measurable in association with amyloidosis and/or early pathological tau aggregation in older people before the onset of mild cognitive impairment. The genetic risk factor apolipoprotein E ε4 (APOEε4) may also influence early neuropsychiatric symptom expression; it has been shown to modify amyloid-related mechanisms involved in memory decline[17] and to promote disease progression[20] at the preclinical stage.

The aim of the present study is to examine the cross-sectional association of in vivo measurements of cortical amyloid burden with loneliness in an ongoing, observational cohort of cognitively normal older adults that includes a subset of individuals with high cortical amyloid burden characteristic of preclinical AD. We hypothesized that higher amyloid burden would predict greater loneliness, after controlling for age, sex, APOEε4 carrier status, and potential confounders such as anxiety, depression, social network, and socioeconomic status.

Key Points

Question

Is higher cortical amyloid burden, a marker of preclinical Alzheimer disease, associated with greater self-reported loneliness in older adults with normal cognition?

Findings

In a cross-sectional study of 79 community-dwelling older adults, higher brain amyloid burden was associated with more frequent feelings of isolation, being left out, and lacking companionship, independent of sociodemographic factors, objective measures of social network, depressive and anxiety symptoms.

Meaning

Loneliness, characterized by subtle feelings of social detachment, may be associated with early brain changes in preclinical Alzheimer disease, prior to mild cognitive impairment.

Methods

Participants

The sample was a subset of participants returning for year 4 assessments as part of the Harvard Aging Brain Study, an ongoing, observational study of older adult volunteers aimed at defining neurobiological changes in the early AD pathway and other trajectories of cognitive aging. The Partners Human Research Committee approved this study, and all participants provided written informed consent.

Participants were English-speaking, community-dwelling men and women who were cognitively normal, aged between 65 and 90 years, and free from active, major psychiatric disorders when originally enrolled in the cohort (eAppendix in the Supplement).[21] For this study, data were obtained from 79 participants undergoing year 4 assessments that included specialized instruments for loneliness, anxiety, and social network characteristics. All participants in this study were cognitively normal based on Clinical Dementia Rating[22] global score 0 and education-adjusted performance for the Wechsler Logical Memory subtest and the Mini-Mental State Examination.[23]

Clinical Measures

Loneliness was measured using the 3-itemversion of the UCLA Loneliness Scale, a validated, self-rated instrument that has been implemented in numerous epidemiologic studies of aging (eAppendix in the Supplement).[9,11,13,24] Study participants were asked the following 3 questions: “How often do you feel you lack companionship?” “How often do you feel left out?” “How often do you feel isolated from others?” Each question was scored on a 4-point scale: 1, never; 2, rarely; 3, sometimes; or 4, often. The total score was the sum of the 3 answers (possible range, 3–12, with higher score indicating greater loneliness). Loneliness ratings were completed in a blinded fashion with regard to other assessments and procedures.

Seven items corresponding to anxiety symptoms from the 14-item Hospital Anxiety and Depression Scale (HADS)[25] were used to calculate an anxiety score; each statement was rated for frequency (range, 0–3), with higher score indicating greater anxiety (total score possible range, 0–21). Self-reported depression was calculated as the total score from the 30-item Geriatric Depression Scale (GDS)[26] (item score, 0–1; total score, 0–30; higher score indicates greater severity).[26] A social network score[27–30] and a social activity score[6,31] were

calculated from questions probing numbers and types of social ties and frequency of social contacts from established epidemiological surveys.[28,31] The social network score was calculated as the sum of 4 binary domain scores based on whether or not the study participant was (1) married or living with a partner; (2) had, in total, 3 or more friends, children, or other relatives who visited monthly; (3) was a member of a community group; and (4) was a participant in religious services or activities (possible range, 0–4, with higher score indicating greater network). A separate measure of social activity was calculated as the total number of children, other relatives, and friends who visited monthly or more (range, 0–36 in the sample).

Based on APOEε4 genotype, participants were classified as either APOEε4 carriers or noncarriers. In addition, a Hollingshead score was calculated according to primary occupation and educational attainment (range, 11–65 in the sample, with higher score indicating lower socioeconomic status).[32]

Pittsburgh Compound B–PET Data

Fibrillar amyloid burden was measured using the Pittsburgh Compound B (PiB)-PET criteria according to established protocols at the Massachusetts General Hospital PET facility.[33–36] PiB distribution volume ratio (DVR) was calculated for an aggregate of cortical regions including frontal, lateral temporal and lateral, and medial parietal regions, a summary measure used in prior studies.[36,37] The primary analyses used a continuous measure of PiB retention, whereas a dichotomous PiB variable was used in secondary models. Using the aggregate PiB DVR value, a dichotomous amyloid variable was defined by a Gaussian mixture modeling approach in which high-amyloid (amyloid-positive) or low-amyloid (amyloid-negative) groups were based on a PiB DVR cutoff value of 1.2, as previously published.[17]

Statistical Analysis

Unadjusted associations between loneliness and the continuous predictor terms, and associations among these predictors, were evaluated using Pearson correlations.

