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RESEARCH ARTICLE

Instrumental activities of daily living, amyloid, and cognition in cognitively normal older adults screening for the A4 Study

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Abstract

Introduction: We examined the associations among instrumental activities of daily living (IADL), cortical amyloid, and cognition in cognitively normal (CN) older adults.

Methods: CN participants screening for the A4 Study (n = 4486) underwent florbetapir (amyloid) positron emission tomography. IADL were assessed using the Alzheimer's Disease Cooperative Study Activities of Daily Living Prevention Instrument. Separate logistic regression models were run with cortical amyloid or cognition as independent variable and IADL as dependent variable, adjusting for age and sex.

Results: IADL difficulties were endorsed infrequently (≤16%). Overall IADL and four select IADL item difficulties ("remembering appointments," "finding belongings," "following TV programs," and "remembering current events") reported by both participant and study partner were significantly associated with greater amyloid burden and worse cognition.

Discussion: Although IADL deficits were infrequent in this CN cohort, greater participant and study partner report of overall IADL deficits and subtle difficulties in specific IADL items were associated with mildly higher amyloid burden and worse cognition.

KEYWORDS
Alzheimer's disease, amyloid, cognition, cognitively normal, florbetapir, instrumental activities of daily living, positron emission tomography

1 | BACKGROUND

Instrumental activities of daily living (IADL) are impaired at the mild stage of dementia, but subtle impairments can be detected at the precursor stage of mild cognitive impairment (MCI) as well.[1–3] Previous work has shown that some sensitive measures of IADL or specific items within those measures differentiate between cognitively normal (CN) older adults and those with MCI at baseline or predict progression from CN to MCI, thereby supporting the clinical meaningfulness of IADL; these studies included a variety of IADL measurement methods, ranging from self (participant) and study partner-report questionnaires, such as the Alzheimer's Disease Cooperative Study Activities of Daily Living Prevention Instrument (ADCS ADL-PI), to performance-based IADL tests.[4–14] However, it remains unclear whether IADL impairment can be detected cross-sectionally in even earlier stages of Alzheimer's disease (AD), in particular in the biomarker-defined stage of preclinical AD.[15] To date, few publications have examined systematic IADL assessment in CN individuals with high cortical amyloid burden consistent with preclinical AD and CN individuals with low amyloid.[16,17]

In the current study, we analyzed the Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease (A4) Study [18] screening data of CN participants who underwent florbetapir positron emission tomography (PET) to determine the cross-sectional associations among IADL, as measured by the participant and study partner-reported ADCS ADL-PI, cortical amyloid deposition as measured by florbetapir PET, and cognition. We hypothesized that subtle difficulties in IADL will be associated with greater cortical amyloid burden and worse cognition.

HIGHLIGHTS

- In this cross-sectional study in which we studied a large cohort of cognitively normal (CN) older participants, we found that subtle difficulties in instrumental activities of daily (IADL) were present in a minority of participants.
- Participants and study partners showed a high level of agreement in reporting IADL performance.
- Overall difficulties in IADL, as well as difficulties in specific IADL activities, reported by both participants and study partners, were associated with mild elevations in cortical amyloid burden and worse cognitive performance at baseline.
- We found more IADL difficulties among men and older participants.
- This is one of the first studies to report an association between IADL difficulties and cortical amyloid burden in CN participants at risk for Alzheimer's disease.

RESEARCH IN CONTEXT

1. **Systematic review**: We have conducted a traditional literature search. The Food and Drug Administration's guidance for appropriate use of outcome measures for prevention trials in preclinical Alzheimer's disease (AD) emphasizes cognition and suggests that there are insufficient validated instrumental activities of daily living (IADL) tests that can be used as clinically meaningful outcomes.
2. **Interpretation**: The A4 Study, a prevention trial, included the Alzheimer's Disease Cooperative Study Activities of Daily Living Prevention Instrument as an outcome measure. Here we demonstrate in 4486 cognitively normal (CN) older adults, who screened for A4, that IADL difficulties were associated with mild elevation in cortical amyloid and worse cognitive performance at baseline. These results complement a smaller study showing a trend of worse IADL performance over 3 years in amyloid-positive versus negative non-demented participants.
3. **Future directions**: Additional observational studies and AD prevention trials are needed to further demonstrate the validity and utility of detecting subtle IADL difficulties in CN older adults with greater cortical amyloid burden.

2 | METHODS

2.1 | Participants

Participants who screened for the A4 Study, met initial cognitive and medical screening criteria, and underwent florbetapir (amyloid) PET from 2013 to 2017 were included in this study. For more details, see the supporting information and a recent detailed description of the screening cohort,[19] which has completed enrollment in December 2017 and is ongoing. The CN participants had study partners willing to provide collateral information about the participants' cognitive function and IADL. Four thousand four hundred and eighty-six participants meeting clinical inclusion criteria underwent florbetapir PET.

2.2 | Clinical assessments

The assessments described below were performed at the first screening visit prior to PET imaging.

2.2.1 | IADL assessment

An adapted form of the ADCS ADL-PI[5] was administered to both participants and study partners to assess IADL. The original ADCS

ADL-PI consisted of 15 items and was previously found to have adequate reliability.[5] Items address IADL, such as managing finances, traveling, and organizing activities (see Tables 2 and 3). For the A4 Study, three technology-related items were added (items 16–18), aimed at capturing aspects of use of cellphones, smartphones, computers, tablets, and e-readers. They were pretested among CN volunteers for clarity of wording and feasibility. The timeframe of reference for all items is within the past 3 months.

Each item was scored on a 4-point scale with the following responses: 0 = You did not do this activity; or You did do the activity: 1 = with a lot of difficulty; 2 = with a little difficulty; and 3 = as well as usual, with no difficulty. For items 16 to 18, the above 4-point scale was preceded by multiple subquestions about the use of the technology-related item for which we provide descriptive data (see Table 3). For study partner responses, an additional option of "You do not know" is given. In the current analyses, a response of "You do not know" was prorated (see supporting information). Total scores for the 15-item version ranged from 0 to 45 and for the 18-item version from 0 to 54, with higher scores indicating better performance.

