

RESEARCH ARTICLE

Quantitative informant- and self-reports of subjective cognitive decline predict amyloid beta PET outcomes in cognitively unimpaired individuals independently of age and APOE ϵ 4

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Abstract

Introduction: Amyloid beta ($A\beta$) pathology is an Alzheimer’s disease early hallmark. Here we assess the value of longitudinal self- and informant reports of cognitive decline to predict $A\beta$ positron emission tomography (PET) outcome in cognitively unimpaired middle-aged individuals.

Methods: A total of 261 participants from the ALFA+ study underwent [¹⁸F]flutemetamol PET and Subjective Cognitive Decline Questionnaire (SCD-Q) concurrently, and 3 years before scan. We used logistic regressions to evaluate the ability of SCD-Q scores (self and informant) to predict $A\beta$ PET visual read, and repeated analysis of variance to assess whether changes in SCD-Q scores relate to $A\beta$ status.

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Results: Self-perception of decline in memory (odds ratio [OR] = 1.2), and informant perception of executive decline (OR = 1.6), increased the probability of a positive scan. Informant reports 3 years before scanning predicted A β PET outcome. Longitudinal increase of self-reported executive decline was predictive of A β in women ($P = .003$).

Discussion: Subjective reports of cognitive decline are useful to predict A β and may improve recruitment strategies.

KEYWORDS

Alzheimer's disease, amyloid, informant reports, preclinical, subjective cognitive decline

1 | BACKGROUND

The conceptualization of Alzheimer's disease (AD) has changed in the last decade thanks to the availability of methods to assess in vivo biomarkers, evolving from a clinical-pathological definition, in which definite diagnosis was achieved by *post mortem* analyses, to a biological one.¹ This conceptual shift settled the definition of a preclinical stage of the disease, characterized by the presence of abnormal core AD biomarkers (amyloid beta [A β] and tau) in the absence of clinical expression. Mounting evidence suggests that brain pathologic changes, mainly A β deposition, begin decades before the emergence of the first symptoms,²⁻⁴ and this period offers a window of opportunity for testing preventive interventions targeting A β .⁵ The establishment of these preventive studies and trials require the identification of individuals at a higher risk of developing AD in the near future. The standard way to measure A β pathology is through positron emission tomography (PET) imaging or cerebrospinal fluid (CSF) analysis. These techniques are, however, expensive and invasive. Therefore, an easier identification of individuals at higher risk of developing dementia (i.e., having positive AD biomarkers) is capital for a more efficient selection of candidates to participate in secondary prevention trials.

Although recent studies have explicitly sought predictors of brain amyloid pathology, they have mainly focused on symptomatic stages of the disease (i.e., mild cognitive impairment [MCI] and/or dementia⁶⁻¹¹). In these studies, the combination of predictors based on genetic (e.g., *APOLIPOPROTEIN* [APOE] $\epsilon 4$ status), demographic (eg, age, sex), clinical, and cognitive data yielded the highest accuracy in predicting amyloid status. For example, Ba et al.⁷ recently reported an area under the curve (AUC) of 0.827 for positive A β PET prediction in MCI individuals from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database using APOE $\epsilon 4$ carriership, age >60 years, and Alzheimer's Disease Assessment Scale-Cognitive 13-item scale >13.5. However, studies in cognitively unimpaired individuals are scarce. A study published by Insel et al. in cognitively unimpaired ADNI individuals found similar results to those obtained in clinical samples: age, APOE $\epsilon 4$ status, baseline cognition, and cognitive decline after 24 months increased the predictive value for A β positivity by 60%.¹²

An additional approach to improve the prediction of A β positivity in preclinical AD may be the use of subjective reports of cognitive decline. As pathology progresses through the preclinical stage, cog-

