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RESEARCH ARTICLE

Relation of modifiable lifestyle and mood factors to cognitive concerns among participants and their study partners in the A4 screen data

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Abstract

Introduction: Subjective cognitive decline (SCD) has been associated with elevated amyloid levels and increased risk of future cognitive decline, as well as modifiable variables, including depression, anxiety, and physical inactivity. Participants generally endorse greater and earlier concerns than their close family and friends (study partners [SPs]), which may reflect subtle changes at the earliest stages of disease among participants with underlying neurodegenerative processes. However, many individuals with subjective concerns are not at risk of Alzheimer's disease (AD) pathology, suggesting that additional factors, such as lifestyle habits, may be contributory.

Methods: We examined the relation between SCD, amyloid status, lifestyle habits (exercise, sleep), mood/anxiety, and demographic variables among 4481 cognitively unimpaired older adults who are being screened for a multi-site secondary prevention trial (A4 screen data; mean ±SD: age = 71.3 ±4.7, education = 16.6 ±2.8, 59% women, 96% non-Hispanic or Latino, 92% White].

Results: On the Cognitive Function Index (CFI) participants endorsed higher concerns compared to SPs. Participant concerns were associated with older age, positive amyloid status, worse mood/anxiety, lower education, and lower exercise, whereas SP concerns were associated with older participant age, male gender of participant, positive amyloid status of participant, and worse participant-reported mood/anxiety.

Discussion: Findings suggest that modifiable/lifestyle factors (e.g., exercise, education) may be associated with participant concerns among cognitively unimpaired individuals and highlight the importance of further examining how modifiable factors impact participant- and SP-reported concerns, which may inform trial recruitment and clinical interventions.

KEYWORDS
exercise, lifestyle, mood, sleep, study partner, subjective cognitive decline (SCD)

1 | INTRODUCTION

Subjective cognitive decline (SCD), broadly defined as concern about self-perceived cognitive decline in the absence of deficits on standardized neurocognitive testing,[1] has emerged as an important concept in Alzheimer's disease (AD) research over the last decade. SCD is associated with elevated amyloid levels among cognitively normal older adults, such as those enrolled in AD prevention trials,[2–5] and increased risk of future cognitive decline.[6–8] Individuals with SCD *and* underlying AD pathology are at an increased risk of dementia and cognitive decline,[9,10] whereas many individuals with SCD without AD biomarkers may not progress to mild cognitive impairment (MCI) or dementia,[11] suggesting that various factors may be associated with SCD.[12,13]

Reports of change in cognitive functioning, not only from participants, but also their study partners (SPs; e.g., close friends or family), can help illuminate which factors may differentially impact subjective reports. Typically, participants endorse greater cognitive concerns than their SPs; however, participant report of cognitive status is not more likely to be associated with AD biomarkers and risk of clinical progression than SP report.[14–17] Among individuals who do progress to MCI, participants tend to endorse cognitive concerns earlier than their SPs,[18] which may be due to very early changes that are not yet observable by others. Another possibility is that additional factors, such as low mood and unhealthy lifestyle habits (e.g., physical inactivity, poor sleep), may explain greater endorsement of cognitive complaints by participants, whereas SP-reported concerns are perhaps less influenced by the participant's lifestyle habits and may reflect early cognitive changes that emerge at preclinical stages of disease for those with underlying AD pathology.

We sought to better understand what demographic and lifestyle variables may be associated with current levels of SCD among participants and their SPs. Participant report of SCD has been associated previously with various non-specific and potentially modifiable factors, such as depression, anxiety, physical inactivity, lower education, and poorer sleep and quality of life.[12–14,19–24] Less is known about whether the association between lifestyle habits and current SCD may differ for participant and SP report, particularly in the context of elevated AD biomarkers. Healthy lifestyle behaviors, such as exercise, may reduce the risk of cognitive decline[25] and are associated with lower levels of AD biomarkers[26] and higher overall well-being in terms of physical and emotional health,[27] all of which could lower one's report of SCD.

In this cross-sectional study, we examined the relation between current SCD, amyloid status, demographic variables, lifestyle habits (exercise and sleep), and mood/anxiety among cognitively unimpaired older adults from a multi-site secondary prevention trial to further understand the association between these factors and participant and SP reports of cognitive concerns. We hypothesized that in addition to amyloid burden[5] and mood/anxiety,[3] decreased exercise and sleep would also be associated with increased participant-, but not SP-, report of cognitive concerns.