For the current study, almost no responses of "With a lot of difficulty" were observed for the individual items, leading to ceiling effects in both the individual item scores and the total scores (see Figure 1A and B). Item scores were therefore dichotomized to performing each activity with difficulty (score = 1) or without difficulty (score = 0). Total scores were also dichotomized and the direction was oriented to match the individual item analyses (15-item version: score $< 45 = 1$ or performing IADL with difficulty, score of $45 = 0$ or without difficulty; 18-item version: score $< 51 = 1$ or performing IADL with difficulty, score $\geq 51 = 0$ or without difficulty).

Based on an initial item-level frequency analysis of the data, items for which >8% of all participants endorsed performing "with difficulty" were selected for subsequent item-level analyses. Four items met this criterion (see Results section).

2.2.2 | Cognition assessment

The Preclinical Alzheimer Cognitive Composite (PACC)[20] was administered to participants to assess cognition. The PACC is the sum of the z-scores of four cognitive tests: The Mini-Mental State Exam (MMSE), the Free and Cued Selective Reminding Test, Logical Memory II subscale delayed paragraph recall, and Digit Symbol. Higher scores indicate better cognitive performance.

2.3 | PET imaging

Cortical amyloid was visualized in vivo with 18F-florbetapir PET using the A4 PET scanning protocol (see supporting information). A continuous measure of aggregate cortical amyloid across frontal, parietal, and temporal regions of florbetapir PET standardized uptake value ratio (SUVR) was used in the primary analyses. The reference region used was whole cerebellum. Analyses were repeated using a dichotomous cortical amyloid measure (elevated amyloid/non-elevated amyloid; see supporting information).

2.4 | Statistical analyses

Statistical programming language R was used in all analyses. We fitted a series of univariate and multivariable logistic regression models, reporting odds ratio (OR), 95% confidence intervals (CI), and *P*-values. Participant demographics and characteristics that had significant associations with ADCS ADL-PI in the univariate analyses were added as covariates in the multivariable logistic models.

In the primary analyses, separate multivariable logistic regression models were fitted to assess the relationship between dichotomous IADL (participant or study partner-reported ADCS ADL-PI items with frequent endorsement or ADCS ADL-PI 15-item or 18-item total scores) and cortical amyloid or cognition as independent variables. We reported models using two different sets of independent variables: one set using continuous cortical amyloid (florbetapir PET SUVR) along with age and sex; the other set replaced continuous cortical amyloid with cognition (PACC). For all models, OR, 95% CI, and *P*-values were reported. *P*-values of $< .05$ were considered statistically significant. No adjustment for multiple comparisons was performed.

3 | RESULTS

A total of 4486 participants, age 71.3 ± 4.7 years and 59% female, were included in these analyses, of which 3163 (70.5%) were found to have non-elevated amyloid and 1323 (29.5%) were found to have elevated amyloid. Study partners were mostly spouses (62%) and female (60%) and were 65.8 ± 11.2 years of age. Table 1 provides the participant demographics and characteristics for all participants, non-elevated amyloid participants, and elevated amyloid participants.

Performance on the ADCS ADL-PI was highly skewed (see Figure 1 for distribution) with a participant-reported 15-item median (interquartile range [IQR]) total score of 45.0 (42.0 to 45.0) in all participants; study partner-reported 15-item median (IQR) total score of 45.0 (42.5 to 45.0); participant-reported 18-item median (IQR) total score of 51.0 (48.0 to 54.0); and study partner-reported 18-item median (IQR) total score of 51.0 (50.0 to 54.0).

Sex and age were significantly associated with IADL performance reported by both participant and study partner on the ADCS ADL-PI such that male sex ($P < .001$) and greater age ($P < .001$) were associated with greater IADL difficulties. However, participant years of education, participant retirement status, and study partner relationship to participant were not significantly associated with IADL performance.

Performance on all participant and study partner-reported 18 items of the ADCS ADL-PI is shown in Tables 2 and 3. Four ADCS ADL-PI items met the > 8% endorsement threshold criterion for self-reported difficulty: item 7 "How well did you remember important dates and times, such as appointments or meetings?"; item 8 "Did you usually find

TABLE 1 Participant demographics and characteristics

		All	Non-elevated amyloid	Elevated amyloid	*P*
N		4,486	3,163	1,323	N/A
Age (years)		71.3 ± 4.7	71.0 ± 4.5	72.1 ± 4.9	<.001[c]
Sex (% male)		41	40	41	.64[a]
Race (% White)		92	91	94	<.001[b]
Education (years)		16.6 ± 2.8	16.6 ± 2.9	16.5 ± 2.8	.53[c]
Married (%)		71	70	71	.66[a]
Retired (%)		76	76	76	.93[a]
Study partner relationship to participant	**Spouse (%)**	62	62	62	1.00[b]
	Adult child (%)	12	11	13	1.00[b]
	Friend/companion (%)	19	19	18	1.00[b]

Age and education values represent mean ± standard deviation.
[a]Fisher's exact test.
[b]Fisher's exact with Holm adjustment test.
[c]T-Test/analysis of variance with unequal variances for two groups.