nitive decline slowly emerges, remaining under the threshold of cognitive impairment as measured by standard neuropsychological tests. However, some individuals perceive changes in their cognitive ability. The self-perception of the subtle cognitive decline that occurs in absence of objective impairment is referred to as subjective cognitive decline (SCD).^{13,14} SCD is an established risk factor for future objective cognitive impairment and dementia¹⁵⁻¹⁷ and when accompanied by worries leads to seeking medical help.¹⁸ SCD is also associated with increased prevalence of AD core biomarkers positivity (A β , t-tau, p-tau)^{13,19} and brain atrophy.^{20,21} Recently, Brunet et al.⁶ found that informant-based reporting of cognitive symptoms predicted amyloid positivity in a mixed sample of MCI and AD dementia patients. Similarly, but in this case in 86 ADNI clinically normal elders (mean age 78 years), Shokouhi et al.²² published a cross-sectional study showing that memory complaints primarily related to A β deposition whereas everyday planning complaints related to tau pathology. Despite these recent advances, AD biomarker prediction studies in younger samples assessing the value of change of subjective cognitive reports are still lacking. Furthermore, the longitudinal dynamics of SCD reports may be useful for such prediction, because reporting SCD consistently over time (assessed by means of a yes/no question about memory decline) has been related to increased incidence of dementia after 6 years.²³

This study aimed to assess the value of longitudinal self- and informant-reports of cognitive decline to predict A β PET outcome in cognitively unimpaired middle-aged individuals. We hypothesized that, beyond age and APOE $\epsilon 4$ status, both self- and informant-reports and their longitudinal change are valuable to predict A β status in cognitively unimpaired individuals.

2 | METHODS

2.1 | Participants

The first 261 consecutively recruited participants from the ongoing Alfa+ (Alzheimer and Families) study were included in the analyses. Alfa+ is a research cohort of middle-aged cognitively unimpaired (CU) subjects, many offspring of AD patients (169 out of 261, 64.8%, having at least one parent diagnosed with AD before age 75), which have been deeply characterized by clinical interviews, lifestyle questionnaires,

cognitive testing, CSF biomarkers, APOE genotyping, and neuroimaging (magnetic resonance imaging [MRI], and A β and fluorodeoxyglucose PET). All these procedures will be repeated every 3 years with the main aim of identifying the earliest pathophysiological changes in the preclinical AD continuum. In this study, data from the inclusion visit to the ALFA parent cohort performed between 2013 and 2014,²⁴ which included clinical and neuropsychological data, and the available data from the first Alfa+ visit, performed between 2016 and 2018 (concurrent visit), which included A β PET studies in addition to cognitive and clinical data, were analyzed. Alfa+ inclusion criteria were: (1) subjects that have previously participated in the ALFA parent cohort²⁴; (2) age between 45 and 65 years at the moment of the inclusion in the parent cohort; (3) long-term commitment to the study: inclusion and follow-up visits and agreement to undergo at all tests and procedures (MRI, PET, and lumbar puncture). Alfa+ exclusion criteria included: (1) cognitive impairment (Clinical Dementia Rating [CDR] >0, Mini-Mental State Examination [MMSE] <27, semantic fluency <12), (2) any significant systemic illness or unstable medical condition which could lead to difficulty complying with the protocol, (3) any contraindication to any test or procedure, or (4) family history of monogenic AD.

2.2 | Self- and informant reports of cognitive decline

Perception of cognitive decline was measured with the participant (MyCog) and informant (TheirCog) versions of the Subjective Cognitive Decline-Questionnaire (SCD-Q).²⁵ The SCD-Q was devised to quantify perceived subjective cognitive decline over the last 2 years and inquiries about the presence or absence of difficulties in cognitive-related activities. It begins with three metacognitive questions: (1) Do you perceive memory or cognitive difficulties? (2) Would you ask a doctor about these difficulties? and (3) In the last 2 years, has your cognition or memory declined? These questions are followed by 24 items assessing perceived decline in cognitive activities of daily living that include memory, language, and executive tasks. Participants must answer if they believe to be performing these activities worse than roughly 2 years ago. Scores ranging from 0 to 24 are computed for both participant and informant reports, with higher scores indicating greater perceived cognitive decline. Subscores for memory (range 0–11), language (range 0–6), and executive (0–7) functions are also computed (see Rami et al.²⁵ for details). The questionnaire was completed twice, at inclusion in the ALFA parent cohort and in the PET concurrent visit (first Alfa+ study visit), which on average was performed 3.2 years after (standard deviation [SD] = 0.7). The SCD-Q was self-completed at the beginning of the sessions, before any cognitive task was performed.

