

# Association of the Informant-Reported Memory Decline With Cognitive and Brain Deterioration Through the Alzheimer Clinical Continuum

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## Abstract

### Background and Objectives

Studies are sparse regarding the association between the informant-reported subjective memory decline (informant report) and Alzheimer disease (AD) biomarkers. This study thus aimed at determining the clinical relevance of the informant report throughout the AD clinical continuum, by assessing its specific relationships with amyloid deposition, cognition, and neurodegeneration.

### Methods

Participants from the Imagerie Multimodale de la maladie d'Alzheimer à un stade Précoce (IMAP+) primary cohort and the Alzheimer Disease Neuroimaging Initiative (ADNI) replication cohort were included; all underwent multimodal neuroimaging and neuropsychological assessments. Follow-up data of IMAP+ participants over up to 36 months were also used for longitudinal analyses. The informant report was measured with the Cognitive Difficulties Scale (IMAP+) and Everyday Cognition (ADNI). General linear models were used to assess the cross-sectional associations between the informant report and amyloid-PET, cognitive performances, and neurodegeneration (atrophy and hypometabolism) in Alzheimer signature areas; while longitudinal links were assessed in IMAP+ with linear mixed-effects models.

### Results

A total of 110 IMAP+ participants were included, including 32 cognitively unimpaired older individuals (controls, age:  $70.91 \pm 6.57$  years, female: 50%), 25 patients with subjective cognitive decline (SCD,  $65.88 \pm 6.64$ , 40%), 35 with mild cognitive impairment (MCI,  $72.49 \pm 7.5$ , 34%), and 18 with Alzheimer-type dementia (AD dementia,  $68.17 \pm 8.59$ , 28%). Seven hundred thirty-one ADNI participants were included, including 157 controls ( $74.21 \pm 5.95$ , 55%), 84 with SCD ( $72.00 \pm 5.41$ , 63%), 369 with MCI ( $71.84 \pm 7.4$ , 44%), and 121 with AD dementia ( $74.29 \pm 7.75$ , 40%). In IMAP+, a higher informant report strongly correlated to greater amyloid-PET, specifically in patients with MCI ( $\beta = 0.48$ ,  $p = 0.003$ ), and to lower cognitive performance in patients with SCD (global cognition,  $\beta = -0.41$ ,  $p = 0.04$ ) and MCI (memory,  $\beta = -0.37$ ,  $p = 0.03$ ). Findings in patients with MCI were replicated in the ADNI (amyloid-PET,  $\beta = 0.25$ ,  $p < 0.001$ ; memory,  $\beta = -0.22$ ,  $p < 0.001$ ) and extended to neurodegeneration in AD signature areas ( $\beta = -0.2$ ,  $p < 0.001$ ). Longitudinal analyses in IMAP+ showed links with global cognitive decline over time in patients with MCI (estimate  $-0.74$ , SE 0.26,  $p = 0.005$ ) and SCD (estimate  $-0.36$ , SE 0.26,  $p = 0.02$ ) where a higher baseline informant report also predicted an increased amyloid-PET over time (estimate 0.008, SE 0.003,  $p = 0.02$ ).

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Data used in preparation of this article were obtained from the Alzheimer Disease Neuroimaging Initiative (ADNI) database ([adni.loni.usc.edu](https://adni.loni.usc.edu)). As such, the investigators within the ADNI contributed to the design and implementation of the ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found in the coinvestigators list at [links.lww.com/WNL/C778](https://links.lww.com/WNL/C778).

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## Glossary

**AD dementia** = Alzheimer-type dementia; **ADNI** = Alzheimer Disease Neuroimaging Initiative; **CDS** = Cognitive Difficulties Scale; **CU** = cognitively unimpaired; **ESR** = Encoding, Storage, and Retrieval; **FDG** =  $^{18}\text{F}$ -fluorodeoxyglucose; **FDR** = false discovery rate; **FLAIR** = fluid-attenuated inversion recovery; **GM** = gray matter; **IMAP+** = Imagerie Multimodale de la maladie d'Alzheimer à un stade Précoce; **I-SMD** = Informant-reported Subjective Memory Decline; **MCI** = mild cognitive impairment; **MMSE** = Mini-Mental State Examination; **SCD** = subjective cognitive decline; **Self-SMD** = self-reported Subjective Memory Decline; **SUVr** = global neocortical standardized uptake value ratio.

## Discussion

Altogether, our findings suggest that the informant report is particularly relevant in patients with MCI where it strongly relates to higher amyloid-PET, indicative of impairment due to AD.

## Trial Registration Information

ClinicalTrials.gov Identifier: NCT01638949.

Subjective cognitive decline (SCD) refers to the perception of worsening cognitive abilities relative to a prior level of performances and can be reported by individuals themselves (self-report) and/or by a close relative (informant report).<sup>1</sup> The interest of the self-report for clinical practice and research is now well documented.<sup>1,2</sup> Research on the informant report is more recent but promising because some studies suggest its clinical interest might exceed that of the self-report in certain circumstances,<sup>3-5</sup> although findings remain discrepant. Several studies showed that a higher informant report was linked to greater cognitive deficits and longitudinal cognitive or clinical decline in cognitively unimpaired (CU) older individuals<sup>5-9</sup> and patients with mild cognitive impairment (MCI)<sup>5,9-11</sup> or Alzheimer-type dementia (AD dementia)<sup>11</sup>; while other studies found no link between the informant report and the risk of cognitive or clinical decline in various settings.<sup>6,10,12</sup> Part of this discrepancy might reflect the fact that the informant report clinical relevance varies according to the clinical group, as shown for the self-report measure.<sup>13</sup> Studies are sparse regarding the association between the informant report and Alzheimer disease biomarkers; overall, they reported a link between a higher informant report and lower amyloid  $\beta$ 42, higher p-tau/t-tau CSF levels,<sup>4,14,15</sup> higher global amyloid-PET<sup>4</sup> and parietal tau-PET,<sup>16</sup> and lower hippocampal volume<sup>4,17</sup> and temporo-parietal glucose metabolism.<sup>18,19</sup> However, the settings in which these associations were found varied greatly from one study to another because most studies assessed only 1 clinical group or a mixed population merging several clinical groups. Only 2 studies assessed this link in several groups separately, but none of them included patients with isolated SCD.<sup>4,19</sup>

We proposed to assess the links between the informant report and Alzheimer disease–related markers/measures within each clinical group of the Alzheimer disease clinical continuum to unravel its relative clinical relevance. Our main objective was to determine the cross-sectional associations between the

informant report and amyloid-PET and cognition in 2 independent cohorts (the Imagerie Multimodale de la maladie d'Alzheimer à un stade Précoce [IMAP+] primary and the Alzheimer's Disease Neuroimaging Initiative [ADNI] replication cohorts). Our secondary objectives were (1) to assess the links with neurodegeneration imaging markers at baseline; (2) to test these associations over time, that is, between changes in informant report and changes in amyloid-PET and cognition; and (3) to assess the specificity of these links with the informant report by replicating all analyses correcting for the self-report.