TABLE 2 Participant and study partner-reported performance on ADCS ADL-PI items 1-15 (dichotomized responses). Values represent % of participants and study partners reporting participants having difficulty performing the task in the past 3 months

	Participant report			Study partner report		
Item	**All**	**Non-elevated amyloid**	**Elevated amyloid**	**All**	**Non-elevated amyloid**	**Elevated amyloid**
1. How well did you balance a credit card statement, pay bills, or use an ATM?	1	1	2	2	1	2
2. Did you drive a car without getting lost, or did you travel to wherever you needed by using public or other transport?	3	2	3	3	3	3
3. Did you use an appliance, or did you carry out household repairs?	1	1	1	1	1	2
4. Did you do the laundry?	0	0	0	0	0	1
5. Did you select and pay for items when shopping?	0	0	0	0	0	1
6. Did you prepare meals or snacks?	1	1	1	1	1	1
7. How well did you remember important dates and times, such as appointments or meetings?	10	9	13	10	9	12
8. Did you usually find your personal belongings at home?	16	14	20	14	13	17
9. How well were you able to write things down so that other people understood them?	1	1	2	1	1	1
10. How well did you follow TV programs or movies and remember the details of the story?	10	9	10	4	3	6
11. How well did you talk about and remember current events that you heard or read about?	9	8	10	4	4	4
12. How well did you make telephone calls, including look up numbers or call directory assistance if necessary?	1	1	1	1	1	1
13. Did you take medications regularly?	3	3	3	2	2	2
14. Did you plan and organize complex activities for yourself or for groups of people?	2	2	2	2	1	3
15. Did you complete complex activities such as hobbies or pastimes?	2	2	3	1	1	2

Abbreviations: ADCS ADL-PI, Alzheimer's Disease Cooperative Study Activities of Daily Living Prevention Instrument; ATM, automated teller machine.

TABLE 3 Participant and study partner-reported performance on ADCS ADL-PI items 16 to 18. Values represent % of participants and study partners reporting a given response

		Participant report			Study partner report		
Item		All	Non-elevated amyloid	Elevated amyloid	All	Non-elevated amyloid	Elevated amyloid
16. Cellphone or smartphone	Did you ever use it (% yes)	99	99	99	99	99	98
	Did you use it in past 3 months (% yes)	99	99	99	99	99	99
	Make a call (% yes)	100	100	100	99	99	100
	Send a text message (% yes)	84	84	82	79	80	77
	Access the internet (% yes)	76	77	74	73	74	71
	Use an app (% yes)	70	70	68	62	64	59
	Did you use it less often than usual (% yes)	4	4	4	3	3	3
	Did you have difficulty using it (% yes)	4	3	6	4	3	5
17. Computer, tablet, or other device with internet access	Did you ever use it (% yes)	98	98	98	98	98	98
	Did you use it in past 3 months (% yes)	99	99	99	99	99	99
	Access website, Facebook, or e-mail (% yes)	100	100	100	99	99	99
	Enter information on device (% yes)	98	98	98	96	96	96
	Make purchases or reservations (% yes)	88	89	87	81	83	78
	Use passwords (% yes)	97	97	97	90	90	88
	Did you use it less often than usual (% yes)	6	6	5	4	4	4
	Did you have difficulty using it (% yes)	3	3	3	3	3	4
18. E-reader	Did you ever use it (% yes)	56	57	53	48	50	45
	Did you use it in past 3 months (% yes)	80	80	79	82	82	82
	Read a book or article (% yes)	95	95	96	92	92	93
	Download reading material (% yes)	86	86	87	78	79	78
	Make an adjustment to appearance (% yes)	74	74	76	51	52	48
	Did you use it less often than usual (% yes)	10	11	9	5	5	5
	Did you have difficulty using it (% yes)	2	1	2	1	1	2

Abbreviation: ADCS ADL-PI, Alzheimer's Disease Cooperative Study Activities of Daily Living Prevention Instrument.

your personal belongings at home?"; item 10 "How well did you follow TV programs or movies and remember the details of the story?"; and item 11 "How well did you talk about and remember current events that you heard or read about?"

In the primary analyses, multivariable logistic regression models were used adjusting for sex and age. Greater cortical amyloid burden was significantly associated with greater participant-reported IADL difficulties across all four ADCS ADL-PI items described above with OR ranging from 2.01 to 3.86 per unit increase in SUVR (see Table 4 and Figure 2A). For study partner-reported assessments, there were similar significant associations in three of the ADCS ADL-PI items with OR ranging from 2.67 to 3.87 per unit increase in SUVR (see Table 4 and Figure 2A). When the analyses were repeated using dichotomous cortical amyloid, similar results were obtained (see Table S1 in supporting information).

In models assessing cognition (PACC), better performance on cognition was significantly associated with less participant and study partner-reported IADL difficulties across all four ADCS ADL-PI items with OR ranging from 0.90 to 0.94 per unit increase in PACC (see Table 4 and Figure 2B).

For both 15-item and 18-item ADCS ADL-PI total scores, greater cortical amyloid burden was significantly associated with greater participant and study partner-reported IADL difficulties with OR ranging from 2.00 to 2.38 per unit increase in SUVR (see Table 4). When the analyses were repeated using dichotomous cortical amyloid, similar results were obtained (see Table S1). In addition, better performance on cognition was significantly associated with less participant and study partner-reported IADL difficulties with OR ranging from 0.89 to 0.93 per unit increase in PACC (see Table 4).

See supporting information for analyses determining agreement between participant and study partner reports and the overlap in responses to the four items, association between ADCS ADL-PI and individual cognitive tests, and association between ADCS ADL-PI and Cognitive Function Index (CFI).