RESEARCH IN CONTEXT

1. **Systematic Review**: Based on search of electronic databases (PubMed, Google Scholar), subjective cognitive decline (SCD) has been associated with elevated amyloid levels and increased risk of future cognitive decline, as well as modifiable variables, particularly depression and anxiety. Participants generally endorse greater and earlier concerns than their study partners (SPs), which may reflect subtle changes at the earliest stages of disease among participants with underlying neurodegenerative processes. However, SCD is not specific to those with AD pathology, suggesting that additional factors, such as lifestyle habits, may be contributory.
2. **Interpretation**: In this study, we examined the relation between SCD, amyloid status, demographic variables, lifestyle habits (exercise, sleep), and mood/anxiety among cognitively unimpaired older adults from a multisite secondary prevention trial (A4 screen data) to further understand factors that may contribute to participant and SP report. Participants endorsed higher cognitive concerns compared to SPs. Participant concerns were associated with older age, positive amyloid status, worse mood/anxiety, lower education, and lower exercise, whereas SP concerns were associated with older participant age, male gender of participant, positive amyloid status of participant, and worse participant-reported mood/anxiety.
3. **Future Directions**: Findings suggest that modifiable/lifestyle factors (e.g., exercise, education) may be associated with participant concerns among cognitively unimpaired individuals and highlight the importance of further examining factors that impact participant- and SP-reported concerns, which may inform trial recruitment and clinical interventions.

2 | METHODS

2.1 | Participants

The following data are from participants who were screened for the Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease (A4) Study, which is a preclinical stage treatment trial being conducted across 67 clinical trial sites in the United States, Canada, Japan, and Australia.[5,14]

Consent Statement: Institutional review board approval was obtained at each site, and across all 67 sites; 6768 individuals signed informed consent. After the initial screening visit, 4486 participants were eligible for positron emission tomography (PET) imaging based

TABLE 1 Demographics, mood/anxiety, cognitive concerns, and lifestyle habits ($n = 4481$).

	Mean (SD) unless otherwise noted
Age	71.29 (4.67)
Education	16.58 (2.84)
Gender (% women)	59%
Ethnicity (% non-Hispanic or Latino)	96%
Race (% White)	92% (total $n = 4454$)
GDS	1.03 (1.47)
STAI	9.94 (3.12)
CFI—Participant	1.99 (2.04)
CFI—Study Partner	1.23 (1.78)
Exercise	2.89 (3.80)
Sleep	7.10 (1.07)

Abbreviations: CFI, Cognitive Function Index. GDS, Geriatric Depression Scale (15-item). STAI, State Anxiety Inventory (6-item).
Exercise, average number of hours of aerobic exercise (i.e., jogging, swimming, bicycling) PER WEEK.
Sleep, average total number of hours slept at night.

on the following: Clinical Dementia Rating (CDR): global score = 0, Mini-Mental State Examination (MMSE): score = 25–30, and Logical Memory Delayed Recall: score = 6–18.[5]

For the following analyses, participants were 4481 cognitively unimpaired older adults from the A4 screen data, assessed pre-randomization, who had complete data for the variables used in our analyses (mean ±SD: age = 71.29 ±4.67, range 64–85; education = 16.58 ±2.84; 59% women; 96% non-Hispanic or Latino; 92% White); Table 1). Based on PET imaging, 1327 of 4481 participants (29.6%) were amyloid positive.

Among SPs, 60% were women, and the mean ±SD age was 65.80 ±11.19 (specific age information was missing for 38 SPs, < 1%). The relationship of SPs to participants was as follows: 62% spouses, 19% friends/companions, 12% adult children, 5% other relatives, 2% other, and < 1% children-in-law or paid caregivers.