## Methods

### Study Setting

This study followed the Strengthening the Reporting of Observational Studies in Epidemiology reporting guideline. Data were obtained from the observational IMAP+ study. IMAP+ participants have been evaluated at a single center (Cyceron, Caen, France), scanned on the same MRI and PET cameras, and followed up every 18 months, over 36 months. Scans used in this study were performed from January 24, 2008, to March 22, 2019. For replication and validation, the ADNI was used as an independent multicenter cohort with a larger sample size, and participants were included from more than 50 sites throughout the United States and Canada (adni-info.org). For this study, data accessed from the ADNI database on October 18, 2018 (ADNI2, ADNIGO, and ADNI3 phases) were used, with scans performed from June 17, 2010, to May 19, 2014 (adni.loni.usc.edu). Analyses were conducted from June 6, 2019, to December 7, 2021.

### Standard Protocol Approvals, Registrations, and Patient Consents

All study participants gave written informed consent after a complete description of the study. IMAP+ study was approved by the local ethics committee (Comité de Protection

des Personnes Nord-Ouest III) and registered at ClinicalTrials.gov (number NTC01638949). The ADNI study was approved by the institutional review boards of all the participating institutions.

## Imagerie Multimodale de la maladie d'Alzheimer à un stade Précoce

### Participants

IMAP+ was the primary cohort used for this study and consisted of CU participants (controls) and patients with SCD, MCI, and AD dementia. The informant-reported subjective memory decline (I-SMD), Mini-Mental State Examination (MMSE)<sup>20</sup> and structural MRI, fluorine 18–labeled fluorodeoxyglucose (FDG), and Florbetapir-PET were available at baseline for all participants. IMAP+ inclusion and exclusion criteria have been described elsewhere.<sup>21–24</sup> In brief, participants were all aged between 51 and 88 years, had at least 7 years of education, had no clinically significant psychiatric (including alcohol or drug abuse) or neurologic disease other than Alzheimer disease, had no significant white matter T2–fluid-attenuated inversion recovery (FLAIR)–weighted hyperintensities, and a modified Hachinski ischemic score  $\leq 2$ <sup>25</sup>. They were recruited from 2 main sources, public advertising for controls and from local memory clinics for patients with SCD, MCI, and AD dementia. The participants inclusion and group classification were based on a clinical interview and a standardized neuropsychological assessment according to internationally agreed criteria for SCD (i.e., memory concern without objective cognitive deficits),<sup>1</sup> amnesic MCI,<sup>26</sup> and probable Alzheimer disease,<sup>27</sup> but did not rely on neuroimaging biomarkers (i.e., amyloid- $\beta$ -tau-neurodegeneration classification). Control participants and patients with SCD had MMSE scores of 26 or higher; patients with MCI had MMSE scores of 22 or higher; and patients with AD dementia had MMSE scores of 12–26.

### Cognitive and Behavioral Assessment

The detailed neuropsychological evaluation encompassed SCD using the Cognitive Difficulties Scale (CDS, 39 items on a 5-point scale, total possible range: 0–156).<sup>28</sup> The CDS rates how often participants experience particular cognitive difficulties in everyday life; higher scores indicate higher subjective cognitive difficulties/decline. Because subjective memory decline is more likely to be associated with Alzheimer disease than subjective decline in other domains of cognition,<sup>1,29,30</sup> a weighted memory score derived from the CDS was used in all analyses (12 items, total possible range: 0–26.38), as defined in a previous publication based on a factorial analysis.<sup>31</sup> This results in 2 scores, the self-reported Subjective Memory Decline (self-SMD) when completed by the patient and the I-SMD when completed by his/her close relative.

Global cognitive functioning was evaluated using the MMSE (possible score range: 0–30).<sup>20</sup> Verbal episodic memory was assessed using the Encoding, Storage and Retrieval (ESR) free recall measure (0–16).<sup>32</sup> Higher scores indicate better performances for all tests.

In this study, we not only used the CDS, MMSE, and ESR scores collected at baseline in all participants (main objective) but also the follow-up data collected 18 months and/or 36 months after baseline in a subsample of participants for longitudinal analyses (secondary objectives).

### Neuroimaging Examinations

All participants underwent a Florbetapir-PET scan with a 20-minute late acquisition (beginning 50 minutes after injection) that reflected amyloid deposition, together with a high-resolution T1-weighted anatomical imaging to measure gray matter (GM) volume and an FDG-PET scan to measure brain glucose metabolism. The detailed acquisition and pre-processing procedures<sup>33,34</sup> are available in eMethods 1 ([links.lww.com/WNL/C777](https://www.lww.com/WNL/C777)). In brief, MRI images were segmented and normalized to the Montreal Neurological Institute space, PET images were preprocessed using MRI for coregistration and normalization, standardized uptake value ratios (SUVr) were calculated using a neocortex mask on Florbetapir-PET images, and Florbetapir-PET and FDG-PET images were corrected for partial volume effects using the 3-compartmental voxelwise Müller-Gärtner method<sup>35</sup> and used for voxelwise statistical analyses.

In this study, we used neuroimaging data acquired at baseline in all participants (main objective). We also used the follow-up data collected 18 months and/or 36 months after baseline in a subsample of participants for longitudinal analyses on the global Florbetapir SUVr only (secondary objectives).

### Replication

The ADNI data have been used as a replication cohort and included controls and patients with SCD, MCI (early-MCI and late-MCI merged) and AD dementia using cross-sectional I-SMD (8 memory items of Everyday Cognition Questionnaire),<sup>36</sup> cognitive testing (assessing global cognition, MMSE,<sup>20</sup> and immediate recall verbal episodic memory, Rey Auditory Verbal Learning Test<sup>37</sup>), and multimodal neuroimaging (structural MRI, FDG-PET and Florbetapir-PET; and global Florbetapir SUVr), within 90 days around the MRI date. Replication cohort description can be found in eMethods 2 ([links.lww.com/WNL/C777](https://www.lww.com/WNL/C777)). Baseline data were used to replicate the main analyses.