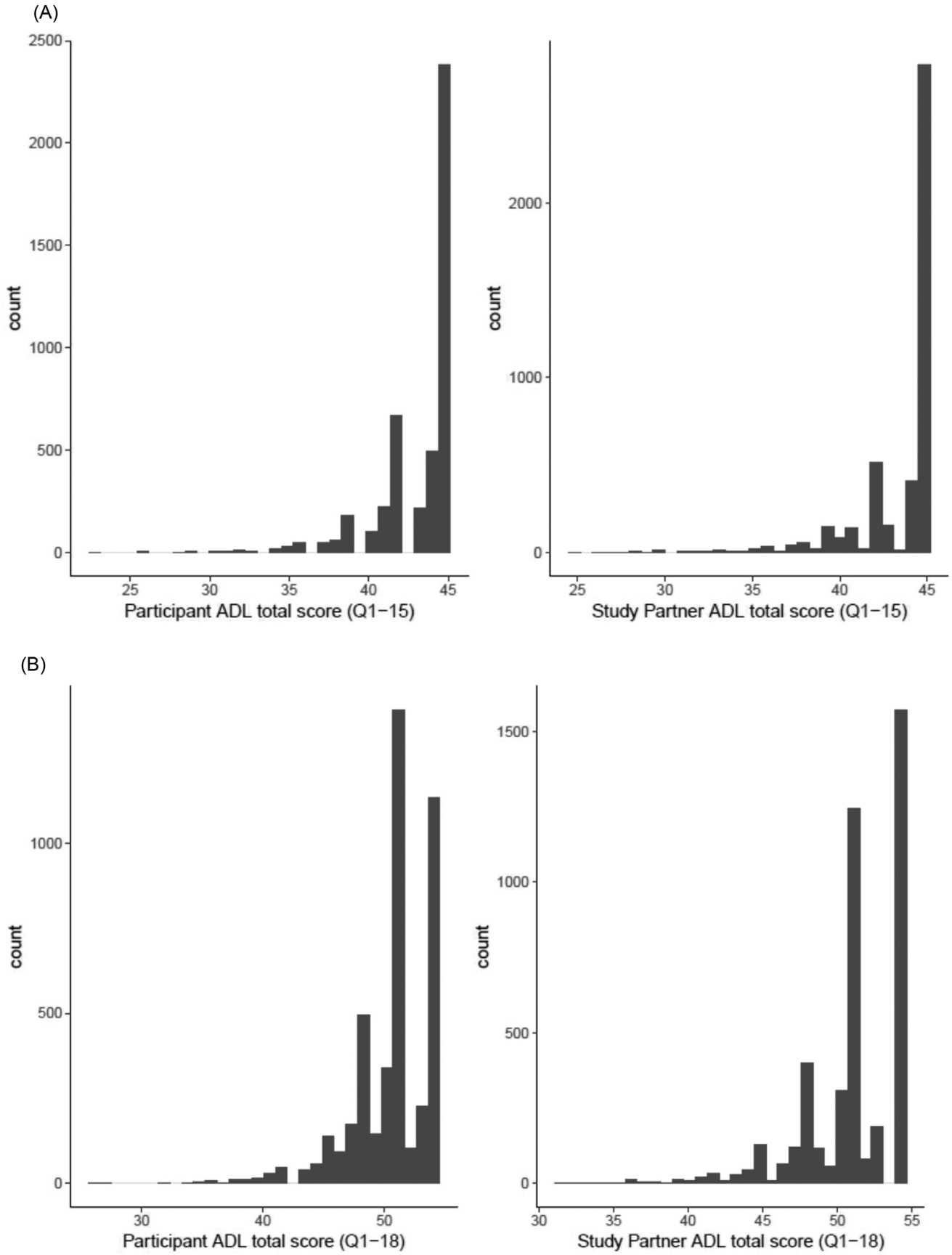

FIGURE 1 Distribution of Alzheimer's Disease Cooperative Study Activities of Daily Living Prevention Instrument 15-item total score (A) and 18-item total score (B). ADCS ADL-PI. ADL, Activities of Daily Living

TABLE 4 The odds of participant and study partner-reported difficulties on ADCS ADL-PI items and total scores (15 item and 18 item) per unit increase in cortical amyloid (florbetapir SUVR) and cognition (PACC). Models are adjusted for age and sex. No adjustment was applied for multiple comparisons

Participant-reported ADCS ADL-PI item	Cortical amyloid			Cognition		
	OR	95% CI	*P*	OR	95% CI	*P*
How well did you remember important dates and times, such as appointments or meetings?	2.77	1.76,4.37	<.001	0.90	0.87,0.94	<.001
Did you usually find your personal belongings at home?	3.86	2.63,5.66	<.001	0.94	0.90,0.97	<.001
How well did you follow TV programs or movies and remember the details of the story?	2.01	1.27,3.17	.003	0.90	0.86,0.93	<.001
How well did you talk about and remember current events that you heard or read about?	2.13	1.30,3.48	.003	0.92	0.88,0.96	<.001
Total score (15 item)	2.38	1.72,3.33	<.001	.91	0.88,0.93	<.001
Total score (18 item)	2.27	1.64,3.13	<.001	.89	0.87,0.92	<.001
Study partner-reported ADCS ADL-PI item	**OR**	**95% CI**	***P***	**OR**	**95% CI**	***P***
How well did the participant remember important dates and times, such as appointments or meetings?	3.26	2.07,5.14	<.001	0.90	0.87,0.94	<.001
Did the participant usually manage to find personal belongings at home?	2.67	1.78,4.00	<.001	0.93	0.90,0.97	<.001
How well did the participant follow TV programs or movies and remember the details of the story?	3.87	2.09,7.16	<.001	0.91	0.86,0.97	.001
How well did the participant talk about and remember current events that he/she heard or read about?	1.36	0.65,2.83	.42	0.90	0.85,0.96	<.001
Total score (15 item)	2.27	1.64,3.13	<.001	0.93	0.91,0.96	<.001
Total score (18 item)	2.00	1.45,2.78	<.001	0.92	0.89,0.94	<.001

Abbreviations: ADCS ADL-PI, Alzheimer's Disease Cooperative Study Activities of Daily Living Prevention Instrument; CI, confidence interval; OR, odds ratio; PACC, Preclinical Alzheimer Cognitive Composite; SUVR, standardized uptake value ratio.