2.3 | Neuropsychological assessment

A Preclinical Alzheimer Cognitive Composite-like (PACC-like) assessment was developed using the longitudinally available measures tapping episodic verbal memory, timed executive function, and seman-

RESEARCH IN CONTEXT

1. Systematic review: The authors reviewed the literature using traditional sources. Publications describing subjective cognitive decline and the use of subjective reports of cognitive decline to improve the prediction of amyloid beta (A β) positivity in preclinical Alzheimer's disease (AD) are cited throughout the article.
2. Interpretation: Our findings show that both self- and informant-reports of cognitive decline in cognitively unimpaired subjects are useful to predict A β positive status assessed by positron emission tomography independently of age and APOE ϵ 4 status.
3. Future directions: This article proposes a framework for the generation of new hypotheses and the conduct of further studies. Some of these include, for example, the gathering of longitudinal data (both cognitive and imaging) to assess whether an increase in Subjective Cognitive Decline Questionnaire scores relates to an increase in amyloid deposition.

tic processing. Specifically, the PACC-like composite includes the total immediate score (total paired recall [TPR, 0–32]) and the total delayed free recall (TDFR, 0–32) from the Memory Binding Test (MBT), the Coding subtest from the Wechsler Adult Intelligence Scale (WAIS)-IV (0–135), and semantic fluency (animals in 1 minute). The PACC-like score was developed as described elsewhere.²⁶ In brief, the four scores are standardized by dividing the difference between subject score and baseline mean by the baseline standard deviation and then summed to obtain the composite. The Goldberg Anxiety and Depression Scale (GADS) and Hospital Anxiety and Depression Scale (HADS) were used to measure anxiety and depressive symptoms at inclusion and PET concurrent visit, respectively. Participants did not receive any feedback regarding their performance at the neuropsychological assessment.

2.4 | A β PET: acquisition and analysis

Participants underwent [¹⁸F]flutemetamol PET scan coincident (mean interval 4.6^{2.5} months) with the second SCD-Q and cognitive assessment (PET concurrent visit). Imaging was conducted in a Siemens Biograph mCT, after a cranial computed tomography (CT) scan for attenuation correction. Participants were injected with 185 MBq of [¹⁸F]flutemetamol, and 4 frames of 5 minutes each were acquired 90 minutes post-injection. A nuclear medicine physician visually rated the scans as positive (A β +) or negative (A β -) using standard clinical criteria as specified in the Summary of Product Characteristics (SmPC; https://www.ema.europa.eu/en/documents/product-information/vizamyl-epar-product-information_en.pdf) of the tracer.

In addition to the visual assessment, PET images were also quantified to obtain a measure of $A\beta$ accumulation in the brain. PET processing was performed following the standard Centiloid pipeline²⁷ using SPM12. In brief, PET images are first coregistered to their respective T1-weighted images and, afterward, moved to Montreal Neurological Institute space using the normalization transformation derived from the segmentation of the T1-weighted image. PET images were intensity normalized using whole cerebellum as reference region. Centiloid values were calculated from the mean values of the standard Centiloid target region (<http://www.gaain.org/centiloid-project>) using the transformation previously calibrated.²⁸ Participants agreed to not receive any information about their amyloid and APOE status.

2.5 | Statistical analyses

2.5.1 | Descriptive analysis

Data were described using means and standard deviations for continuous variables and percentages for categorical ones. We compared $A\beta+$ and $A\beta-$ groups for sociodemographic characteristics and clinical data by means of t-tests and Chi-square tests as appropriate.

2.5.2 | Predictive analysis of $A\beta$ status

The ability of SCD-Q scores to predict positive amyloid status was assessed by means of logistic regressions, adjusting for age, sex, time between PET acquisition and SCD-Q, and APOE $\epsilon 4$ carriership status. SCD-Q Total Scores as well as subscores (Memory, Language, and Executive) for both the MyCog and TheirCog were analyzed. Prospective prediction, using data from the inclusion visit, and concurrent prediction, using data from the PET concurrent visit, were explored. Secondly, for the most significant predictors, the classification performance of several cut-offs were also tested with logistic regressions using binarized SCD-Q variables as categorical independent variables. The ability of the cognitive composite (PACC-like) to predict amyloid outcomes was also assessed by means of a logistic regression, including education as an additional covariate. Main predictive analyses (i.e., SCD-Q prediction of $A\beta$ PET outcome) were also carried out without introducing APOE $\epsilon 4$ as a covariate to assess the prediction ability blind to APOE genotype, and also after stratifying the sample by APOE $\epsilon 4$ status.

