

Cognitive & Behavioral Assessment

Using subjective cognitive decline to identify high global amyloid in community-based samples: A cross-cohort study

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Abstract

Introduction: We aimed to examine the contribution of subjective cognitive decline (SCD) to reduce the number of β -amyloid ($A\beta$) positron emission tomography scans required for recruiting $A\beta+$ clinically normal individuals in clinical trials.

Methods: Three independent cohorts (890 clinically normal: 72 yrs \pm 6.7; Female: 43.4%; SCD+: 24%; apolipoprotein E [*APOE*] $\epsilon 4+$: 28.5%; $A\beta+$: 32%) were used. SCD was dichotomized from one question. Using logistic regression, we classified $A\beta+$ using the SCD dichotomy, *APOE* $\epsilon 4$, sex, and age.

Results: SCD increased odds of $A\beta+$ by 1.58 relative to non-SCD. Female *APOE* $\epsilon 4$ carriers with SCD exhibited higher odds of $A\beta+$ (OR = 3.34), whereas male carriers with SCD showed a weaker, opposing effect (OR = 0.37). SCD endorsement reduces the number of $A\beta$ positron emission tomography scans to recruit $A\beta+$ individuals by 13% and by 9% if *APOE* $\epsilon 4$ status is known.

Conclusion: SCD helps to classify those with high $A\beta$, even beyond the substantial effect of *APOE* genotype. Collecting SCD is a feasible method for targeting recruitment for those likely on the AD trajectory.

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Keywords: Subjective cognitive decline; Amyloid; *APOE* $\epsilon 4$; Alzheimer's disease

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found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf and <https://aibl.csiro.au/about/aibl-research-team/>

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1. Introduction

As the field increasingly moves toward earlier intervention for Alzheimer's disease (AD), there is a growing need for reliable and cost-effective ways of screening for individuals who will benefit most from timely prevention. Current prevention efforts are predominantly focused on interrupting the pathological β -amyloid ($A\beta$) cascade in its earliest stages [1]. As such, recruitment is predicated on identifying individuals with biomarker evidence of abnormal $A\beta$ using positron emission tomography (PET) neuroimaging [2]. $A\beta$ -PET imaging is expensive and invasive, and so to reduce cost and patient burden, prevention trials may harness easily accessible demographic factors to prescreen individuals before neuroimaging. Beyond gathering information about apolipoprotein E ϵ 4 (*APOE* ϵ 4) status, which is closely associated with risk for abnormal $A\beta$ [3,4], and age [5,6], evidence also supports the inclusion of measures of subjective cognitive decline (SCD) for prescreening [7–9].

As a quick and inexpensive marker, SCD has been repeatedly associated with $A\beta$ burden in clinically normal older adults [3,7,8,10–16]. When examining the predictive utility of SCD to identify high $A\beta$, Mielke et al. [5] reported that SCD reduced the number of individuals needed to screen for high $A\beta$ burden by approximately 37% for clinically normal individuals between 70 and 79 years. Furthermore, a study from the Australian Imaging, Biomarker and Lifestyle (AIBL) study of aging reported that SCD increased the odds of high $A\beta$ by 1.90 in clinically normal individuals, raising to an odds ratio (OR) of 4.58 in *APOE* ϵ 4 carriers [17]. A current gap in the literature, however, is the reporting of risk estimates for high $A\beta$ using SCD across multiple independent cohorts. This is a salient issue for SCD, which is a multifaceted construct [18] that does not currently possess a standardized form of measurement [19]. As such, the aim of this study was to examine the generalizability and consistency of SCD to identify high $A\beta$ across three well-characterized cohorts, and in the context of demographic and genetic factors.

Here, we examined the utility of SCD (as measured with a single question with a binary response) to identify high $A\beta$ in isolation and in combination with moderative effects of *APOE* ϵ 4 status, age, and sex across 890 clinically normal older adults from three independent cohorts. We hypothesized that SCD would exert an independent effect on the identification of those with high $A\beta$ and that combinatorial relationships between SCD and demographic factors would significantly reduce the numbers to screen for high $A\beta$.