4 | DISCUSSION

Analyzing the A4 Study screening cohort of nearly 4500 well-characterized CN participants who underwent amyloid PET imaging, we found that overall IADL difficulties, as well as difficulties in specific IADL activities, reported by both participants and knowledgeable study partners, while generally uncommon in this CN screening sample, were associated with mild elevation in cortical amyloid burden and worse cognitive performance at baseline.

To our knowledge, this is one of the first studies to report an association between IADL difficulties and cortical amyloid burden in CN participants at risk for AD. Our findings replicate and extend previous studies. A recent smaller cross-sectional study using the Financial Capacity Instrument Short Form in 144 CN participants showed an association between greater IADL difficulties (time to completion of the financial tasks) and greater cortical amyloid burden visualized with florbetapir PET.[17] Another recent smaller longitudinal study using the ADCS ADL-PI and florbetapir PET followed 269 non-demented participants (59% with global Clinical Dementia Rating [CDR] = 0 [equivalent to CN] and 41% with global CDR = 0.5 [equivalent to MCI]) over 3 years and showed a trend for an association between worsening IADL performance in amyloid-positive compared to amyloid-negative participants; looking at the groups separately, the amyloid-positive participants remained stable in their IADL, while the amyloid-negative participants improved.[16] Thus, our analyses and these two studies support the notion that there is a relationship between IADL difficulties and amyloid burden even in CN older adults.

As expected of CN participants, the overall endorsement of IADL difficulties was low. However, difficulties with certain activities were reported more frequently by both participants and their study partners. The four activities that were endorsed the most relied primarily on memory. Other studies analyzing IADL activities in participant or study partner-reported questionnaires (the Functional Activities Questionnaire and Everyday Cognition) similarly showed that difficulties remembering appointments distinguished between CN and MCI participants and that difficulties following a TV program predicted progression from CN to MCI.[8,9] Several studies have demonstrated that financially related IADL, including performance of simulated transactions, distinguish well between CN and MCI or predict progression from CN to MCI.[8–10] However, in the current study, only 1% of all participants and 2% of their study partners reported difficulties with financial transactions.

The ADCS ADL-PI was designed as a brief but comprehensive questionnaire to capture subtle IADL changes in CN individuals at risk for AD.[5] In the current study, in addition to finding an association between ADCS ADL-PI scores and greater cortical amyloid burden, we showed that overall IADL difficulties were associated with worse cognition, measured by the PACC,[20] which has been designed to capture

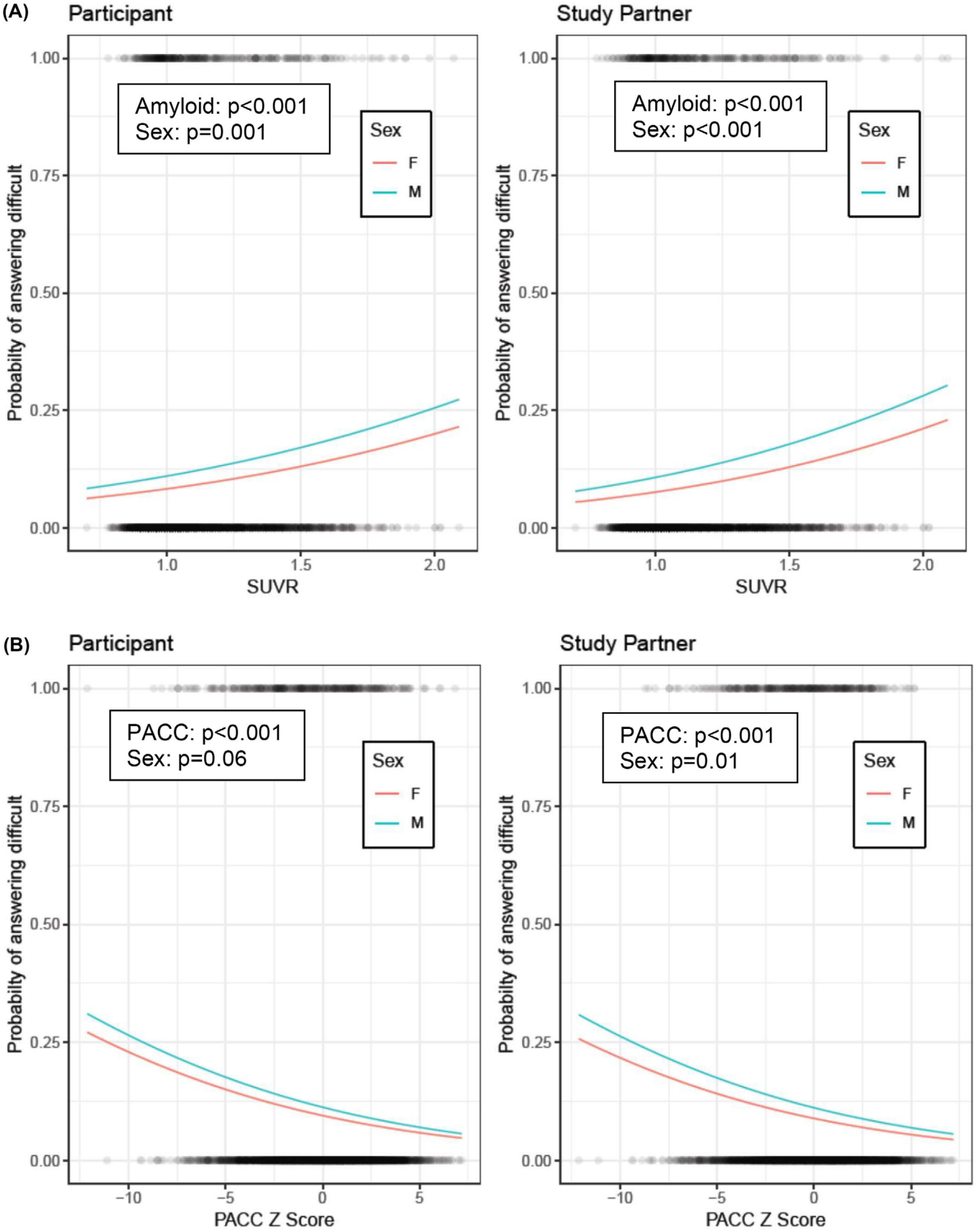

FIGURE 2 ADCS ADL-PI performance versus cortical amyloid burden and cognition. The graph represents performance on item 7 of the ADCS ADL-PI (How well did you remember important dates and times, such as appointments or meetings?) as reported by the participant (**LEFT**) and study partner (**RIGHT**) versus cortical amyloid (**A**) or cognition (**B**). The y-axis indicates probably of having difficulty on the ADCS ADL-PI item,