### Statistical Analyses

To aid comparability between scores and cohorts, I-SMD, objective cognitive or memory raw scores, and global Florbetapir SUVr described earlier were transformed into *w*-scores; that is, age-adjusted, sex-adjusted, and education-adjusted *z* scores relative to controls at baseline.<sup>38,39</sup>

Baseline differences in demographic, clinical, and cognitive features across clinical groups were analyzed using analysis of variance with post hoc Tukey tests for continuous variables and  $\chi^2$  tests for categorical variables. Baseline associations between I-SMD and amyloid-PET (global SUVr and voxelwise) and cognition (global and memory) were determined by general

linear models within each clinical group, and analyses were replicated within the ADNI cohort (main objective).

To respond to our secondary objectives, the same model was used to assess the links with neurodegeneration (GM volume and glucose metabolism) in Alzheimer signature areas, as previously defined<sup>34</sup> (i.e., regions of interest corresponding to areas of greatest neurodegeneration in Alzheimer disease), within each clinical group from both cohorts. Moreover, linear mixed-effects models were used to analyze IMAP+ longitudinal data, modeling the participant as a random effect, to assess the links between baseline I-SMD (independent variable) and changes over time in global amyloid-PET load and cognition and the links between changes over time in I-SMD (independent variable) and changes in global amyloid-PET load and cognition. Models included all main effects and their interactions with time (in months after the baseline visit). Finally, all analyses were repeated with the self-SMD as a covariate to control for its potential influence and show the links with the I-SMD that are independent from the self-reported subjective memory decline and by adjusting for depressive symptoms and the presence of concomitant cardiovascular disease to control for their potential influence on cognitive function.

All analyses were performed with R 4.0.3 (R Foundation, Vienna, Austria) and Statistical Parametric Mapping software (Wellcome Centre for Human Neuroimaging, UCL Queen Square Institute of Neurology).  $p < 0.05$  was considered statistically significant after applying a false discovery rate (FDR) correction for multiple comparisons, and voxelwise analyses were conducted with a full factorial design and an uncorrected cluster-level threshold of  $p < 0.001$  combined with a minimum cluster size determined by Monte-Carlo simulation using the Cluster-Sim program to achieve a statistical significance corrected for multiple comparisons of  $p < 0.05$ . Voxelwise neuroimaging analyses were adjusted for age, sex, and education.

## Data Availability

IMAP+ data used within this study are available from the corresponding author to research groups wishing to reproduce/confirm results under reasonable request and pending approval by the study coordinator. ADNI data used in this study were obtained from the public ADNI database (adni.loni.usc.edu).

## Results

### Participants' Characteristics

Data of 32 CU participants and 25 patients with SCD, 35 with MCI, and 18 with AD dementia were analyzed. Of the 110 participants, 67 participants had an 18-month follow-up, and 36 participants had a 36-month follow-up with I-SMD measurement obtained from the same relatives. Participants' characteristics, including demographic and behavioral variables, neuropsychological and SCD scores, and corresponding baseline between-group differences are detailed in Table 1. Patients

with SCD were younger than controls and patients with MCI. Patients with AD dementia and MCI include more allele e4 APOE carriers and have a higher global amyloid load and lower cognitive scores than controls and patients with SCD. I-SMD significantly increased from one clinical stage to another, except between patients with SCD and MCI, whereas the self-SMD was higher in all patient groups compared with that in controls and did not differ between patient groups.

Baseline informant report information are provided in eTable 1 (links.lww.com/WNL/C777). In brief, there were 81 spouses (73.64%), 15 children (13.64%), 4 friends (3.64%), 5 others (4.55%), and 5 missing information (4.55%), of which 82 lived with the participants (74.55%) and for those not living together, 17 met at least once a week.

### Links Between I-SMD, Amyloid Deposition, and Cognition at Baseline

#### Association With Amyloid Deposition and Cognition in the IMAP+ Primary Cohort

Results of general linear models exploring the association between I-SMD and amyloid deposition are presented in Figure 1 and detailed in eTables 2 and 3 (links.lww.com/WNL/C777). A significant interaction with the clinical group was found ( $F$  value 4.67,  $p_{\text{unadjusted}} = 0.004$ ), with a higher I-SMD being associated with a higher global amyloid load only in patients with MCI ( $p_{\text{FDR}} = 0.02$ ) and with Florbetapir-PET in extended brain areas including frontal, medial parietal, and lateral temporoparietal areas.

Results of general linear models exploring the association between I-SMD and cognition are presented in Figure 2 and detailed in eTable 2 (links.lww.com/WNL/C777). In patients with SCD, a higher I-SMD was associated with lower global cognition  $w$ -scores. In patients with MCI, a higher I-SMD was associated with lower memory  $w$ -scores and tended to be associated with lower global cognition  $w$ -scores. None of these associations survived FDR correction for multiple comparisons (all  $p_{\text{FDR}} > 0.14$ ), and no associations were found in other clinical groups.

#### Association With Amyloid Deposition and Cognition in the ADNI Replication Cohort

Data of 157 controls, 84 patients with SCD, 369 with MCI, and 121 with AD dementia were analyzed. ADNI participants' characteristics and supplementary results are provided in Figure 3 and detailed in eTables 4–6 (links.lww.com/WNL/C777). Substrates of I-SMD resembled those found in IMAP+, including the strong association with global amyloid load in patients with MCI only ( $p_{\text{FDR}} < 0.001$ ; interaction with the clinical group,  $F$  value 2.26,  $p_{\text{unadjusted}} = 0.08$ ) and the voxelwise correlations including the same brain regions and extending to almost the entire cortex (Figure 3, A and B). An association with the memory  $w$ -score ( $p_{\text{FDR}} < 0.001$ ), and as a trend for the global cognition  $w$ -score ( $p_{\text{FDR}} = 0.21$ ), was found in patients with MCI only (Figure 3, C and D).