2. Methods

2.1. Participants

Cohort-specific inclusion criteria for recruitment have been published previously in the following studies: Harvard Aging Brain Study (HABS), Alzheimer's disease Neuroimaging Initiative (ADNI), and AIBL [20–22]. For this

cross-sectional study, data from each cohort were based on an individual's first $A\beta$ positron emission tomography (PET) scan. In the present study, participants were required to be clinically normal (Global Clinical Dementia Rating [CDR] score = 0), with ADNI's SCD group included, given that these participants attained a Clinical Dementia Rating score of 0. For analysis, 890 participants (ADNI, $n = 297$; AIBL, $n = 284$; and HABS, $n = 309$) were included. We conducted the procedures for this study under the ethical guidelines stipulated by the Partners Human Research Committee, which is the Institutional Review Board for the Massachusetts General Hospital and Brigham and Women's Hospital.

2.2. Subjective cognitive decline

We examined SCD using three binary outcome questions—from ADNI, we used the Everyday Cognition battery [23] memory question: “Are you concerned that you have a memory or other thinking problem?” [24]; from AIBL: “Do you have difficulties with your memory?” [21]; and from HABS, we used the first question from the Structured Telephone Interview for Dementia Assessment [25]: “Have you recently experienced any change in your ability to remember things?” [26]. These questions were used to identify SCD, with endorsement (“yes”) signifying those with a subjective observation of poor memory.

2.3. $A\beta$ positron emission tomography

ADNI uses the ^{18}F -AV45 (florbetapir or FBP) $A\beta$ -PET tracer, whereas AIBL and HABS use the ^{11}C -Pittsburgh compound-B (PiB) $A\beta$ -PET tracer. The PET acquisition parameters and processing pipelines for each study have been published previously [3,22,27]. AIBL and HABS used cerebellar gray matter as the reference region, whereas ADNI used the whole cerebellum as the reference region. While ADNI and AIBL used standardized uptake value ratios, HABS used distribution value ratio. We used dichotomous $A\beta$ status using previously published cutoff values [3,27,28]: AIBL > 1.40 standardized uptake value ratios; ADNI > 1.11 standardized uptake value ratios; and HABS > 1.185 distribution value ratio.

2.4. Statistical analysis

Analyses were performed using *R*, version 3.5.1, using the *glm*, *pscl*, and *epiDisplay* packages. To examine the ability of SCD to classify high/low $A\beta$ burden in clinically normal older adults, we ran a series of generalized linear mixed models including age, sex, *APOE* ϵ 4, and education as fixed effect covariates and modeling cohort as a random effect. Our first model included demographics, followed by a second model which included SCD as a predictor of interest. The next model examined demographics and *APOE* ϵ 4 status as a predictor of interest. Our examination of *APOE* ϵ 4 status as the primary contrast against the effect of SCD on

Table 1
Demographic differences by amyloid status and cohort

	Aβ− (n = 607)			Aβ+ (n = 283)			P
Age	71.6 (6.9)			75.0 (6.3)			<.001
Education (yrs)	15.1 (3.2)			14.9 (3.4)			.31
Sex (F%)	337 (56)			165 (58)			.48
APOE (ε4+ %)	116 (20)			131 (48)			<.001
SCD (yes %)	272 (49)			157 (56)			.004
	ADNI (n = 201)	AIBL (n = 182)	HABS (n = 224)	ADNI (n = 96)	AIBL (n = 102)	HABS (n = 85)	
Age	72.9 (6.1)	70.2* (6.2)	71.7 (7.7)	75.9 (6.2)*	74.0 (6.4)*	75.3 (6.3)*	<.001
Education (yrs)	16.8 (2.4)	12.6 (2.6)*	16.1 (2.8)	16.1 (2.8)	12.5 (3.0)*	16.2 (2.9)	
Sex (F%)	95 (47)	109 (60)*	109 (49)	63 (66)*	51 (50)	51 (60)	.02
APOE (ε4+ %)	41 (20)	37 (21)	38 (18)	42 (44)*	41 (43)*	48 (59)*	<.001
SCD (yes %)	87 (43)	126 (69)*	59 (26)	45 (47)	72 (71)*	40 (47)	<.001

NOTE. * = significantly different from other groups.

Abbreviations: ADNI, Alzheimer's disease Neuroimaging Initiative; AIBL, Australian Imaging, Biomarker and Lifestyle; HABS, Harvard Aging Brain Study; APOE, apolipoprotein E.