cognitive deficits related to amyloid burden. These findings were also noted when focusing on the four most endorsed IADL activities. Moreover, similar associations were noted when looking at individual cognitive domains (episodic memory and processing speed and executive function). However, it must be noted that the associations were relatively small. For a clinically significant difference in cognition (1 standard deviation on the PACC z-score), there was about a 10% increase in the likelihood of reporting IADL difficulties, while for a clinically significant difference in cortical amyloid (0.15 florbetapir SUVR), there was about a 5% increase in the likelihood of reporting IADL difficulties. That said, the IADL difficulties observed in the current study are cross-sectional, and the effect size for longitudinal change in IADL cannot be accurately predicted from this data. Nonetheless, it is encouraging that mild IADL difficulties align with mild elevations in cortical amyloid and subtle cognitive deficits.

Over the past several years multiple secondary prevention trials in AD have been launched. These trials have enrolled CN participants at risk for AD dementia based on either genetic risk or biomarker positivity, namely amyloid, the latter being the focus of the A4 Study. The Food and Drug Administration (FDA) has recently provided new draft guidance for early-stage AD clinical trial outcome measures.[21,22] In this guidance, the FDA suggests a single cognitive outcome measure may be sufficient for approval in prevention trials. However, they add that with an accelerated approval, it may be necessary to confirm eventual clinical benefit. Therefore, a functional measure that is sensitive enough to directly demonstrate clinical benefit by detecting IADL difficulties in individuals with preclinical AD during the time frame of such prevention trials would minimize the need for further follow-up when the trial is over.

Prior studies in CN participants have shown associations between amyloid burden and objective and subjective cognitive function[23–26] but only limited evidence for a relationship with IADL difficulties.[16,17] The current analyses demonstrated an association among IADL, amyloid burden, objective cognition, and subjective cognitive concerns. IADL represent a person's level of independence and as such are linked to self-esteem, self-worth, and quality of life, as well as caregiver well-being and societal costs.[27,28] Impairment in IADL necessitates that someone else assist or care for the affected person. The caregiver is prone to a number of burdens—physical, psychological, financial, and time that could be spent doing many other things. The association between amyloid burden and a clinically meaningful test assessing difficulties in IADL raises the possibility that functional ratings may identify plausible subtle changes in the context of a prevention trial.

The original ADCS ADL-PI consisted of 15 items.[5] The version used in the A4 Study also examined three new items focused on technology use (cellphone/smartphone, computer/tablet, and e-reader). Participants and study partners reported frequent use of cellphones, smartphones, computers, and tablets, including common activities performed with these devices. Given claims of the digital divide between the young and the old, this was somewhat unexpected. However, there is a recruitment bias toward higher education levels in the A4 Study cohort (on average participants had >16 years of education), possibly accounting for the widespread use of digital technology. Additionally, participants and study partners infrequently endorsed difficulties with these activities (<5%). When analyzing the association between cortical amyloid or cognition and the ADCS ADL-PI using total scores with either the 15 items or 18 items, there was no meaningful difference. Therefore, in this cohort the new items did not appear to add value to the assessment of IADL cross-sectionally. This could be due to the different scoring of the new items or an inability to capture fine-grained decline in these activities. It remains to be seen if these new items will have more of an impact with longitudinal follow-up.

Regardless, this is encouraging for the feasibility of future use of electronic clinical assessments as digital biomarkers in this older adult population. It would be helpful to compare such participant or study partner reports with passively collected use of devices in future studies, which could provide a more precise assessment than participant or study partner ratings. Furthermore, the use of everyday technology is a quickly changing field, and it might need constant adaptations. It is possible that the three activities assessed here did not adequately probe the cognitively complex aspects of everyday technology use.

In an attempt to determine whether certain participants were driving our results by endorsing difficulties with multiple IADL, we assessed the overlap in responses to the four items on which participants endorsed the most difficulties with IADL. Only 1% of participants endorsed difficulties on all four items, and 29% of participants endorsed difficulties with one or more of these items, suggesting that there was more variability in responses to individual items within participants. Moreover, to capture early changes in IADL across participants, a variety of activities rather than one sensitive activity may need to be assessed.

As with some subjective assessments of cognition, mood, and behavior, the ADCS ADL-PI provides both participant and study partner reports about IADL performance. This allowed us to explore the possibility of discordant responses. We found that most of the responses for the highly endorsed items (>80%) provided by participants were in agreement with study partner responses. When looking at the total score, the agreement was lower (>65%). Generally, as AD progresses, we expect less agreement between participants or patients and study partners or caregivers in the report of symptoms due to a lack of awareness on the part of participants or patients with prior studies focusing primarily on cognition and to a lesser extent on mood and behavior.[29,30] Therefore, with longitudinal follow-up of the CN participants in the A4 Study, we may see an increasing discordance in report of IADL between

while the x-axis represents cortical amyloid measured by continuous aggregate florbetapir PET SUVR (**A**) or cognition measured by PACC z-score (**B**). Performance is depicted by sex (red line = female; blue line = male). Age is set to 70 years, which is approximately the median age of participants in this sample. ADCS ADL-PI, Alzheimer's Disease Cooperative Study Activities of Daily Living Prevention Instrument; PACC, Preclinical Alzheimer Cognitive Composite; PET, positron emission tomography; SUVR, standardized uptake value ratiosp

participants and study partners as the participants start to develop cognitive impairment.