**Table 1** Demographic and Clinical Features at Baseline by Diagnostic Group

Characteristic	Controls	SCD	MCI	AD dementia	<i>p</i> Value for baseline group differences ( <i>F</i> or $\chi^2$ )	Post hoc Tukey test, pairwise comparisons
<b>No. of participants, n</b>						
Baseline	32	25	35	18		
Follow-up 18 mo	18	20	22	7		
Follow-up 36 mo	12	12	12	0		
Follow-up duration, mo, mean (SD)	25.47 (10.02)	25.56 (9.52)	25.47 (9.08)	19.29 (4.50)	0.41 (0.97) <sup>a</sup>	
Female sex, n (%)	16 (50)	10 (40)	12 (34)	5 (28)	0.40 (2.92) <sup>b</sup>	
Age, y, mean (SD)	70.91 (6.57)	65.88 (6.64)	72.49 (7.5)	68.17 (8.59)	<b>0.005 (4.60)<sup>a</sup></b>	SCD < controls ( <i>p</i> = 0.05), MCI ( <i>p</i> = 0.004)
Education, y, mean (SD)	12.22 (3.68)	13.52 (3.25)	11.46 (3.86)	11.5 (3.17)	0.14 (1.87) <sup>a</sup>	
APOE e4 carrier, n (%)	7 (22)	4 (17)	16 (46)	12 (67)	<b>0.001 (15.48)<sup>b</sup></b>	AD dementia, MCI > controls, SCD (all <i>p</i> < 0.05 except MCI-controls, <i>p</i> = 0.07)
Global amyloid load (global Florbetapir SUVR, <i>w</i> -score), mean (SD)	0.99 (0.16)	0.99 (0.15)	1.29 (0.32)	1.52 (0.39)	<b>&lt;0.001 (17.88)<sup>c</sup></b>	Controls, SCD < MCI < AD dementia (all <i>p</i> < 0.02)
Global cognition (MMSE), mean (SD)	28.69 (1.20)	28.88 (1.13)	26.71 (2.08)	19.78 (4.81)	<b>&lt;0.001 (66.17)<sup>c</sup></b>	Controls, SCD < MCI < AD dementia (all <i>p</i> < 0.01)
Free recall verbal episodic memory (ESR), mean (SD)	7.08 (1.70)	7.00 (1.93)	3.69 (1.49)	1.88 (0.88)	<b>&lt;0.001 (47.89)<sup>c</sup></b>	Controls, SCD < MCI < AD dementia (all <i>p</i> < 0.001)
Self-SMD (self-report CDS), mean (SD)	8.86 (3.65)	12.39 (3.79)	13.71 (4.46)	13.44 (4.39)	<b>&lt;0.001 (10.02)<sup>c</sup></b>	Controls < SCD, MCI, AD dementia (all <i>p</i> < 0.001)
I-SMD (informant-report CDS), mean (SD)	6.69 (3.38)	10.53 (4.41)	13.47 (4.2)	18.11 (3.78)	<b>&lt;0.001 (37.93)<sup>c</sup></b>	Controls < SCD, MCI < AD dementia (all <i>p</i> < 0.001)

Abbreviations: AD dementia = Alzheimer-type dementia; ANOVA = analysis of variance; APOE e4 = allele e4 APOE; CDS = Cognitive Difficulties Scale; ESR = Encoding, Storage, and Retrieval task; I-SMD = informant-reported subjective memory decline; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; SCD = subjective cognitive decline; Self-SMD = self-reported subjective memory decline; SUVR = standardized uptake value ratio.

<sup>a</sup> Based on raw data: ANOVA between clinical groups (i.e., controls, SCD, MCI, AD dementia), post hoc Tukey pairwise tests.

<sup>b</sup> Based on raw data:  $\chi^2$  between clinical groups (i.e., controls and patients with SCD, MCI, and AD dementia).

<sup>c</sup> Based on *w*-scores: ANOVA between clinical groups (i.e., controls and patients with SCD, MCI, and AD dementia), post hoc Tukey pairwise tests.

## Links Between I-SMD and Neurodegeneration at Baseline in Both Cohorts

In the IMAP+ cohort, no significant associations were found with GM volume or glucose metabolism in Alzheimer signature areas (i.e., the medial temporal lobe, and the temporoparietal and precuneus/posterior cingulate cortex, respectively) in any clinical group; while in the ADNI, a higher I-SMD was related to lower glucose metabolism ( $p_{\text{FDR}} < 0.001$ ; Figure 4A) and GM volume ( $p_{\text{FDR}} = 0.004$ ; Figure 4B) in Alzheimer signature areas in patients with MCI only (detailed in eTable 2, [links.lww.com/WNL/C777](https://links.lww.com/WNL/C777)).

## Links Between I-SMD, Amyloid Deposition, and Cognition Over Time From the IMAP+ Longitudinal Data

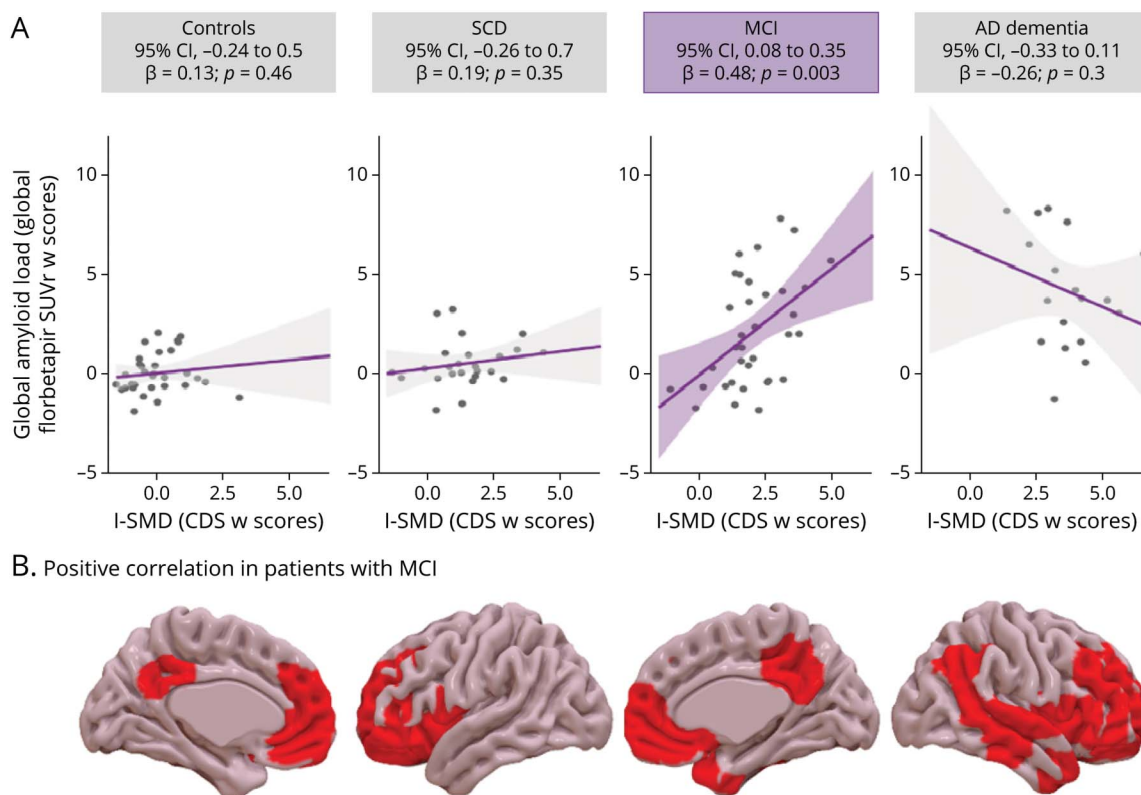
A decrease over time in global cognition (estimate  $-0.06$ , SE 0.02, *t* value  $-3.61$ ,  $p_{\text{unadjusted}} = 0.001$ , and  $p_{\text{FDR}} = 0.01$ ) and increase over time in I-SMD (estimate 0.02, SE 0.007, *t* value 3.72,  $p_{\text{unadjusted}} = 0.001$ , and  $p_{\text{FDR}} = 0.01$ ) were found in