Aβ status was motivated by the fact that *APOEε4* represents one of the strongest risk factors for high Aβ [4,29]. To examine the added effect of SCD beyond knowing *APOEε4* status, we examined the main effects of SCD and *APOEε4* within the same model. To examine interactive effects, we examined the combined effect of SCD and *APOEε4* status on Aβ status. We also examined two additional models that included three-way interactions between (a) sex, SCD, and *APOEε4* status and (b) age, SCD, and *APOEε4* status on Aβ status. We investigated the fit of these models with area under the curve (AUC) calculations. Although we proceeded with three-way interactions as we had >20 individuals in each cell for both Aβ+ and Aβ− individuals (see [Supplementary Table A](#)), we interpreted results within the context of reduced power. In addition, we calculated the numerical advantage to including SCD as a parameter when attempting to recruit 1000 Aβ+ clinically normal individuals from the community. Here, we used the predictive models to calculate the percentage reduction in numbers needed to recruit 1000 Aβ+ individuals by predicting the \hat{y} from a reference version of the model (that is, all variables at “zero”) and comparing it against the target version of the model (that is, with the variable of interest now set to be the indicator).

3. Results

3.1. Demographics

Clinically normal older adults who had high Aβ burden were older and had greater proportion of *APOEε4* and endorsement of SCD (see [Table 1](#)) across all cohorts. There were no differences in years of education or proportion of females across all cohorts.

3.2. Classifying Aβ status using SCD and *APOEε4* status

In the most basic model examining demographics alone, the AUC was 66%. As education level did not add significant

explanatory variance to classifying Aβ+, we removed it from subsequent models. When including SCD in the model, we found it elevated the odds of being Aβ+ by 1.58 ($P = .006$, 95% confidence interval [CI]: 1.21-2.07) relative to non-SCD, with an AUC of 66.2% (see [Table 2](#) for model estimates). This model was significantly better fitting than that including demographics alone ($\chi^2 = 7.35$, $P < .001$). In a model that included *APOEε4* status and demographics, being an *APOEε4* carrier increased the odds of being Aβ+ by 4.94 ($P < .001$, 95% CI: 2.08-11.72) and the AUC was 74.8% model fitting against demographics alone ($\chi^2 = 88.6$, $P < .001$). Including the main effects of both SCD and *APOEε4* status, SCD maintained its significance (OR = 1.52, 95% CI: 1.17-1.98, $P = .01$), with the AUC at 74.7% (see [Fig. 1](#)). This model fit better than that including only *APOEε4* status and demographics ($\chi^2 = 6.03$, $P = .01$). We found no significant two-way interaction between SCD and *APOEε4* status to identify Aβ+ (OR = 0.95, 95% CI: 0.69-1.32, $P = .89$; AUC = 74.8%) (see [Fig. 1](#)).

For the three-way interactions, there were none between age, SCD, and *APOEε4* status to identify Aβ+ (OR = 1.06, 95% CI: 1.00-1.13, $P = .25$; AUC = 74.8%). A three-way interaction was found to exist, however, between sex, SCD, and *APOEε4* status (OR = 6.60, 95% CI: 1.63-25.32, $P = .007$; AUC = 75.7%). This model fit better than that of a main-effect-only model ($\chi^2 = 13.05$, $P = .01$). Stratified by *APOEε4* carriers, females had significantly greater odds of being Aβ+ if they endorsed SCD (OR = 3.34, 95% CI: 1.65-7.00, $P = .001$) (see [Fig. 2](#)). Unexpectedly, male *APOEε4* carriers exhibited trend-level lower odds of being Aβ+ if they endorsed SCD (OR = 0.37, 95% CI: 0.13-1.00, $P = .05$). A visual inspection of the three-way estimate across cohorts also suggests that they were largely aligned across cohorts (see [Supplementary Figure A](#)). When examining the stratifications within each study, the ORs for female ε4 carriers were relatively similar across all studies (ADNI: 4.25