2.2 | Measures

1. *Self-report of lifestyle habits*: This self-report questionnaire consists of eight items inquiring about current lifestyle habits, namely exercise ("average number of hours of aerobic exercise [i.e., jogging, swimming, bicycling] PER WEEK"), sleep ("average total number of hours slept at night"), and substance use (caffeine ["average number of cups of caffeine consumed per day"], alcohol ["average number of alcoholic drinks consumed per day"], tobacco ["average number of packs smoked per day"], other substances ("has the participant used other substances [e.g., non-pharmacologic substances such as medical marijuana?"]), but not diet.[5]
2. *Geriatric Depression Scale-15 item (GDS)*: The GDS-short consists of 15 yes/no items inquiring about mood, with higher scores reflecting greater concerns.[28] We ran analyses using the total GDS score, but also examined results when using a GDS score that excluded the memory-related item ("Do you feel you have more problems with memory than most?"), as described below.
3. *State Anxiety Inventory-6-item (STAI)*: The STAI consists of six items inquiring about state anxiety (e.g., current feelings of worry or tension), with higher scores reflecting greater concerns.[29,30]
4. *Cognitive Function Index (CFI)*: The CFI was originally developed as a 14-item questionnaire inquiring about cognitive concerns and daily functioning reported by the participant and their SPs (completed separately) and specifically asks about change within the past year, with response options of Yes, No, and Maybe.[31] The A4 version of the CFI includes an additional item "In the past year, have you seen a doctor about memory concerns?" with response options of Yes or No.[14] CFI responses were coded as follows: No = 0, Maybe = 0.5, Yes = 1, Does not apply = 0; all 15 items were then summed for a total of 15 possible points on both the participant and SP scales. Higher total scores reflected greater concerns.
5. *Amyloid status*: after in-clinic screening visits, a subset of eligible and cognitively unimpaired participants (described above) completed florbetapir amyloid PET imaging, acquired 50–70 minutes after injection of 10 mCi of florbetapir F 18.[5] For the following analyses, amyloid status consisted of a dichotomous variable on whether the amyloid PET eligibility scan was positive or negative for amyloid, based on a combination of quantitative standardized uptake value ratio (SUVr) methods and qualitative visual reads at a central lab.[5]

2.3 | Statistical analysis

Using multiple linear regression models, we examined whether demographic variables (age, education, gender of participant), participant-reported mood (GDS), anxiety (STAI), lifestyle habits (exercise, sleep), and/or amyloid status were associated with current cognitive concerns on the CFI, as reported by the participants and their SPs. We ran multiple linear regression models, with all predictors entered into the model at once. For all regression analyses, the sample was restricted to only those individuals with complete data for all variables used in the regression analyses (age, education, gender, mood, anxiety, CFI, exercise, sleep, amyloid status; $n = 4481$).

3 | RESULTS

For lifestyle habits in this study, we focused on exercise (average number of hours of aerobic exercise per week) and sleep (average total hours of sleep at night). Information on diet was not collected in this sample, and participants reported very low substance use (82% reported having 0–1 alcoholic drinks per day and 98% were non-smokers), so substance use was not examined due to the limited range in response.

Higher cognitive concerns were endorsed by participants on the CFI compared to their SPs ($t(4480) = 23.95$, $p < 0.001$). Mean ±SD scores on the CFI were 1.99 ±2.04 for participants and 1.23 ±1.78

TABLE 2 Association of *participant concerns* with participant demographic and lifestyle variables.

	Unstandardized Coefficients		Standardized Coefficients		
	B	*Std. Error*	*Beta*	*t*	*Significance*
(Constant)	−0.039	0.529		−0.074	0.941
Gender	−0.048	0.059	−0.012	−0.828	0.408
Age	0.025	0.006	0.058	4.184	<0.001*
Education	−0.038	0.010	−0.053	−3.790	<0.001*
Aerobic exercise (h/week)	−0.022	0.007	−0.041	−2.969	0.003*
Sleep (h/night)	−0.029	0.026	−0.015	−1.112	0.266
GDS	0.442	0.021	0.319	21.486	<0.001*
STAI	0.062	0.010	0.095	6.383	<0.001*
Amyloid status	0.419	0.062	0.094	6.798	<0.001*

Note: Dependent variable: Cognitive Function Index (CFI)—Participant.
GDS, Geriatric Depression Scale (15-item). STAI, State Anxiety Inventory (6-item).
*Significant at $p < 0.01$.

TABLE 3 Association of *study partner concerns* with participant demographic and lifestyle variables.