We also explored the capacity of the change in SCD-Q measures to predict $A\beta$ PET positivity. For this aim, a set of repeated measures analyses of variance (ANOVAs) was used to explore differences in the mean change of SCD-Q scores between $A\beta+$ and $A\beta-$ groups (group \times time interaction). Age, sex, APOE $\epsilon 4$ status and interval time between visits were included in all the models. Additionally, differences in the cognitive composite PACC-like change between $A\beta+$ groups were also tested. Education was included as a covariate in these models. Interac-

TABLE 1 Characteristics at inclusion by $A\beta$ status measured at PET-concurrent visit 3 years after

	$A\beta-$	$A\beta+$	P
N	228	33	
Time to PET, years M(SD)	3.2(0.7)	3.0(0.7)	.123
Age M(SD)	56.4 (4.9)	60.4 (4.5)	<.001
Education, years M(SD)	13.6 (3.5)	12.3 (3.9)	.049
Females N (%)	151(66.2%)	23 (69.7%)	.693
MMSE M(SD)	29.1 (1.0)	29.1 (1.1)	.926
GADS Total M(SD)	0.69 (1.44)	0.82 (1.61)	.633
APOE $\epsilon 4$ carriers N (%)	96(42.1%)	24 (72.7%)	<.001
$A\beta$ PET CL M(SD)	-2.3(8.3)	34.1(24.3)	<.001

Note: Independent t-tests or Chi-square tests were used.

Abbreviations: $A\beta$, amyloid beta; APOE, APOLIPOPROTEIN E; CL, Centiloids; GADS, Goldberg Anxiety and Depression Scale; MMSE, Mini-Mental State Examination; PET, positron emission tomography; SD, standard deviation.

tions among predictors were also tested and kept in final models when significant.

In secondary analyses, general linear models were constructed to assess the SCD-Q scores ability to predict continuous Centiloid $A\beta$ measures, adjusted by age, sex, and APOE $\epsilon 4$ status.

3 | RESULTS

3.1 | Characteristics of the sample

The scans of 33 out of 261 participants (12.6%) were classified as $A\beta$ positive in PET visual read. Table 1 shows descriptive sociodemographic, clinical, and basic inclusion data by $A\beta$ status. Participants with positive scans were older than those with negative ones and were more frequently APOE $\epsilon 4$ carriers. There were no differences in the mean interval between inclusion and PET concurrent visits between groups; 70.1% of the informants did not change between visits. No difference in percentage of change of the informants was observed between $A\beta+$ and $A\beta-$ groups (28.3% vs 31.3% chi-square $P = .4$).

3.2 | Prospective and concurrent prediction of $A\beta$ status with SCD-Q and cognitive scores

Table 2 and Figure 1 show the results of the logistic regression for $A\beta$ status prediction using SCD-Q scores. Self-reports at inclusion (MyCog) did not predict $A\beta$ status 3 years after. Only memory subscores showed a trend to significant prediction (odds ratio [OR] = 1.175; $P = .057$), that became significant at PET concurrent visit (OR = 1.221; $P = .022$). Regarding informant reports (TheirCog), they displayed a similar pattern in memory subscores, that is a trend for prospective prediction (OR = 1.114; $P = .055$) and a significant prediction at PET concurrent visit (OR = 1.291; $P = .039$), and, for total

TABLE 2 Logistic regression results for positive A β PET as outcome and inclusion and PET-concurrent SCD-Q scores as predictors

Predictor	Inclusion visit			PET-concurrent visit		
	OR	CI (95%)	P	OR	CI (95%)	P
SCD-Q MyCog						
Total score	1.036	0.957–1.121	.384	1.083	0.994–1.180	.070
Memory subscore	1.175	0.995–1.389	.057	1.221	1.029–1.449	.022
Language subscore	1.078	0.853–1.363	.528	1.137	0.880–1.470	.326
Executive subscore	0.818	0.590–1.134	.228	1.156	0.861–1.553	.334
SCD-Q TheirCog						
Total score	1.114	1.013–1.224	.026	1.133	1.002–1.281	.047
Memory subscore	1.237	0.995–1.537	.055	1.291	1.013–1.645	.039
Language subscore	1.219	0.880–1.688	.234	1.146	0.805–1.630	.450
Executive subscore	1.474	1.061–2.047	.021	1.639	1.088–2.468	.018

Note: Age, sex, time between PET and SCD-Q, and APOE ϵ 4 status were used as covariates.