Table 2
Odds ratios for variables of interest in examined models

	Odds ratio	95% CI lower	95% CI upper	P-value
A β status ~ SCD + covariates: AUC = 66.2				
SCD+	1.58	1.21	2.07	0.006
Female	1.32	0.97	1.79	0.08
Age	1.09	1.06	1.11	<0.001
A β status ~ APOE + covariates: AUC = 74.8				
APOE ϵ 4+	4.94	2.08	11.72	<0.001
Female	1.29	1.05	1.60	0.11
Age	1.10	1.09	1.12	<0.001
A β status ~ SCD + APOE + covariates: AUC = 74.7				
SCD+	1.52	1.17	1.98	0.01
APOE ϵ 4+	4.87	3.47	6.89	<0.001
Female	1.24	0.90	1.72	0.20
Age	1.11	1.08	1.14	<0.001
A β status ~ SCD*APOE + covariates: AUC = 74.8				
SCD+	1.56	1.05	2.34	0.03
APOE ϵ 4+	5.04	3.11	8.24	<0.001
APOE ϵ 4+:SCD+	0.95	0.69	1.32	0.89
A β status ~ SCD*APOE*Age + covariates: AUC = 74.8				
SCD+	1.66	1.08	2.58	0.02
APOE ϵ 4+	5.17	3.15	8.61	<0.001
Age	1.12	1.07	1.17	<0.001
APOE ϵ 4+:Age:SCD+	1.06	1.00	1.13	0.25
A β status ~ SCD*APOE*Sex + covariates: AUC = 75.7				
SCD+	1.51	0.83	2.75	0.18
APOE ϵ 4+	10.74	5.18	22.94	<0.001
Female	1.38	0.78	2.45	0.28
APOE ϵ 4+:Female:SCD+	6.60	1.63	25.32	0.007
A β status ~ SCD + covariates in female APOE ϵ 4 carriers (n = 150)				
SCD+	3.34	1.65	7.00	0.001
Age	1.09	1.04	1.16	0.001
A β status ~ SCD + covariates in male APOE ϵ 4 carriers (n = 97)				
SCD+	0.37	0.13	1.00	0.05
Age	1.21	1.12	1.34	<0.001

Abbreviations: APOE, apolipoprotein E; AUC, area under the curve; SCD, subjective cognitive decline.

[1.24-16.69]; AIBL: 3.98 [0.86-22.31]; and HABS: 2.38 [0.78-7.53]), with ADNI providing the strongest effect. Although the direction of the OR estimates was similar for male carriers, the estimate was far lower in ADNI in comparison with AIBL and HABS samples (ADNI: 0.02 [0.00-0.51]; AIBL: 0.30 [0.04-1.48]; and HABS: 0.86 [0.14-5.71]).

3.3. Estimated scans needed to identify 1000 A β + in clinically normal older adults

Knowing SCD alone beyond the average demographics of the cohorts (age = 72 years, sex = 56% female treated as numeric, cohort treated as numeric) reduced the numbers needed to scan by 13% [95% CI: 11-16%] (from 3276 to 2867 scans, saving 409 scans [95% CI: 393-485 scans saved]). Knowing both APOE ϵ 4 status and SCD translated to a reduction in the number of scans by 49% [95% CI: 49-51%] over and above basic demographics (3276 scans to 1655; saving 1621 scans [95% CI: 1531-1832]). In addition to knowing APOE ϵ 4 status, SCD itself only contributed to a reduction in the number of scans by approximately 9%

[95% CI: 8-9%] in comparison with a model including APOE ϵ 4 and demographics saving 154 scans [95% CI: 144-165]). Across the cohorts, there was some level of variability in the estimation of number of scans saved here; within AIBL, ADNI, and HABS, the number of scans estimated to be saved by knowing SCD above APOE ϵ 4 and demographics was 4%, 2%, and 13%, respectively.

It is important to note here, however, that simply estimating the numbers needed to be scanned does not take into account the costs of genotyping and other issues that may be pertinent to decision-making with recruitment. The intent of these estimations is primarily to highlight the utility of including an SCD measure to increase the efficiency of preclinical recruitment (with the inclusion of CIs).