In the first of 3 multiple linear regression models, we examined the cross-sectional association of cortical amyloid burden, as a continuous variable (PiB), with UCLA loneliness score (UCLA-loneliness), adjusting for age, sex, and APOEε4 carrier status (model 1). Building on model 1, we then estimated the association of PiB with UCLA-loneliness, adjusting for the original set of predictors as well as Hollingshead score, levels of depression (GDS) and anxiety (HADS-anxiety) symptoms, and social network score (model 2). Neuropsychiatric and psychosocial explanatory variables and potential confounders were included in the second analysis, as in prior research on loneliness,[6,16] to closely define the unique association between amyloid burden and loneliness.

In a third analysis (model 3), we tested whether APOEe4 modifies the association between PiB and UCLA-loneliness by repeating model 2 but including an additional term for the multiplicative interaction of APOEε4 and PiB.

For linear regression models, we reported unstandardized coefficient estimates (β) and standardized estimates with confidence intervals (CI), significance test results (*P* values), and percent variance accounted for by the model as a whole, adjusted for the degrees of freedom (adjusted R^2). Residuals from the final models were examined to ensure that their distributions reasonably satisfied model assumptions of normality and homoscedasticity.

For secondary logistic models, the significance test for the overall model was a likelihood ratio test, and significance tests for individual predictors and 95%CIs for odds ratios (ORs) were based on a Wald χ^2 test.

Analyses were performed using SAS, version 9.3 (SAS Institute Inc) and SPSS 23 (IBM) statistical software.

Results

Demographic, clinical, and imaging data are reported in Table 1. The mean score for UCLA-loneliness was 5.3 (range for participants, 3–10; possible range, 3–12). Nineteen percent of the sample (n=15) endorsed feelings of lacking companionship sometimes or often, while 19% (n=15) reported feeling left out sometimes or often, and 14% (n=11) felt isolated from others sometimes or often. Often, the highest rating for these items, was endorsed a total of 3 times in the sample (once for each item), each by a different participant. The individual UCLA-loneliness items were moderately correlated with each other ($r = 0.5$ for all pairs; $P < .001$), consistent with inter-item correlations reported elsewhere.[13] All 3 items were correlated with the UCLA-loneliness total score ($r = 0.8$; $P < .001$).

There was an unadjusted association of UCLA-loneliness score with PiB ($r = 0.3$; $P = .03$), age ($r = -0.2$; $P = .04$), GDS ($r = 0.3$; $P = .005$), and HADS-anxiety scores ($r = 0.3$; $P = .01$) but not with Hollingshead score or measures of social network or social activity. In addition to its unadjusted association with loneliness, PiB was also correlated with HADS-anxiety score ($r = 0.2$; $P = .04$) but not with GDS score ($r = -0.0003$; $P = .90$). Only 6 participants (8%) exceeded the GDS cutoff for mild depression (>11), and 5 participants (6%) exceeded the HADS-anxiety threshold for mild anxiety (>8).

Association of Amyloid Burden With Loneliness

We found that higher PiB was associated with greater UCLA-loneliness, adjusting for age, sex, and APOEε4 carrier status (for PiB, $\beta = 3.0$ and $P = .005$; for the model, adjusted $R^2 = 0.11$ and $P = .01$). Age, but not sex or APOEε4, was also significantly associated in the model (for age, $\beta = -0.09$ and $P = .02$). We also found that higher PiB was associated with greater UCLA-loneliness, in the second model, adjusting for the full complement of explanatory variables and potential confounders, and the model as a whole was significant (see Table 2 and Figure for supporting data). Other factors significantly associated with UCLA-loneliness were higher GDS score and younger age (Table 2), findings consistent with those of prior research.[14,24] Results of model 2 were unchanged when the analysis was repeated with the social network score replaced by the measure of social activity or by dichotomous variables relating to being married or partnered or being a widow or widower.

To enhance interpretability of the associations between PiB and UCLA-loneliness, we used logistic regression models to evaluate the association of higher PiB (as a continuous measure) or greater amyloid burden with being lonely rather than non-lonely. Those participants who endorsed any of the 3 UCLA-loneliness items as present sometimes or often were classified as lonely, a group that made up 32% of the sample (n = 25).