When looking at the association between IADL report and demographic variables, we found that men and older participants were more likely to have IADL difficulties. This indicates that this measure of IADL (the ADCS ADL-PI) may be biased by gender roles and age, which has been previously described for other IADL questionnaires administered across CN, MCI, and AD dementia participants (the Functional Activities Questionnaire); however, for some instruments (the Amsterdam IADL Questionnaire and the Everyday Technology Use Questionnaire) this bias was not observed.[31–35] Therefore, this relationship might be instrument-specific. On the other hand, participant years of education and retirement status and study partner relationship to participant were not significantly associated with IADL performance. Only 10% of the participants in the current study were minorities, making it hard to determine the influence of race on IADL performance. A prior study showed that non-demented Black women had worse IADL performance compared to non-Hispanic Whites.[36]

The current study had several strengths. First, this is one of the largest cohorts of CN participants to undergo amyloid PET imaging and clinical assessments. Second, participants were well characterized, allowing in-depth analyses to be performed. Third, an IADL measure with both participant and study partner report was used, allowing us to corroborate reports from either source. There were also several limitations to the study. First, this was a clinical trial sample of highly motivated participants, who were highly educated and mostly White. Therefore, these efforts will need to be replicated in more diverse population-based studies. Second, IADL difficulties were endorsed on only a few ADCS ADL-PI items frequently enough to be analyzed in this cross-sectional study, and we were only able to use dichotomized scores due to the ceiling effects. Therefore, potentially more sensitive IADL tests are necessary to capture more robust IADL difficulties cross-sectionally in preclinical AD. With longitudinal follow-up in the A4 Study, the range of IADL impairment is likely to increase as participants decline over time, as will divergence in report between participant and study partner. Third, measures of tau pathology or broader neurodegeneration, which may relate to clinical symptoms such as IADL more closely, were not included in the current analyses. Future studies will be performed with these measures as they become available.

In conclusion, we have shown that within CN older adults at risk for AD dementia, difficulties in IADL are associated with both modestly greater cortical amyloid burden and lower cognitive performance at baseline. Therefore, our findings suggest that subtle yet potentially clinically meaningful difficulties in IADL may be captured with sensitive assessments during preclinical AD. In other words, the ability to detect subtle IADL difficulties in CN older adults with greater cortical amyloid burden is a first step in demonstrating the potential utility of functional assessments in preclinical AD prevention trials. Longitudinal follow-up will be important to determine when further changes in IADL performance become apparent and their relationship to changes in cognition and biomarkers.