patients with MCI, surviving FDR correction. No other significant changes over time were found (eTable 2, [links.lww.com/WNL/C777](https://links.lww.com/WNL/C777)).

A higher baseline I-SMD was associated with an increased global amyloid load over time in patients with SCD (estimate  $-0.008$ , SE 0.003, *t* value 2.69,  $p_{\text{unadjusted}} = 0.02$ , and  $p_{\text{FDR}} = 0.14$ ), but not surviving FDR correction. No other significant associations were found (eTable 2, [links.lww.com/WNL/C777](https://links.lww.com/WNL/C777)).

Finally, an increased I-SMD over time was associated with decreased global cognition (estimate  $-0.36$ , SE 0.14, *t* value  $-2.52$ ,  $p_{\text{unadjusted}} = 0.02$ , and  $p_{\text{FDR}} = 0.05$ ) in patients with SCD and with decreased global cognition (estimate  $-0.74$ , SE 0.26, *t* value  $-2.88$ ,  $p_{\text{unadjusted}} = 0.005$ , and  $p_{\text{FDR}} = 0.03$ ) and memory (estimate  $-0.26$ , SE 0.10, *t* value  $-2.79$ ,  $p_{\text{unadjusted}} = 0.007$ , and  $p_{\text{FDR}} = 0.03$ ) in those with MCI, all surviving FDR correction. No other significant associations were found (eTable 2, [links.lww.com/WNL/C777](https://links.lww.com/WNL/C777)).

**Figure 1** Relationships at Baseline Between the I-SMD and Amyloid Deposition



Graphs illustrate the results of general linear models for the cross-sectional correlations between the I-SMD *w*-scores and either the global Florbetapir SUVr across the different stages of the AD clinical continuum (A.  $p_{\text{unadjusted}} < 0.05$  in purple) or the Florbetapir-PET in the group of patients with MCI (B. Thresholded at  $p < 0.001$  with a cluster-level correction for multiple comparisons;  $k > 582$  voxels; no significant association was found in the other groups). AD = Alzheimer disease; CDS = Cognitive Difficulties Scale Questionnaire; I-SMD = informant-reported subjective memory decline; MCI = mild cognitive impairment; SCD = subjective cognitive decline; SUVr = standardized uptake value ratio.

### Correcting for Self-Reported Subjective Memory Decline, Depressive Symptoms, and Cardiovascular Disease

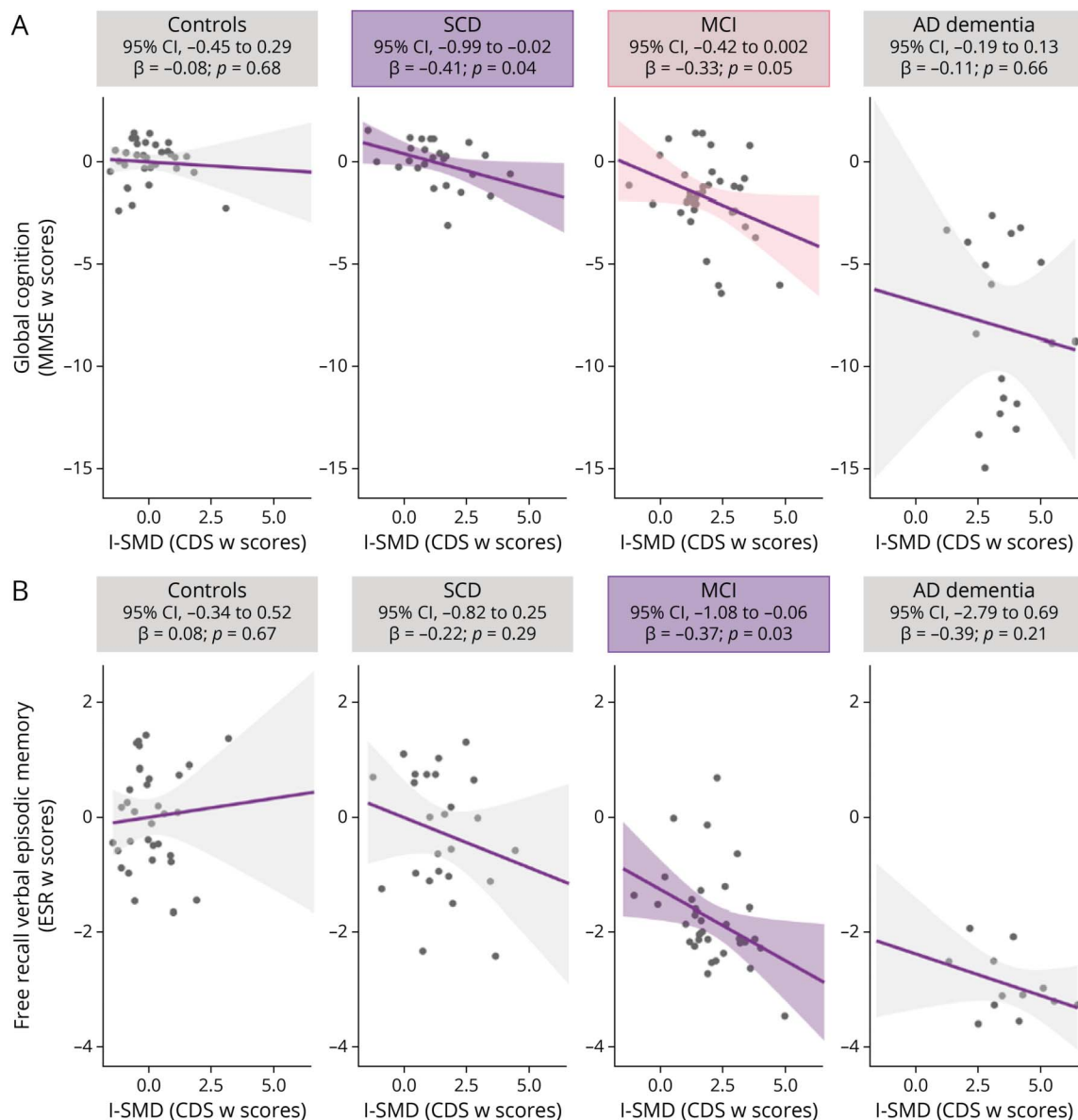
Results of models exploring the associations between baseline I-SMD and self-SMD are detailed in eTable 2 ([links.lww.com/WNL/C777](https://links.lww.com/WNL/C777)), and those between baseline I-SMD and multimodal Alzheimer disease biomarkers or cognition, independently of the effect of the self-SMD measure, depressive symptoms, and the presence of concomitant cardiovascular disease, are shown in eFigure 1 and detailed in eTable 6. The same cross-sectional associations were recovered, except for the association in IMAP+ between baseline I-SMD and baseline global cognition (SCD, estimate  $-0.30$ , SE  $0.23$ ,  $t$  value  $-1.30$ ,  $p_{\text{unadjusted}} = 0.22$ ) or memory *w*-scores (MCI, estimate  $-0.20$ , SE  $0.32$ ,  $t$  value  $0.64$ ,  $p_{\text{unadjusted}} = 0.53$ ). Only the links with global amyloid load, memory *w*-scores, and Alzheimer-like neurodegeneration in patients with MCI in the ADNI survived the FDR correction (all  $p_{\text{FDR}} < 0.03$ ); all voxelwise findings were recovered at the same threshold. Regarding IMAP+ longitudinal analyses, the sample sizes were considerably reduced when including only participants with all covariates available, and no relationships were found at the selected statistical threshold. The findings were, however, recovered with only adjusting for self-SMD (without depressive symptoms and cardiovascular disease, not shown).