Modeling amyloid burden as a continuous variable and adjusting for the full set of covariates as in model 2, we found that higher PiB was significantly associated with being lonely. For each interval change of 0.1 DVR of PiB, there was a 75%increased odds of being lonely rather than nonlonely: for 0.1 DVR PiB, OR, 1.75 (95%CI, 1.2–2.5); $P = .003$; for the model, $P < .001$. Comparing the amyloid-positive and amyloid-negative groups, we found that individuals in the amyloid-positive group had 7.5 times higher odds of being lonely vs nonlonely than those in the amyloid-negative group: amyloid-positive, OR, 7.5 (95% CI, 1.7–34.0); $P = .01$); model, $P = .002$. In a simplified model controlling only for age, the OR for being lonely in the amyloid-positive vs the amyloid-negative group was 3.1 (95%CI, 1.01–9.5), $P = .04$; for the model, $P = .01$.

Supplemental data regarding vascular health, health behaviors, and psychiatric characteristics are reported in the eTable in the Supplement, and additional secondary analyses were performed (eAppendix in the Supplement).

Interaction of PiB and APOEε4 Status in Association With UCLA-Loneliness

We further evaluated whether the association of PiB to UCLA-loneliness was modified by APOEε4 status, controlling for age, sex, Hollingshead score, GDS, HADS-anxiety, and social network score. We found that the association of PiB with UCLA-loneliness was greater in the APOEε4 carriers than in noncarriers (Table 3). For each 0.1 DVR of PiB, the mean UCLA-loneliness score was increased by an additional 0.5 units in APOEε4 carriers vs noncarriers.

Discussion

In a community-based sample of cognitively normal older people, we found that higher in vivo cortical amyloid burden was associated with greater feelings of loneliness, suggesting that loneliness is a novel neuropsychiatric symptom in preclinical AD. Amyloid-positive individuals were 7.5 times more likely than amyloid-negative persons to endorse any loneliness item sometimes or often. In addition, the association of amyloid burden and loneliness was stronger in carriers of the AD genetic risk factor APOEε4 than in noncarriers, further strengthening the link between AD pathophysiology and loneliness.

These results reveal that the distinct construct of loneliness may be a symptom of amyloid accumulation. Feelings of isolation, lacking companionship, or being left out were endorsed as sometimes present by 14% (n=11) to 19% (n=15) of our participants, a few of whom reported frequent loneliness or elevated depression. Importantly, our analyses controlled for symptoms of depression, anxiety, and for objective measures of social connection. Therefore, relatively subtle, self-reported feelings of social detachment may be among the first symptoms of brain changes due to AD prior to the stage of mild cognitive impairment.

Loneliness or other subtle impairments in social-emotional perception or behavior could arise in preclinical AD due to amyloid-related alterations in neural activity at a local or network level. In young adults, loneliness has been associated with smaller gray matter volume in the left posterior superior temporal sulcus, a key area involved in sensory processing and social perception.[38] This area of the brain has multiple connections with limbic, frontal, and parietal structures including the amygdala and regions of the default mode network involved in social cognition and emotional regulation.[39,40] Functional neuroimaging studies of grieving persons have shown that the posterior cingulate cortex, a major node of the default mode network, is coactivated in response to grief-related photographs and words and may be important in regulating other emotional and cognitive inputs to mediate adaptive behavioral responses.[41–45]

It is also possible that the subjective experience of loneliness or detachment may promote amyloid accumulation, or there may be dynamic and reciprocal effects over time. Numerous epidemiological studies have established that antecedent social and psychosocial factors, including loneliness, are related to adverse outcomes such as depression, cognitive decline, functional impairment, and earlier mortality in older people.[11,16,46–48] Social disengagement, manifesting as low numbers of social ties, contacts, and group activities, has been associated with cognitive decline in population-based studies of older people, even in those individuals with relatively high baseline cognitive and functional status.[46,47] Many studies have also found independent effects on long-term cognition for more qualitative social and socioemotional constructs such as emotional support,[47] negative social interactions,[49] and loneliness.[6,9] Within this body of work, loneliness has been viewed as a marker of psychosocial stress, closely related to depression,[50] bereavement,[15] and other experiences of social disconnection,[51,52] with downstream effects on neural networks and systemic health, mediated by stress-related[53–55] and inflammatory processes.[56,57] Examining a relatively healthy, older-age sample, we found that measures of depressive symptoms and amyloid burden were each strongly and independently associated with loneliness, which may indicate that there are dissociable dimensions and pathological mechanisms involved in loneliness in aging adults.