Abbreviations: A β , amyloid beta; APOE, APOLIPOPROTEIN E; CI, confidence interval; OR, odds ratio; PET, positron emission tomography; SCD-Q, Subjective Cognitive Decline Questionnaire.

score and executive subscore, they predicted A β status both prospectively and concurrently.

We also tested the classification ability of all the possible cut-offs of PET-concurrent MyCog memory and TheirCog executive subscores (which were the measures that displayed the highest ORs) using logistic regression with covariates. The cut-off that yielded best results was two in both cases. Thus, endorsing two or more out of the 11 memory items displayed an OR of 2.88 (confidence interval [CI] 95% = 1.26–6.57; $P = .012$; sensitivity = 0.61; specificity = 0.65), and endorsing two out of the seven executive ones achieved an OR of 2.79 (CI 95% = 1.12–6.92; $P = .027$; sensitivity = 0.30; specificity = 0.83). Similarly, for the inclusion SCD-Q MyCog memory subscore we found that endorsing three or more items prospectively predicted A β status (OR = 2.6; CI 95% = 1.15–6.17; $P = .022$; sensitivity = 0.49, specificity = 0.70).

Predictive analyses without including APOE ϵ 4 as a covariate yielded similar results to those obtained when including it (see Table S1 in supporting information). Further analyses after stratification of the sample by APOE ϵ 4 status showed that prediction with the SCD-Q was mainly observed in the non-carriers (see Tables S2 and S3 in supporting information).

The results from logistic regressions using cognitive performance as predictor of A β status did not show significant results for the PACC (prospective: OR = 1.006, 95% CI = 0.851–1.189, $P = .948$; PET concurrent: OR = 0.994, 95% CI = 0.791–1.127, $P = .523$), or for the specific tests used to calculate it (all $P > .4$, data not shown).

3.3 | Prediction of amyloid positivity with longitudinal change of SCD-Q and cognition

We observed a global trend in which participants from the A β - group tended to reduce SCD-Q scores at their PET-concurrent visit com-

pared to the inclusion one, while A β + tended to maintain them (see Table 3 descriptive data). However, the difference in the change between groups in ANOVA for repeated measures was only significant in the MyCog executive subscore. While this score decreased in A β - individuals, it increased in A β +. In this model, we also found an interaction with sex ($P = .022$) and further analyses performed separately in women and men revealed that the effect was driven by females ($P = .003$; males $P = .435$). No differences in longitudinal change were observed for TheirCog scores or for cognitive variables.

3.4 | Association between quantitative A β measures and SCD-Q and cognition

Independent general linear models with Centiloid values as dependent variable and SCD-Q scores as predictors, with age, sex, and APOE ϵ 4 as covariates, revealed significant associations between TheirCog executive subscore at inclusion and the observed A β load 3 years later ($B = 1.92$; $P = .039$; partial $\eta^2 = 0.017$), and a trend to significance at PET-concurrent assessment ($B = 2.07$; $P = .067$; partial $\eta^2 = 0.013$). No association was observed between Centiloids and cognitive performance as measured by the PACC-like composite at any time point.

4 | DISCUSSION

This study explored the ability of participant and informant quantitative reports of cognitive changes to predict A β PET positivity in cognitively unimpaired participants at risk for AD. The main results show that self-perception of decline in memory increases the probability of having a positive A β PET scan and that informant perception of executive decline is even more useful to predict A β status. Furthermore, informant reports predicted A β PET outcome not only concurrently,