### Discussion

The main goal of this study was to determine the neurobiological meaning and clinical value of the I-SMD by providing a comprehensive overview of its associations with brain and cognitive changes from normal cognition to Alzheimer-type dementia stages. We found that I-SMD was strongly associated with amyloid deposition, and slightly with cognition and neurodegeneration, in patients with MCI. In patients with SCD, it was slightly associated with global cognitive performances and decline and predictive of increased global amyloid load over time.

The higher level of I-SMD across the Alzheimer disease clinical continuum contrasts with the similar level of self-SMD between patients with SCD, MCI, and Alzheimer-type dementia. This result is consistent with previous studies showing that I-SMD measure was better than the self-report one to differentiate between diagnostic groups in group comparisons<sup>3,9,40-42</sup> or sensitivity/specificity analyses.<sup>4,43</sup> This might reflect the fact that, as the disease progresses, patients are less aware of their cognitive deficits due to increasing levels of anosognosia, leading to unreliable self-report. By contrast, the I-SMD seems to be more closely linked to the increasing level of the patient's cognitive impairment.

**Figure 2** Relationships at Baseline Between the I-SMD and Objective Cognitive or Memory Performances Across the Different Stages of the AD Clinical Continuum



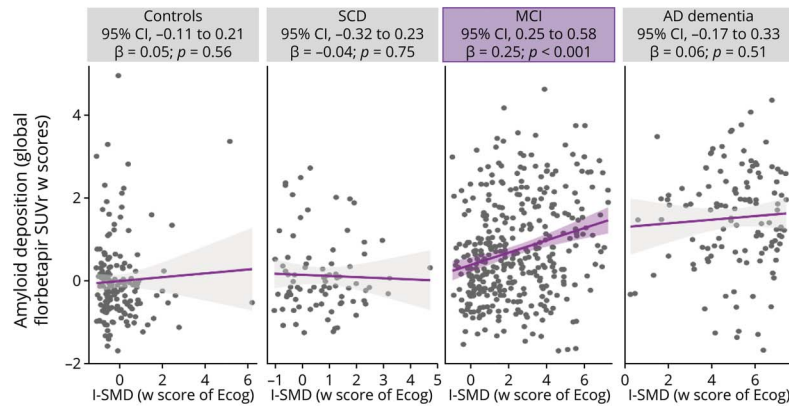
Graphs illustrate the results of general linear models for the correlations between I-SMD *w*-scores and either global cognition (A. MMSE *w*-scores) or verbal episodic memory (B. ESR free recall *w*-scores) at baseline.  $p_{\text{unadjusted}} < 0.10$  in pink and  $p_{\text{unadjusted}} < 0.05$  in purple. AD = Alzheimer disease; CDS = Cognitive Difficulties Scale; ESR = Encoding, Storage, and Retrieval; I-SMD = informant-reported subjective memory decline; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; SCD = subjective cognitive decline.

This study also reveals a strong association between the I-SMD and amyloid deposition in patients with MCI only. This finding is consistent with a previous study showing a correlation between a higher I-SMD measure and a higher global amyloid load in patients with late-MCI.<sup>4</sup> Beyond, our findings show (1) the specificity of this association to the MCI stage as it was not found in other clinical groups (i.e., CU, SCD, and Alzheimer-type dementia), (2) the value of this information beyond self-reported subjective memory decline, participant's depressive symptoms, and concomitant cardiovascular disease, (3) the topography of the links with the voxelwise correlations, and (4) the strength and

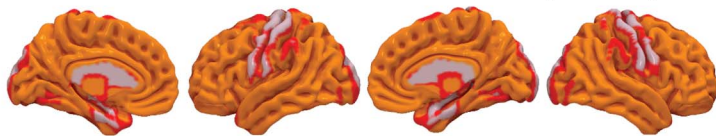
reliability of this result as it was found in 2 independent samples and survived the FDR correction. Of interest and consistent with previous studies,<sup>4,17,19</sup> this association in patients with MCI extended to lower GM volume (i.e., medial temporal lobe) and glucose metabolism (i.e., precuneus/posterior cingulate cortex and angular gyrus) in the ADNI and was also found in IMAP+ at a more permissive threshold (see eFigure 2, [links.lww.com/WNL/C777](https://links.lww.com/WNL/C777)). The report by a close relative thus seems to be particularly meaningful at the MCI stage, where a higher score is indicative of greater amyloid deposition and Alzheimer-like neurodegeneration.