	Unstandardized Coefficients		Standardized Coefficients		
	B	*Std. Error*	*Beta*	*t*	*Significance*
(Constant)	0.028	0.491		0.057	0.954
Gender	−0.367	0.054	−0.101	−6.748	<0.001*
Age	0.020	0.006	0.054	3.632	<0.001*
Education	−0.003	0.009	−0.004	−0.283	0.777
Aerobic exercise (h/week)	−0.011	0.007	−0.024	−1.639	0.101
Sleep (h/night)	−0.026	0.025	−0.016	−1.070	0.285
GDS	0.191	0.019	0.157	10.005	<0.001*
STAI	0.030	0.009	0.053	3.366	<0.001*
Amyloid status	0.282	0.057	0.072	4.923	<0.001*

Note: Dependent variable: Cognitive Function Index (CFI)—Study partner.
GDS, Geriatric Depression Scale (15-item). STAI, State Anxiety Inventory (6-item).
*Significant at $p < 0.01$.

for SPs, of 15 possible points. Participants endorsed healthy lifestyle habits (mean ±SD: hours of aerobic exercise/week = 2.89 ±3.80, range: 0–40, with 37% of the sample reporting 0 h of exercise per week; hours of sleep/night = 7.10 ±1.07, range: 2–12). Participants endorsed minimal mood and anxiety symptoms (mean ±SD: GDS = 1.03 ±1.47, STAI = 9.94 ±3.12), with 88% of participants scoring in the 0–2 range on the GDS. When looking at individual GDS items, 13% of the sample (n = 596/4474) endorsed the memory-related item ("Do you feel you have more problems with memory than most?"; n = 7 [< 1%] with missing data for that one item). The results did not change when a GDS total score was used that excluded this memory item, so we elected to report the standard total GDS score in the models below.

There was a significant moderate positive correlation between mood and anxiety ($r = 0.36$, $p < 0.001$), and significant, but weak, negative correlations between mood and lifestyle habits (exercise: r = -0.10, $p < 0.001$; sleep: r = -0.05, $p < 0.001$), as well as between anxiety and lifestyle habits (exercise: r = -0.05, $p < 0.001$; sleep: r = -0.10, $p < 0.001$). Compared to women, men reported higher levels of aerobic exercise (means: 3.36 vs 2.57 h per week, $p < 0.001$) and slightly less sleep (means: 7.07 vs. 7.13 h per night, $p = 0.045$). Participant CFI scores did not differ by gender ($p > 0.76$), but SP CFI scores were higher when reporting on male participants ($t(3493) = 6.73$, $p < 0.001$). Self-reported lifestyle habits (exercise, sleep) did not differ by amyloid status ($p > 0.11$).

3.1 | Regression analyses

Amyloid status ($\beta = 0.094$, $p < 0.001$), older age ($\beta = 0.058$, $p < 0.001$), higher depressive symptoms ($\beta = 0.319$, $p < 0.001$), higher anxiety ($\beta = 0.095$, $p < 0.001$), lower education (β = -0.053, $p < 0.001$), and lower exercise (β = -0.041, $p = 0.003$) were significantly associated with participant concerns on the CFI (sleep and gender n.s. [p's > 0.26]; overall regression model: [$F(8, 4472) = 105.49$, $p < 0.001$]; Table 2). Among SPs (Table 3), amyloid status ($\beta = 0.072$, $p < 0.001$), higher participant-reported depressive symptoms ($\beta = 0.157$, $p < 0.001$),

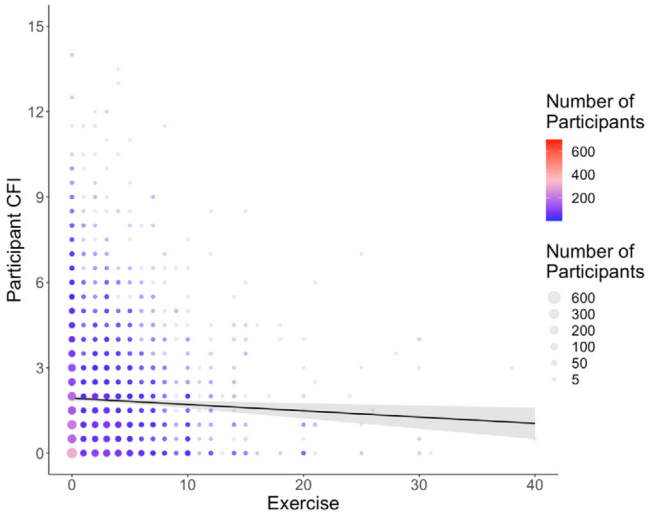

FIGURE 1 *Participant* concerns and participant-reported exercise. Number of participants shown by both color and size of datapoints. CFI. Exercise, average number of hours of aerobic exercise (i.e., jogging, swimming, bicycling) PER WEEK. CFI, Cognitive Function Index.