4. Discussion

The field is currently focused on better, and more efficiently, identifying the most at-risk, yet clinically healthy, individuals who are "trial ready." In the present study, we aimed to quantify the contribution of a relatively simple and cheap approach to classifying abnormal A β , assessing

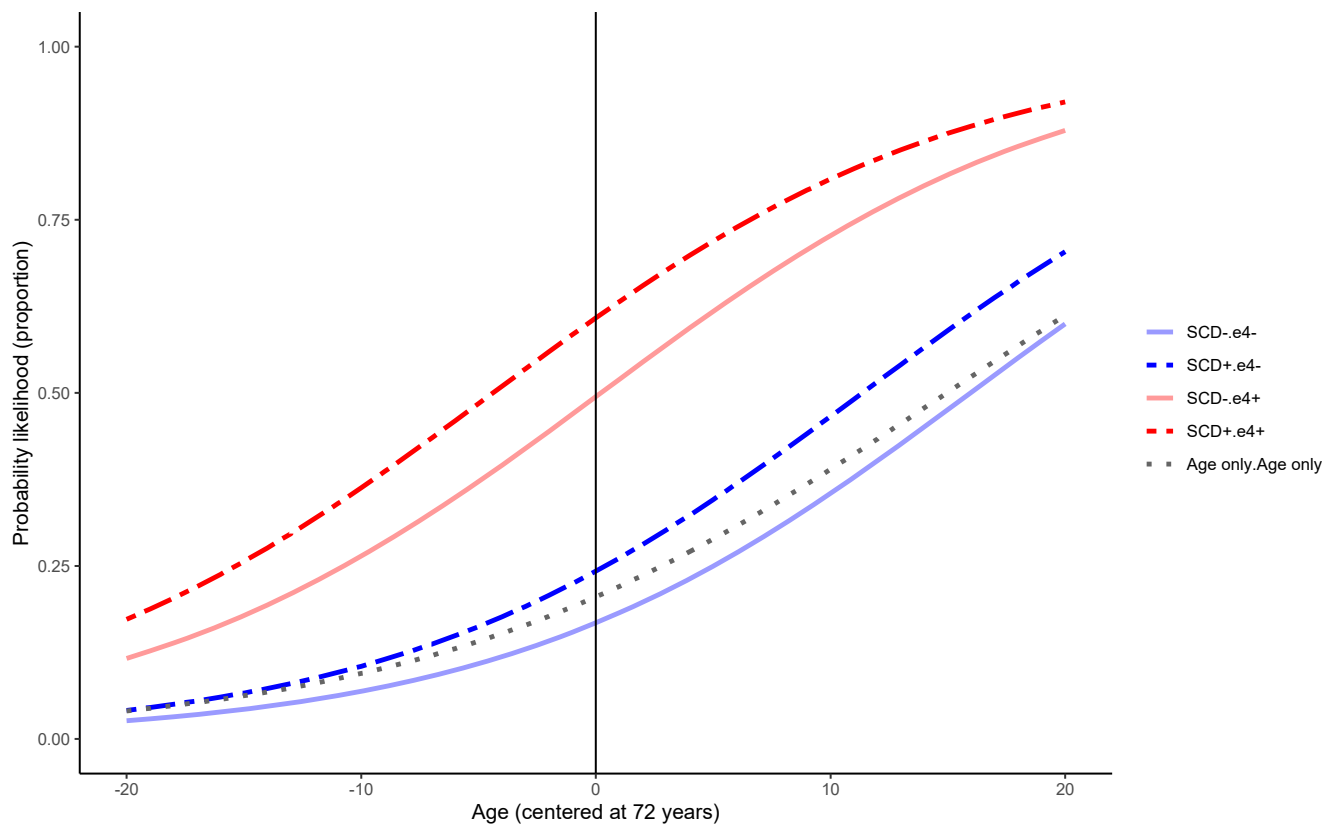


Fig. 1. Probability of having high Aβ according to SCD endorsement and APOEε4 carrier status. Abbreviations: APOE, apolipoprotein E; SCD, subjective cognitive decline.