Loneliness has rarely been examined as a potential outcome of neurobiological changes due to cognitive disorders such as AD.[6] A large clinical-pathological cohort study of nondemented elderly participants found that, over the course of 4 years, greater loneliness was independently associated with declines in multiple cognitive domains and a doubling of the risk of AD dementia.[6] Despite this, the researchers found no association of loneliness at baseline with density of β-amyloid plaques, neurofibrillary tangles, or cerebral infarctions at autopsy (adjusting for age at death, sex, and education), and they concluded that other neurobiological mechanisms, possibly linked to depression pathophysiology, may be involved.[6] While their results point toward loneliness as a factor that potentiates cognitive decline and AD, our methods and cross-sectional analyses differed by focusing exclusively on in vivo measurements of amyloid in a more select, elderly sample with normal cognition, relatively low vascular disease burden, and a low burden of depressive symptoms. In models adjusting for depression, anxiety, and social network, our findings provide a snapshot of loneliness as a possible stage-specific, social perception strongly related to higher amyloid

burden in older adults who may also be experiencing subtle cognitive changes in preclinical AD.

We also found that the association of higher cortical amyloid burden with greater loneliness was stronger in APOEε4 carriers than noncarriers. In addition to its known direct effects on amyloid aggregation and clearance,[58] the APOEε4 allele may also indirectly affect AD pathogenesis and memory decline[17] through increased neuroinflammation,[59] altered neuroenergetics,[60,61] or impaired synaptic plasticity.[62,63] Future longitudinal studies are planned to examine whether APOEε4 influences unidirectional and/or bidirectional associations of amyloid burden and loneliness over time. In addition, studies of loneliness in association with both amyloid and regional tau burden are ongoing to further validate loneliness as an early neuropsychiatric symptom in the preclinical AD staging framework.

Limitations

A limitation of the present study is the demographic profile of the participants, who, on average, had high intelligence and educational attainment and limited racial and socioeconomic diversity. These characteristics, together with the participants' more favorable mental and physical health, may reduce the external validity of our findings. We did not assess personality factors, such as neuroticism, that may share variance with loneliness or predictors in these analyses. Importantly, our findings are preliminary. Loneliness is commonly associated with loss and depression in older people. In a clinical setting, we do not have a method to adjust for these factors for a given individual when considering AD risk.

Conclusions

We report a novel association of loneliness and cortical amyloid burden in cognitively normal older adults and present evidence for loneliness as a neuropsychiatric symptom relevant to preclinical AD. This work will inform new research into the neurobiology of loneliness and other socioemotional changes in late life and may enhance early detection and intervention research in AD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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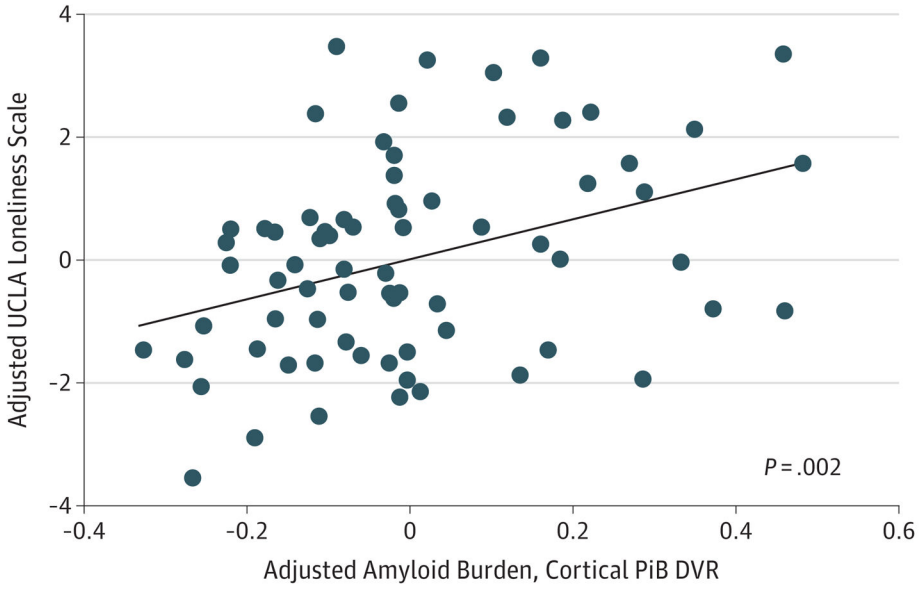

Figure. Cross-sectional Relation of Cortical Amyloid Burden and Loneliness

Multiple linear regression analysis was performed for loneliness, measured by the 3-item UCLA-3 Loneliness Scale (higher score indicates greater loneliness), as the dependent variable. Evaluated associations included amyloid burden (a continuous aggregate measure of cortical amyloid by Pittsburgh Compound B–positron emission tomography [PiB-PET] distribution volume ratio [DVR]), age, sex, apolipoprotein E ε4 (APOEε4) carrier status, Hollingshead score, depression, anxiety, and social network score.