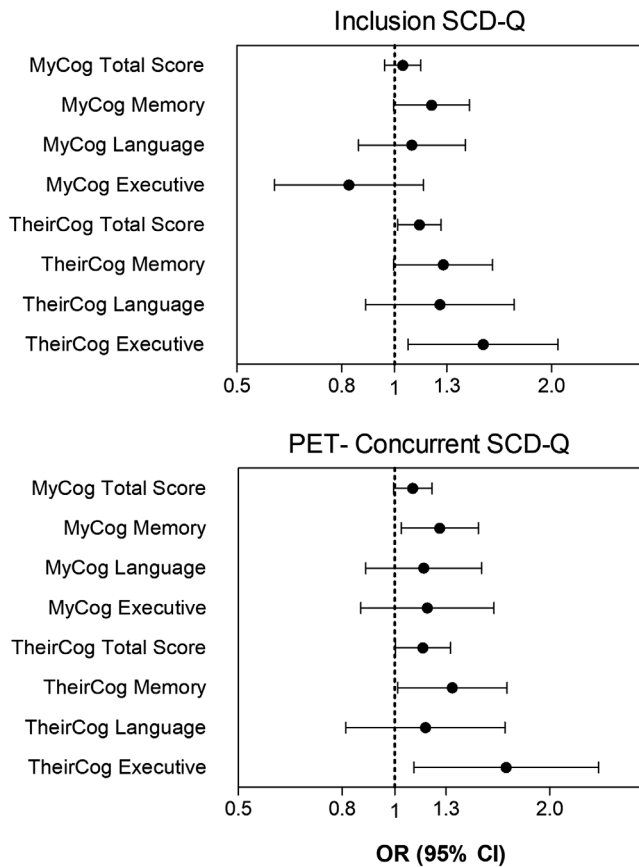


FIGURE 1 Odds ratios (ORs) with 95% confidence intervals (CIs) for positive amyloid beta scan prediction using Subjective Cognitive Decline Questionnaire (SCD-Q) scores. Models were adjusted by age, sex, and APOE $\epsilon 4$ status

but also prospectively 3 years before the scan. We also observed that the longitudinal increase of self-reported executive decline is predictive of $A\beta$ deposition, but only in women. Notably, objective cognitive performance failed to predict $A\beta$ status in this study.

By using a validated questionnaire to assess SCD, the SCD-Q, we observed that cross-sectional scores and longitudinal change have value to predict $A\beta$ PET status by visual read, which is the common measure of amyloidosis in clinical settings and the inclusion criterion in most clinical trials, independently of age and APOE $\epsilon 4$ status. In our sample, we found that memory subscores from both self- and informant-reports were useful to predict PET outcome concurrently, and informant reported executive subscores were also predictive concurrently and even prospectively using information collected 3 years before the scan. Globally, our results on the association between PET-concurrent SCD-Q and $A\beta$ are in line with previous studies that found a moderate association between the intensity of subjective complaints and amyloid-PET measures in cognitively unimpaired subjects.^{29–34} The use of a quantitative measure using a validated SCD questionnaire allowed us to find these associations. Indeed, the binary variable presence/absence of SCD, defined by the answers to the first initial question of the SCD-Q “Do you perceive memory or cognitive difficulties?” was

not able to predict PET outcome at inclusion or at PET-concurrent visit ($P = .9, P = .15$, data not shown).

The observed pattern, in which informant scores displayed higher and earlier ability to predict $A\beta$ status than self-reports, gives support to the longitudinal studies that found a superior value of informant reports in predicting future cognitive decline in cognitively unimpaired elders.^{35–40} However, their value in predicting biomarker status in unimpaired subjects is far less explored and yielded mixed results. A study in the ADNI cohort showed that informant reports were more strongly associated to amyloid PET standard uptake value ratio than self-reports, when the global sample, including cognitively unimpaired, MCI, and AD dementia participants, was analyzed. However, within-group analysis revealed that the relationship was significant only in MCI participants.⁴¹ Likewise, a recent study in the SCIENCE cohort showed that informant reports of decline did not significantly predict preclinical AD,⁴² but our results cannot be directly compared to these. The SCIENCE cohort are exclusively composed of subjects with SCD recruited from a memory clinic setting, and they used a dichotomized variable for positive/negative complaint instead of analyzing it as a continuous variable. Study setting, in which participants are worried enough to seek medical advice, and the cut-off used to define positive complaint, may explain the divergence of results. On the other hand, we identified two reports that are in line with our findings. Using the same questionnaire as we used, Valech et al.⁴³ found that TheirCog scores, but not MyCog ones, significantly differed between controls and preclinical AD (defined by $A\beta_{42}$ levels in CSF), with a significant AUC of 0.75 for discriminating between them. Similarly, Cacciamani et al.,⁴⁴ by means of a subject-informant discrepancy index approach, found that amyloid burden was more frequent (47%) in the low-awareness group (informant >subject perception of decline) than in the highly aware group (24%). In their study, they argue that low awareness may represent a very early form of anosognosia and, as such, might serve as a specific indicator of AD pathology.