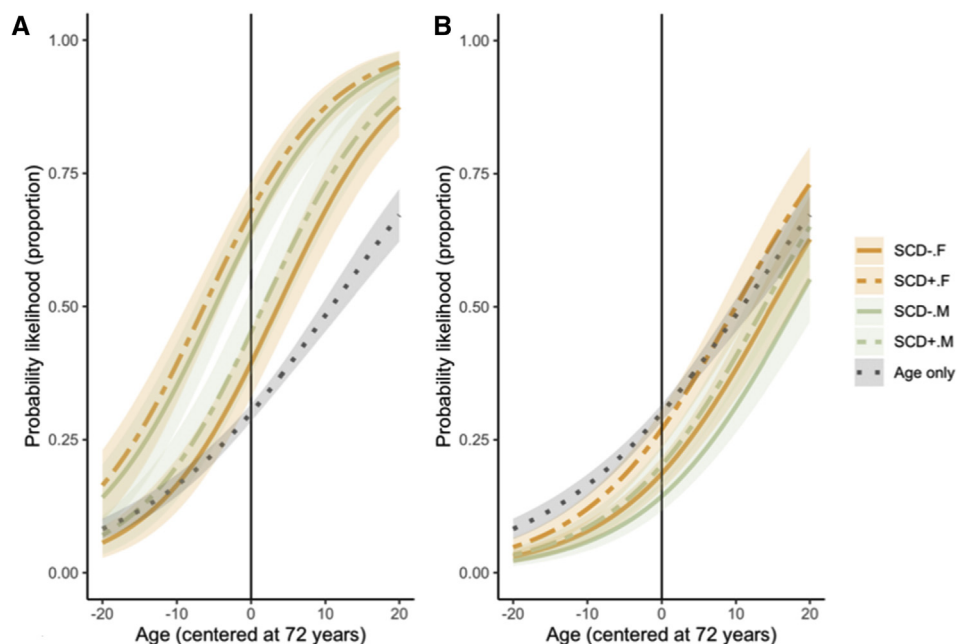


Fig. 2. Probability of having high Aβ according to SCD endorsement and sex in (A) APOEε4 carriers and (B) noncarriers. Abbreviations: APOE, apolipoprotein E; SCD, subjective cognitive decline.

SCD using a single item, across three independent observational cohorts. We found that SCD significantly predicted high A β , and this effect remained after accounting for *APOE* ϵ 4 status, although it was relatively small in comparison with the *APOE* effect. Including SCD in the identification of those with high A β reduced the numbers needed to screen by 13% beyond solely knowing basic demographics, such as age and sex, and by 9% if *APOE* ϵ 4 status was known. If one assumes the cost of an A β PET scan is ~US \$3500, recruitment strategies based on inclusion of SCD, over and above basic demographics, could boost economic efficiency by approximately \$1,431,500 [95% CI \$1,375,500-\$1,697,500], estimated from the 409 scans saved. This may not be considered a large margin of reduction; however, the inclusion of an additional one question is both low in cost and time expenditure and would be of net benefit for screening procedures of those with high A β . An important consideration, however, is the extent to which the endorsement of SCD differed in its predictive utility across the cohorts, suggesting that some items may be more sensitive to identifying high A β . The issue of other idiosyncratic differences between the cohorts, however, cannot be discounted to explain this variation.

Taken together, the literature supports our findings that SCD, age, and *APOE* ϵ 4 can inform the likelihood of high A β burden in community samples of clinically normal individuals. Elevated SCD, as a continuous measure, is associated with continuous measures of A β [7,8,13,30]. Our estimates of high A β frequency in *APOE* ϵ 4 carriers and noncarriers also align with those from an unrelated cohort [29], and meta-analyses incorporating some of the cohorts used in the present study [4], implying that our sample is representative. Similarly, we replicated findings from other independent cohorts of the relationship between higher A β and increased age [5,6]. Meta-analyses do not support a relationship between sex and high A β [4,31,32], although one observational study reported a female bias [33]. We extend these findings by reporting the magnitude of predictive utility that SCD measurement can provide about the likelihood of A β positivity in combination with predominating factors (e.g., age, *APOE*).

Our estimate of SCD to identify high A β was lower than that presented by Mielke et al. (13% vs. 34% [5]). One possibility for this discrepancy is the use of only a single binary SCD question in the present study, which may result in reduced sensitivity. In addition, the cohorts we examined displayed a trend-level protective effect of SCD in males, which may have obscured the impact of SCD in females. We also did not find interactions between SCD and age to predict high A β , as per previous findings [5,17], suggesting that although age exerts a strong main effect, the effect of SCD is not more salient in certain age groups.