**Figure 3** Relationships at Baseline Between I-SMD and Amyloid Deposition and Objective Cognitive or Memory Performances Within the ADNI Replication Cohort

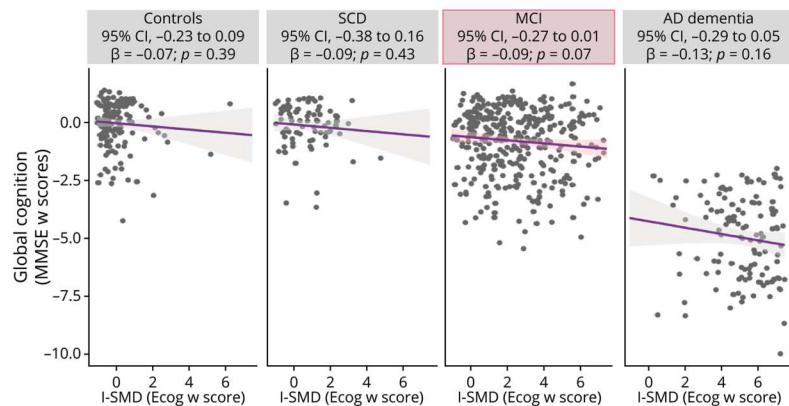
**A. Relationships at baseline between I-SMD and amyloid deposition**



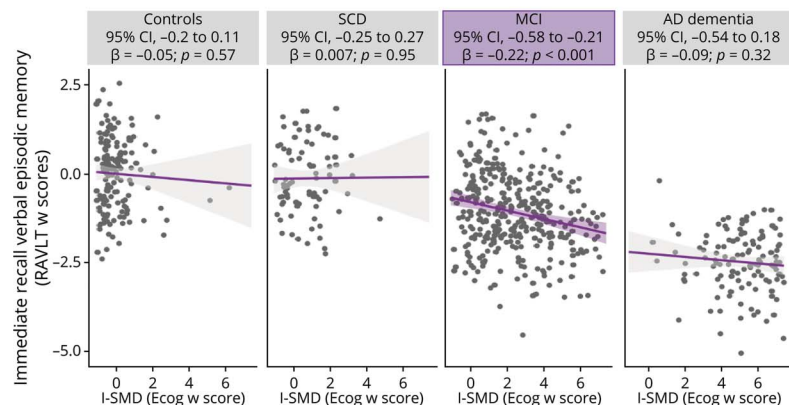
**B. Positive correlation between I-SMD and voxel-wise amyloid deposition in patients with MCI**



**C. Relationships at baseline between I-SMD and cognitive performances**



**D. Relationships at baseline between I-SMD and memory performances**



Graphs illustrate the results of general linear models for the cross-sectional correlations between the I-SMD  $w$ -scores and either the global Florbetapir SUVr across the different stages of the AD clinical continuum (A.  $p_{\text{unadjusted}} < 0.05$  in purple), the Florbetapir-PET in the group of patients with MCI (B. Thresholded at  $p < 0.001$  with a cluster-level correction for multiple comparisons (red) and at  $p_{\text{FWE}} < 0.05$  with a  $k > 200$  voxels (orange); no significant association was found in the other groups), global cognition (C. MMSE  $w$ -scores), or verbal episodic memory (D. RAVLT immediate recall  $w$ -scores) at baseline.  $p_{\text{unadjusted}} < 0.10$  in pink and  $p_{\text{unadjusted}} < 0.05$  in purple. AD = Alzheimer disease; ADNI = Alzheimer Disease Neuroimaging Initiative; CDS = Cognitive Difficulties Scale; ECog = Everyday Cognition Questionnaire; I-SMD = informant-reported subjective memory decline; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; RAVLT = Rey Auditory Verbal Learning Test; SCD = subjective cognitive decline; SUVr = standardized uptake value ratio.

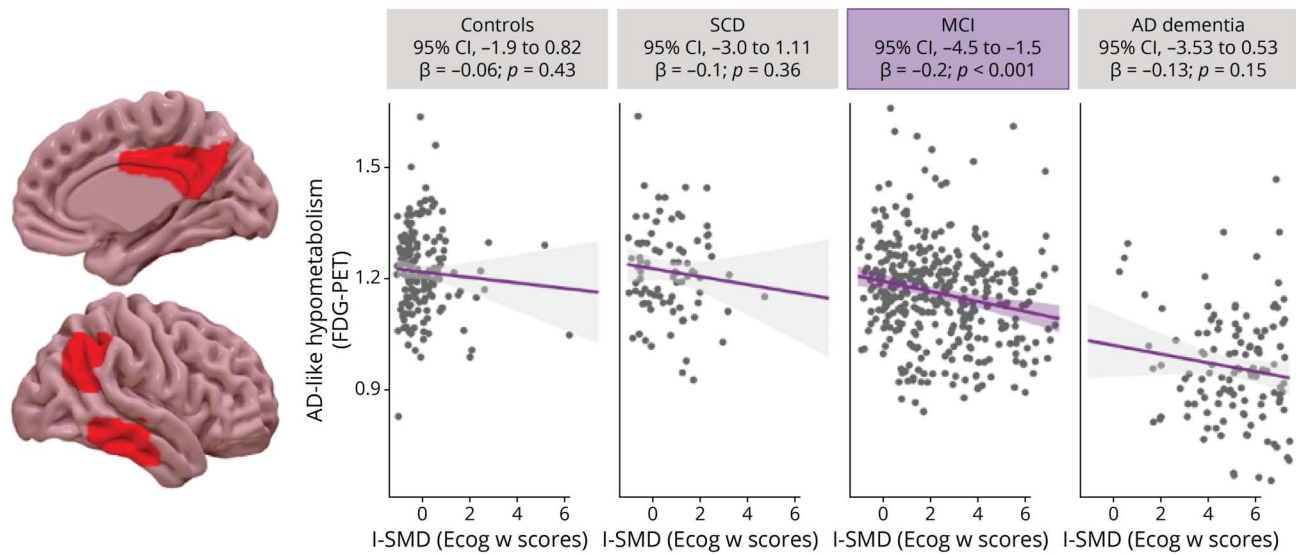
Our findings also highlight a link between the I-SMD and cognition in patients with MCI from both cohorts, and in patients with SCD in IMAP+. In IMAP+, these links were also found longitudinally in both clinical groups, with an increased