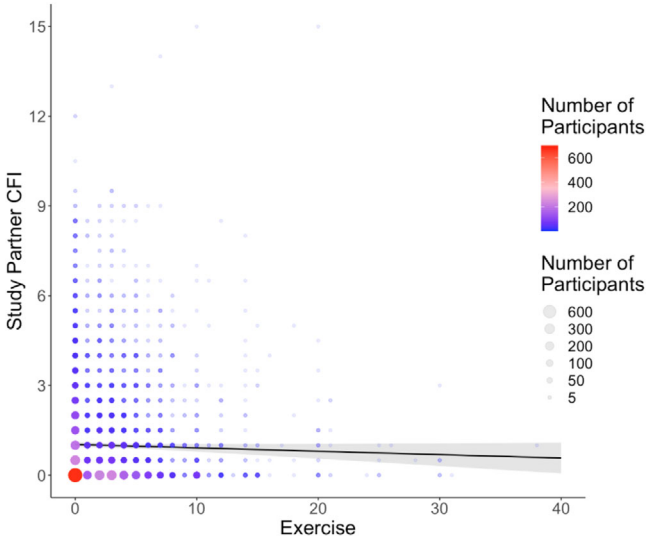

FIGURE 2 *Study partner* concerns and participant-reported exercise. Number of participants shown by both color and size of datapoints. CFI. Exercise, average number of hours of aerobic exercise (i.e., jogging, swimming, bicycling) PER WEEK. CFI, Cognitive Function Index.

higher participant-reported anxiety ($\beta = 0.053$, $p < 0.001$), older participant age ($\beta = 0.054$, $p < 0.001$), and male gender of participant ($\beta = -0.101$, $p < 0.001$) were associated with SP concerns; participant education, exercise, and sleep were not significantly associated with SP concerns (all p-values > 0.10l overall regression model: $F(8, 4472) = 33.28$, $p < 0.001$. Please see figures for visualization of the associations between exercise and participant concerns (Figure 1) and exercise and SP concerns (Figure 2), with the latter showing a greater density of values at the very low end of the variable ranges.

4 | DISCUSSION

Cognitively unimpaired participants endorsed higher cognitive concerns on the CFI compared to their SPs, consistent with prior studies using the A4 data set.[14] To further explore this finding, we sought to examine various factors that might contribute to participant and SP concerns, including amyloid status, mood/anxiety, lifestyle habits (exercise, sleep), and demographic factors. We found that both participant and SP concerns were associated with older participant age, positive amyloid status of participant, and worse participant-reported mood and anxiety. In addition, lower participant education and exercise were associated with participant concerns, and male gender of the participant was associated with SP concerns. One possible explanation is that cognitively unimpaired participants may be more aware of their own cognitive changes and endorse concerns reflecting a combination of factors, including personal lifestyle habits and overall well-being/health, whereas SP report may be more specific to cognitive changes due to age and/or amyloid burden among participants, and less influenced by modifiable variables, such as participant-reported exercise and level of education, among cognitively unimpaired individuals. Other studies have reported increased accuracy of spousal SP report (but not other categories of SP) to predict current participant cognition relative to participant report,[32] suggesting that SP concerns may more accurately reflect objective cognitive decline of the participant. Regarding the association between male gender of participant and SP concerns, the majority of SPs in this sample were female, and prior studies have reported higher concerns among female SPs compared to males in the A4 data set.[14]

Furthermore, consistent with the previous literature,[14,23,33] mood and anxiety were strongly associated with participant and SP concerns, and lower education contributed to current participant concerns. Future research is needed to elucidate the mechanisms driving associations between modifiable variables (e.g., mood, anxiety, education, exercise) and participant and SP concerns. There is some evidence to suggest that healthy lifestyle behaviors may cluster together, including associations between higher education and improved health behaviors (e.g., exercise, diet, and substance use).[34] As such, higher levels of exercise and education may reduce participant concerns in a synergistic manner by positively impacting overall mood and well-being,[35] cognitive/social engagement, and self-efficacy. In addition, select lifestyle behaviors, namely exercise, could potentially reduce subjective concerns by positively impacting cognition via enhanced cardiovascular health and noradrenergic activation, as observed in both mild cognitive impairment (MCI) and cognitively normal older adults.[36,37]