The highest explanatory power for identifying high A β resulted from combinations of factors. We found the highest odds in female *APOE* ϵ 4 carriers with SCD, with our findings showing a paradoxical protective effect in male carriers with

SCD. SCD and sex have not traditionally been associated with one another in relation to A β burden; however, some meta-analyses have suggested elevated SCD overall in females relative to males [34]. Medical-seeking behaviors are reported more strongly in females relative to males (in the present study, 51% of females endorsed SCD relative to 45% of males), supporting the notion that SCD may be more common in females. It remains unclear, however, why SCD in females may be more sensitive to high A β . One possible rationale is a higher awareness for detecting cognitive changes [35]. Alternatively, a single binary outcome measure could be perceived differently by each sex, although this remains to be explored further.

As these cohorts are community based, it is unclear what the utility of SCD is for identifying A β in clinical settings. Because memory-clinic groups with SCD are at greater risk for clinical progression to AD dementia than the general population [36] (with SCD potentially more informative for clinical progression [37]), it is entirely possible that our estimates may be underestimating the risk for high A β in this type of population. Alternatively, SCD endorsement likely underlies the presenting symptom to a memory clinic, thus reducing the utility of a single binary outcome of SCD in this type of population. An additional consideration is that a variety of methods of SCD measurement exist, from single binary outcome measures to longer Likert-scale questionnaires [19]; we did not examine the sensitivity of different SCD measures to identify high A β . Our aim was to examine the generalizability of SCD based on items that were most comparable across the three cohorts while still retaining face validity. It is important to note, however, that this approach to testing SCD may not be the most sensitive to detecting abnormal A β in the community. Generalized SCD questions may promote reflection on a compilation of experiences related to SCD [38] and thus result in a heterogeneous association with AD pathophysiology. Arguably, however, all forms of SCD measurement are more feasible and cost-effective than attaining *APOE* genotype and, as such, should be considered for implementation as a recruitment and screening tool in the first instance [9].

Strengths of the present study include the consolidation of three independent cohorts to form a large sample of community-based older adults, as well as considering cohort variance. Some limitations exist in this study. First, we did not have the same measure of SCD across all three cohorts, which could lead to some level of measurement error and subsequent misestimation of risk. We did find our estimates of interest were largely aligned across cohorts, thus supporting the notion of generalizability of the SCD construct to identify high A β . Some heterogeneity did exist in our models, however; in particular, ADNI seemed to exhibit the strongest effect of SCD on high A β . We attempted to account for this by including cohort as a random effect; however, this limitation should be acknowledged. There are also previously acknowledged issues with these convenience-sample cohorts that reduce generalizability, such as high

education, good physical health, low racial diversity, and in the case of the AIBL study, enrichment for *APOE* ϵ 4 status [21]. An additional consideration is that each of these binary outcome questions asks about a slightly different component of SCD: one asks about concern, another about difficulties, whereas the last asks about experiencing change. All of these questions tap into different facets of SCD [19], and so it remains unclear which elements may have the greatest sensitivity to high A β or whether they are interchangeable. We did find a difference in the frequency of SCD endorsement across the cohorts, suggesting that they may not be entirely interchangeable. Regardless, asking a single question about SCD is time-efficient, cost-effective, and does not require training or clinical acumen to acquire, making this form of measurement an ideal addition to gathering simple demographic information in a first level of screening for recruitment [9].

In this large, combined sample, we found a single, binary SCD question independently identified high A β in clinically normal older adults. The predictive utility remained even after including *APOE* genotype in the model. Future aims will be to examine the predictive utility of SCD to identify groups according to the A/T/N model [39]. In addition, it will be necessary to examine the impact of screening questions for SCD that hone on different features that reflect elements in the new NIA-AA criteria [39] and/or SCD-*plus* criteria from the SCD-Initiative [18].

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Supplementary Data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.dadm.2019.08.004>.

RESEARCH IN CONTEXT

1. Systematic review: The authors reviewed literature in PubMed and Google Scholar. Some literature exists on the predictive utility of subjective cognitive decline (SCD) to identify high A β for Alzheimer's disease prevention trials. Studies have yet to determine the generalizability of these predictive estimates across independent cohorts.
2. Interpretation: Our findings underscore the importance of including a measure of SCD in prescreening recruitment methods for high A β , even if it is a single binary question (as reported across three cohorts in the present study).
3. Future directions: Because identifying high A β using A β positron emission tomography is so expensive, but currently represents the gold standard for recruitment into prevention trials, our results highlight the utility of a cheap and time-efficient measure of SCD to identify clinically normal older adults with high A β . Further work should explore the use of different items of SCD to classify A β .

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