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CONFLICTS OF INTEREST

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REFERENCES

1. Marshall GA, Amariglio RE, Sperling RA, Rentz DM. Activities of daily living: where do they fit in the diagnosis of Alzheimer's disease. *Neurodegener Dis Manag*. 2012; 2(5): 483-491.
2. Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's Dement*. 2011; 7(3): 270-279.
3. Morris JC. Revised criteria for mild cognitive impairment may compromise the diagnosis of Alzheimer's disease dementia. *Arch Neurol*. 2012;69(6):700-708.
4. Farias ST, Mungas D, Reed BR, et al. The measurement of everyday cognition (ECog): scale development and psychometric properties. *Neuropsychology*. 2008; 22(4): 531-544.
5. Galasko D, Bennett DA, Sano M, Marson D, Kaye J, Edland SD. ADCS Prevention Instrument Project: assessment of instrumental activities of daily living for community-dwelling elderly individuals in dementia prevention clinical trials. *Alzheimer Dis Assoc Disord*. 2006; 20(4 Suppl 3): S152-169.
6. Goldberg TE, Koppel J, Keehlisen L, et al. Performance-based measures of everyday function in mild cognitive impairment. *Am J Psychiatry*. 2010; 167(7): 845-853.
7. Marshall GA, Dekhtyar M, Bruno JM, et al. The Harvard Automated Phone Task: new performance-based activities of daily living tests for early Alzheimer's disease. *J Prev Alzheimer's Dis*. 2015; 2(4): 242-253.
8. Marshall GA, Zoller AS, Kelly KE, Amariglio RE. Initiative AsDN. Everyday Cognition scale items that best discriminate between and predict progression from clinically normal to mild cognitive impairment. *Curr Alzheimer Res*. 2014; 11(9): 853-861.
9. Marshall GA, Zoller AS, Lorius N, et al. A.s.D.N. Initiative. Functional Activities Questionnaire items that best discriminate and predict progression from clinically normal to mild cognitive impairment. *Curr Alzheimer Res*. 2015; 12(5): 493-502.
10. Triebel KL, Martin R, Griffith HR, et al. Declining financial capacity in mild cognitive impairment: a 1-year longitudinal study. *Neurology*. 2009; 73(12): 928-934.
11. Zoller AS, Gaal IM, Royer CA, et al. SIST-M-IR activities of daily living items that best discriminate clinically normal elderly from those with mild cognitive impairment. *Curr Alzheimer Res*. 2014; 11(8): 785-791.
12. Luck T, Luppa M, Wiese B, et al, G. AgeCoDe Study. Prediction of incident dementia: impact of impairment in instrumental activities of daily living and mild cognitive impairment-results from the German study on ageing, cognition, and dementia in primary care patients. *Am J Geriatr Psychiatry*. 2012; 20(11): 943-954.
13. Roehr S, Riedel-Heller SG, Kaduszkiewicz H, et al. Is function in instrumental activities of daily living a useful feature in predicting Alzheimer's disease dementia in subjective cognitive decline?. *Int J Geriatr Psychiatry*. 2019; 34(1): 193-203.
14. Sikkes SA, Visser PJ, Knol DL, et al. Do instrumental activities of daily living predict dementia at 1- and 2-year follow-up? Findings from the Development of Screening guidelines and diagnostic Criteria for Predementia Alzheimer's disease study. *J Am Geriatr Soc*. 2011; 59(12): 2273-2281.
15. Sperling RA, Aisen PS, Beckett LA, et al. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011; 7(3): 280-292.
16. Lilamand M, Cesari M, Cantet C, Payoux P, Andrieu S, Vellas B. Relationship Between Brain Amyloid Deposition and Instrumental Activities of Daily Living in Older Adults: a Longitudinal Study from the Multidomain Alzheimer Prevention Trial. *J Am Geriatr Soc*. 2018; 66(10): 1940-1947.
17. Tolbert S, Liu Y, Hellegers C, et al. Financial management skills in aging, MCI and dementia: cross sectional relationship to 18F-florbetapir PET cortical β-amyloid deposition. *J Prev Alzheimers Dis*. 2019; 6(4): 274-282.
18. Sperling RA, Rentz DM, Johnson KA, et al. The A4 study: stopping AD before symptoms begin?. *Sci Transl Med*. 2014; 6(228): 228fs213.
19. Sperling RA, Donohue MC, Raman R, et al. Team A4S. Association of factors with elevated amyloid burden in clinically normal older individuals. *JAMA Neurol*. 2020;77(6):735-745. press.
20. Donohue MC, Sperling RA, Salmon DP, et al. B Australian Imaging, A. Lifestyle Flagship Study of, I. Alzheimer's Disease Neuroimaging, S. Alzheimer's Disease Cooperative. The preclinical Alzheimer cognitive composite: measuring amyloid-related decline. *JAMA Neurol*. 2014; 71(8): 961-970.
21. Kozauer N, Katz R. Regulatory innovation and drug development for early-stage Alzheimer's disease. *N Engl J Med*. 2013; 368(13): 1169-1171.
22. Sabbagh MN, Hendrix S, Harrison JE, FDA position statement "Early Alzheimer's disease: Developing drugs for treatment, Guidance for Industry". *Alzheimer's Dement. (N.Y.)*. 2019; 5: 13-19.
23. Amariglio RE, Becker JA, Carmasin J, et al. Subjective cognitive complaints and amyloid burden in cognitively normal older individuals. *Neuropsychologia*. 2012; 50(12): 2880-2886.
24. Hedden T, Mormino EC, Amariglio RE, et al. Cognitive profile of amyloid burden and white matter hyperintensities in cognitively normal older adults. *J Neurosci*. 2012; 32(46): 16233-16242.
25. Mormino EC, Betensky RA, Hedden T, et al. I. Alzheimer's Disease Neuroimaging, B. Australian Imaging, A. Lifestyle Flagship Study of, S. Harvard Aging Brain. Amyloid and APOE epsilon4 interact to influence short-term decline in preclinical Alzheimer's disease. *Neurology*. 2014; 82(20): 1760-1767.
26. Amariglio RE, Sikkes SAM, Marshall GA, et al. Item-level investigation of participant and study partner report on the Cognitive Function Index from the A4 Study screening data. *J Prev Alzheimers Dis*. 2020;4: 64-75. press.
27. O'Shea E, Hopper L, Marques M, et al. A comparison of self and proxy quality of life ratings for people with dementia and their carers: a European prospective cohort study. *Aging Ment Health*. 2018: 1-9.
28. Reed C, Belger M, Vellas B, et al. Identifying factors of activities of daily living important for cost and caregiver outcomes in Alzheimer's disease. *Int Psychogeriatr*. 2016; 28(2): 247-259.
29. Guercio B, Donovan NJ, Munro CE, et al. The Apathy Evaluation Scale: a comparison of subject, informant, and clinician report in cognitively normal elderly and mild cognitive impairment. *J Alzheimers Dis*. 2015; 47(2): 421-432.
30. Vannini P, Hanseeuw B, Munro CE, et al. Anosognosia for memory deficits in mild cognitive impairment: insight into the neural mechanism using functional and molecular imaging. *NeuroImage Clin*. 2017: 15408-15414.
31. Jutten RJ, Peeters CFW, Leijdesdorff SMJ, et al. Detecting functional decline from normal aging to dementia: development and validation of a short version of the Amsterdam IADL Questionnaire. *Alzheimers Dement (Amst)*. 2017: 826-835.

32. Kottorp A, Malinowsky C, Larsson-Lund M, Nygard L. Gender and diagnostic impact on everyday technology use: a differential item functioning (DIF) analysis of the Everyday Technology Use Questionnaire (ETUQ). *Disabil Rehabil*. 2018: 1-7.
33. Sikkes SA, Knol DL, Pijnenburg YA, de Lange-de Klerk ES, Uitdehaag BM, Scheltens P. Validation of the Amsterdam IADL Questionnaire(c), a new tool to measure instrumental activities of daily living in dementia. *Neuroepidemiology*. 2013; 41(1): 35-41.
34. Marshall GA, Lorius N, Locascio JJ, et al. A'sDN Initiative. Regional cortical thinning and cerebrospinal biomarkers predict worsening daily functioning across the Alzheimer disease spectrum. *J Alzheimers Dis*. 2014; 41(3): 719-728.
35. Dubbelman MA, Verrijp M, Facal D, et al. The influence of diversity on the measurement of functional impairment: an international validation of the Amsterdam IADL Questionnaire in eight countries. *Alzheimers Dement (Amst)*. 2020; 12(1): e12021.
36. Garrett SL, Kennedy RE, Sawyer P, Williams CP, Brown CJ, Allman RM. Association Between Executive Dysfunction and Instrumental Activities of Daily Living: racial and Ethnic Differences Among Community-Dwelling Older Adults in the Southeastern US. *J Natl Med Assoc*. 2019; 111(3): 320-327.

SUPPORTING INFORMATION

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

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