In addition to examination of potential mechanisms, future longitudinal studies are needed, as the cross-sectional design of the current study does not allow us to speak to directionality of effects between lifestyle factors and SCD. Also notable is that measures of lifestyle habits in the current study were limited to brief self-report questions, which may not correlate strongly with objective measures.[38] Future studies will benefit from further characterization of the relation between SCD and lifestyle factors via inclusion of both participant- and SP-reported concerns, objective measures of physical activity/sleep,

and biomarker data. Regarding exercise, studies have shown that physical activity in early adulthood and in mid-to-late life is associated with lower risk of late-life SCD, although this particular study was limited to self-reported concerns with male participants,[39] highlighting the need to incorporate SP-reported concerns and biomarker data in more diverse samples when studying SCD and lifestyle habits. Regarding sleep, in contrast with prior studies,[24] we found that self-reported sleep duration was not significantly associated with participant or SP cognitive concerns, which may reflect the fact that the majority of the sample reported adequate sleep duration (67% of participants reported averaging 7–8 h of sleep per night). Inclusion of objective measures of sleep quality in future studies are needed to clarify the relation between sleep quality and SCD. It may also be valuable to explore other lifestyle habits as related to SCD, to determine if cognitive and social activity and/or diet, may differentially contribute to participant- and SP-reported cognitive concerns. The current sample did not include data on dietary habits, but high-vegetable diets have been associated with higher scores on objective cognitive measures among individuals with SCD[40]; additional work would be helpful to clarify how dietary habits may contribute to subjective concerns.

Relatedly, a more nuanced understanding of how demographic and modifiable factors contribute to participant- and SP-reported SCD also has the potential to inform research recruitment/design[41] and interventions. Recent studies have identified aspects of SCD (e.g., onset of cognitive decline in the past 5 years, worry about decline, and SP concern of decline) that best predict AD pathology, referred to as SCD-plus.[42] Our findings highlight the importance of also considering how modifiable factors (e.g., mood, anxiety, exercise, education) may impact participant concerns above and beyond amyloid burden among individuals screening for preclinical AD trials. Relatedly, lifestyle interventions for SCD may benefit from characterizing how lifestyle habits contribute to baseline cognitive concerns and then tailoring interventions accordingly (e.g., specifically targeting exercise) and including measures of lifestyle habits and subjective cognitive concerns as outcome measures. To date, many intervention studies have focused on physical activity, which has been found to improve global cognition among individuals with SCD or MCI, with mixed findings for executive function and memory, typically measured in trials of ≈6–12 months in duration.[43] Future intervention trials focused on SCD may especially benefit from expanding outcome measures to include lifestyle habits in addition to biomarker data and participant- and SP-reported concerns, and assessing for any pre–post changes and/or interactions among these variables.

In conclusion, our findings expand our understanding of how various factors (e.g., biomarkers, mood, anxiety, lifestyle habits, demographics) may contribute to participant and SP cognitive concerns among cognitively unimpaired individuals. The current data were limited to a small number of self-report measures of lifestyle habits among a homogenous, cross-sectional sample, highlighting the importance of examining these factors longitudinally in more diverse samples and including more nuanced and objective measures of physical activity[38] and other lifestyle habits, in addition to participant- and SP-report and biomarker data. Even so, in this large data set, we examined how demographic, biomarker, and modifiable/lifestyle variables may contribute to current participant- and SP-reported cognitive concerns. These findings assist in the characterization of SCD, which may inform trial screening/recruitment, lifestyle interventions, and ultimately clinical care, by considering how modifiable factors may contribute in part to current cognitive concerns and then developing tailored intervention approaches and targets for treatment.

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CONFLICT OF INTEREST STATEMENT

G. Reynolds, R. Buckley, K. Papp, S. Schultz, and R. Amariglio have nothing relevant to disclose. D. Rentz has nothing to disclose related to this project but other disclosures include the Dana Corporation, and Scientific Advisory Boards at Northwestern and UC Davis. R. Sperling has served as a paid consultant for AC Immune, Alector, Acumen, Alnylam, Genentech, Janssen, Neuraly, Oligomerix, Prothena, Renew, and Vaxxinity; receives research support from Eisai and Eli Lilly (these relationships are not related to the content in the manuscript); and also receives research support from the following grants: P01 AG036694,U24 AG057437, R01 AG063689, R01 AG054029, R01 AG053798, GHR Foundation, Fidelity Biosciences, and the Alzheimer's Association. Author disclosures are available in the Supporting Information.

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SUPPORTING INFORMATION

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

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