We found that endorsement of at least 2 out of the 11 items in the memory subscore of the MyCog, or 2 out of 7 items in the executive one of the TheirCog scale almost tripled the chance of being classified as $A\beta$ positive. However, we observed a different classification pattern between self- and informant reports. While sensitivity and specificity of the self-reported memory cut-off was more balanced (both above 60%), the informant reported executive cut-off enhanced specificity (83%) over sensitivity (30%). Thus, absence of informant perception of decline in executive items was highly associated to a negative $A\beta$ PET visual read, but presence of perception of decline in these items does not necessarily indicate a positive $A\beta$ PET scan. This fact may be related in many cases to other non-AD changes, such as physiological aging. It is noteworthy that the range of OR of the cut-offs in predicting amyloidosis are similar to the effect of being an APOE $\epsilon 4$ carrier observed in our sample (OR = 3.1 $P = .005$ adjusted for age and sex), and in general population at 70 years old (OR ≈ 3),^{34,45,46} but less than the reported effect of the combination of being APOE $\epsilon 4$ carrier and classified as having SCD (OR ≈ 7), and far from the effect of

TABLE 3 Inclusion and PET-concurrent data for cognitive and self- and informant reports. Comparison of longitudinal change between A β groups (defined by PET outcome at PET-concurrent visit) using repeated measures ANOVA adjusting for covariates

	Inclusion visit		PET-concurrent visit		Group x Time P
	A β -	A β +	A β -	A β +	
PACC M(SD)	0.21 (2.72)	-0.64 (2.53)	0.55 (2.88)	-0.99 (0.62)	.574
MBT-TDFR M(SD)	17.3 (5.1)	17.0 (4.9)	17.9 (5.3)	16.3 (3.9)	.550
MBT-TPR M(SD)	24.3 (4.1)	24.7 (3.8)	25.4 (4.1)	23.7 (3.2)	.106
Coding WAIS IV M(SD)	67.5 (14.2)	60.5 (15.4)	67.2 (14.0)	58.7 (15.7)	.254
Semantic fluency M(SD)	23.1 (5.1)	21.1 (4.1)	23.2 (5.1)	21.6 (4.9)	.630
SCD-Q MyCog					
Total score M(SD)	5.02 (4.99)	5.73 (3.87)	3.85 (4.31)	5.88 (3.97)	.175
Memory subscore M(SD)	2.03 (2.42)	2.67 (2.35)	1.39 (2.00)	2.51 (2.40)	.533
Language subscore M(SD)	1.75 (1.78)	1.97 (1.67)	1.56 (1.60)	2.00 (1.32)	.464
Executive subscore M(SD)	1.25 (1.47)	1.09 (1.10)	0.91 (1.30)	1.28 (1.02)	.029
SCD-Q TheirCog					
Total score M(SD)	2.22 (3.18)	3.33 (3.92)	1.57 (2.71)	2.76 (3.11)	.801
Memory subscore M(SD)	0.99 (1.54)	1.48 (2.03)	0.70 (1.36)	1.33 (1.70)	.773
Language subscore M(SD)	0.66 (1.14)	0.85 (1.20)	0.48 (0.96)	0.82 (1.16)	.794
Executive subscore M(SD)	0.57 (1.02)	1.00 (1.99)	0.39 (0.86)	0.61 (0.99)	.533

Note: Group x Time interaction adjusted by age, sex, APOE ϵ 4 and time between visits. Education was also included as covariate in cognitive variables. Abbreviations: A β , amyloid beta; ANOVA, analysis of variance, APOE, APOLIPOPROTEIN E; MBT, Memory Binding Test; PACC, Preclinical Alzheimer's Cognitive Composite; SCD-Q, Subjective Cognitive Decline Questionnaire; MyCog, Participant scores; PET, positron emission tomography; SD, standard deviation; TDFR, Total Delayed Free Recall; TheirCog, Informant scores; TPR, Total Paired Recall; WAIS, Wechsler Adult Intelligence Scale.