Table 1

Demographic, Clinical, and Imaging Data for Study Participants

Characteristic	Value[a]	Range
Age, y	76.4 (6.2)	68–89
Men, No. (%)	36 (45)	NA
Hollingshead score	27.4 (15.8)	11–65
MMSE	29.2 (0.9)	26–30
UCLA-3 loneliness (range 3–12)	5.3 (1.8)	3–10
HADS anxiety (0–21)	3.5 (2.8)	0–12
GDS (range 0–30)	3.5 (3.4)	0–17
Social network (range 0–4) (n = 75)	2.5 (1.0)	0–4
APOEε4 carrier status, positive, No. (%) (n = 78)	22 (28)	NA
Amyloid burden, cortical PiB DVR	1.230 (0.209)	0.996–1.817
Amyloid-positive group (cortical PiB DVR >1.2), No. (%)	25 (32)	NA

Abbreviations: APOEε4, apolipoprotein E ε4; DVR, distribution volume ratio; GDS, Geriatric Depression Scale–30 item; HADS, Hospital Anxiety and Depression Scale; MMSE, Mini-Mental State Examination; NA, not applicable; PiB, Pittsburgh Compound B, UCLA-3, 3-item UCLA Loneliness Scale.

[a] Unless otherwise indicated, 79 participants were included in the analysis, and data are reported as mean (SD) values.

Table 2

Multivariate Model for Association of UCLA Loneliness Scale With Amyloid Burden[a]

Predictor	β Estimate (95% CI)	Standardized β (SE)	*P* Value
Amyloid burden in PiB DVR (unit = 1)	3.3 (1.2 to 5.3)	0.38 (1.03)	.002
Age	−0.10 (−1.50 to −0.04)	−0.34 (0.03)	.002
Male sex	0.009 (−0.787 to 0.804)	0.002 (0.400)	>.99
Hollingshead	−0.002 (−0.027 to 0.024)	−0.12 (0.01)	.90
GDS	0.17 (0.05 to 0.28)	0.32 (0.06)	.005
HADS-anxiety	0.06 (−0.09 to 0.21)	0.09 (0.08)	.43
Social network	−0.05 (−0.44 to 0.34)	−0.03 (0.20)	.81
Positive APOEε4 carrier status	−0.90 (−1.87 to 0.02)	−0.23 (0.47)	.06

Abbreviations: APOEε4, apolipoprotein E ε4; DVR, distribution volume ratio; GDS, Geriatric Depression Scale–30 item; HADS, Hospital Anxiety and Depression Scale; PiB, Pittsburgh Compound B.

[a] $F_{64} = 3.8$, $P = .001$, and adjusted $R^2 = 0.23$.

Table 3

Multivariate Model of UCLA Loneliness Scale Association With Interaction of PiB Retention and APOEε4 Carrier Status[a]

Predictor	β Estimate (95% CI)	Standardized β (SE)	*P* Value
Amyloid burden in PiB DVR (unit = 1)	0.7 (−2.1 to 3.5)	0.08 (1.40)	.61
Positive APOEε4 carrier status	−7.5 (−12.6 to −2.5)	−1.8 (2.5)	.004
Interaction of PiB and APOEε4 carrier status	5.2 (1.2 to 9.1)	1.8 (2.0)	.01
Age	−0.08 (−0.14 to −0.02)	−0.30 (0.03)	.008
Sex	0.05 (−0.72 to 0.81)	0.01 (0.40)	.90
Hollingshead	0.002 (−0.022 to 0.026)	0.02 (0.01)	.88
GDS	0.20 (0.07 to 0.29)	0.30 (0.06)	.002
HADS-anxiety	0.03 (−0.12 to 0.18)	0.04 (0.07)	.70
Social network	−0.04 (−0.42 to 0.34)	−0.02 (0.20)	.84

Abbreviations: APOEε4, apolipoprotein E ε4; DVR, distribution volume ratio; GDS, Geriatric Depression Scale–30 item; HADS, Hospital Anxiety and Depression Scale; PiB, Pittsburgh Compound B.

[a] $F_{64} = 4.4$, $P < .001$, and adjusted $R^2 = 0.3$.