homozygosity (OR \approx 18).⁴⁵ Indeed, we showed that informant report predictive ability is independent from the effect of APOE ϵ 4, because we have included it as a covariate in main models. When APOE ϵ 4 status was excluded from the models the associations were weaker but still significant. Interestingly, in a stratified analysis by APOE ϵ 4 status we observed that A β PET outcome was mainly predicted by SCD-Q in non-carriers. This fact suggest that SCD reports may be able to capture amyloid-related subtle cognitive changes that are independent of APOE ϵ 4. The weight of APOE ϵ 4 in predicting amyloidosis is so strong that SCD reports do not add significant predictive value in ϵ 4 allele carriers. Our results, rather than going against the view of APOE ϵ 4 being an SCD-plus feature, highlight the relevance of SCD reports in predicting amyloidosis when the main biological driver is absent.

We also explored, retrospectively, the longitudinal change in SCD-Q scores. Globally, we observed a trend showing that decreases in scores related to A β - status. In contrast, the A β + group tended to maintain, and in some cases increase, the scores, reflecting a higher degree of subjective complaint. Some longitudinal evidence pointed out that stability, or persistence, of SCD through time increased the risk of cognitive decline^{23,47} and the concept of persistence has been recently added to the SCD-plus features, a series of characteristics that increases the risk of cognitive decline and underlying AD pathology.⁴⁸ When longitudinal change was formally tested in our study by means repeated ANOVA adjusting for age, sex, interval between visits, and

APOE ϵ 4 status, A β groups only differ in the change of the self-reported executive subscore, that decreases in the A β - group and increases in the A β + one. Since a significant interaction with sex was found in this analysis, we reran it separately in men and women and observed that the effect was driven exclusively by the latter. In line with our finding, it has been recently suggested that reporting SCD may be a stronger predictor of incident dementia in women than in men.⁴⁹ Although in this study the authors explored only memory complaints, it may be possible that subtle increments in perceived difficulties in other domains, such as executive function, may be noticed more by A β + women, because women seem to outperform men in perceiving subtle pathological changes.⁵⁰

Although memory is the commonly studied domain in preclinical AD, mounting evidence has shown that cognitively unimpaired A β + subjects display lower performance not only in memory but also in executive function compared to A β - ones (see Baker et al.⁵¹ for a review). In our study, we have not found differences in cognitive outcomes. Nevertheless, the results in informant reports suggest that a close relative may be able to notice a subtle attentional/executive decline related to amyloid deposition, even before this is apparent in neuropsychological group analysis. This subtle decline would be expressed in challenging, highly demanding tasks in daily living, such as planning complex activities or dual tasking.

Our study is not free of limitations. The main one is having available only a PET scan performed at follow-up visit. We do not know the

participants' amyloid status at inclusion and, therefore, we cannot assess whether an increase in SCD-Q scores relates to an increase in amyloid deposition. However, further scans and cognitive follow-up visits are underway and will eventually permit further analyses. Another caveat relates to the limited information available for informants. Their mood, knowledge, and fears about AD may well affect the assessment of participants' cognitive status.

In summary, we found that both self- and informant reports of cognitive decline in cognitively unimpaired subjects are useful to predict A β positive status assessed by amyloid PET independently of age and APOE ϵ 4 status. Informant reports of change in executive items showed the higher predictive value, followed by self-reports of memory decline. In longitudinal reports, women that increase their executive complaints over time are more likely to have a positive amyloid PET.

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The ALFA+ study was approved by the Independent Ethics Committee "Parc de Salut Mar," Barcelona, and registered at Clinicaltrials.gov (Identifier: NCT02485730). All participants signed the study's informed consent form that had also been approved by the Independent Ethics Committee "Parc de Salut Mar, Barcelona.

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

CONFLICTS OF INTEREST

José Luis Molinuevo has served/serves as a consultant or on advisory boards for the following for-profit companies, or has given lectures in symposia sponsored by the following for-profit companies: Roche Diagnostics, Genentech, Novartis, Lundbeck, Oryzon, Biogen, Lilly, Janssen, Green Valley, MSD, Eisai, Alector, BioCross, GE Healthcare, ProMIS Neurosciences. Juan Domingo Gispert has given lectures in symposia sponsored by the following for-profit companies: General Electric, Philips, and Biogen. The remaining authors declare that they have no conflicts of interest.

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SUPPORTING INFORMATION

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

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