I-SMD over time associated with cognitive decline. Those findings are in line with previous studies showing that a higher I-SMD measure was associated with poorer global cognitive/memory performances and faster rate of cognitive/memory

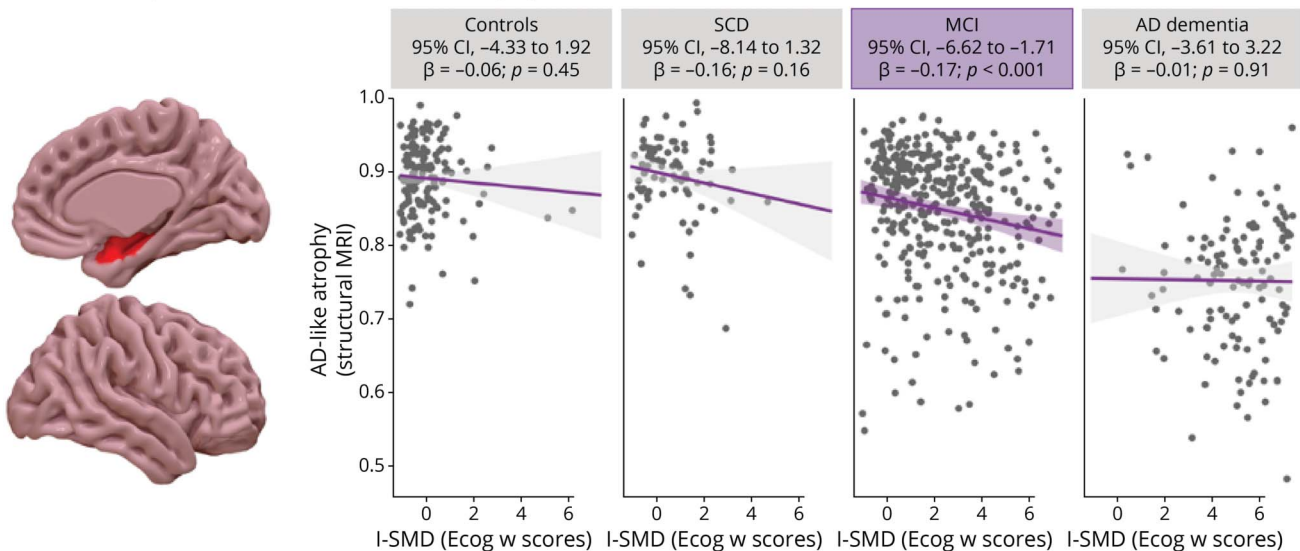


**Figure 4** Relationships at Baseline Between I-SMD and Glucose Metabolism and Gray Matter Volume in Alzheimer Signature Areas Within the ADNI Replication Cohort

**A.** Relationships at baseline between I-SMD and glucose metabolism



**B.** Relationships at baseline between I-SMD and gray matter volume



Graphs illustrate the results of general linear models for the cross-sectional correlations between the I-SMD *w*-scores and either the glucose metabolism (A) or gray matter volume (B) in Alzheimer signature areas determined in a previous study across the different stages of the AD clinical continuum ( $p_{\text{unadjusted}} < 0.05$  in purple). Results of the whole-brain voxelwise correlations between the I-SMD score and glucose metabolism and gray matter volume are provided in eFigure 1 and detailed in eTables 3 (IMAP+) and 6 (ADNI) ([links.lww.com/WNL/C777](https://links.lww.com/WNL/C777)). AD = Alzheimer disease; ADNI = Alzheimer's Disease Neuroimaging Initiative; FDG =  $^{18}\text{F}$ -fluorodeoxyglucose; I-SMD = informant-reported subjective memory decline.

decline in patients with SCD<sup>7,8,11</sup> and in patients with MCI.<sup>5,9-11,44,45</sup> Note that data in ADNI for patients with SCD should be considered with caution, given the criteria for SCD specifying that “the informant should not equate the expressed concern with progressive memory impairment.” This is likely to explain the lack of result in patients with SCD in the ADNI, together with the fact that they were recruited from the community and not from a memory clinic as in IMAP+.<sup>22,46</sup>

Finally, complementary longitudinal analyses showed that baseline I-SMD was not predictive of further cognitive decline

over a 2-year follow-up in any clinical group; while it predicted a 2-year increase in global amyloid load in patients with SCD in the IMAP+ cohort. Although weak (not surviving FDR correction), this relationship suggests that patients combining a significant concern about their memory (i.e., patients with SCD) and a high I-SMD level could be at a higher risk of increased subsequent amyloid pathology. Conversely, the lack of direct association with cognitive decline could probably be related to the relatively short follow-up period and small sample size compared with previous studies that highlighted such an association.<sup>6,9,47</sup>

This is a comprehensive study examining informant-reported subjective memory decline in relation to cognitive and neuroimaging disease biomarkers in samples of well-characterized individuals from normal cognition to AD dementia and within 2 independent cohorts with complementary strengths. This allowed us to get a better understanding of the differential clinical relevance of I-SMD depending on the clinical stage. This is useful to support the clinician in determining when to use and how to interpret the results of this scale in the framework of the clinical assessment—to make decision on patient monitoring, diagnosis, and on the choice of additional examinations. In addition, our results suggest that this measure could be of interest to enrich AD clinical trials for biomarker positivity at the screening stage, especially for patients with MCI. However, this study has some limitations. Our findings may not be generalized to all MCI subtypes because patients were selected based on their memory impairment in both cohorts. Moreover, cases of vascular or mixed cognitive impairment cannot be totally ruled out because small vessel disease was not assessed at every time point on MRI. However, this might have a modest or no impact because all individuals were selected to have no severe brain lesions on T2-weighted or FLAIR MRI scans and a modified Hachinski ischemic score  $\leq 2$ .<sup>24</sup> In addition, potential confounds such as the nature of the relationship between the informant and the patient, the informant's cognitive status, and psychological burden<sup>48</sup> need to be further investigated in future studies. Finally, further longitudinal analyses through longer follow-up periods and with larger samples, and studies assessing the link with tau biomarkers as well, are needed.

Beyond some confounders (i.e., self-SMD, depressive symptoms, and concomitant cardiovascular disease), I-SMD seems particularly clinically relevant in patients with MCI because it strongly correlates to higher amyloid deposition and slightly to worse cognition and greater Alzheimer-like neurodegeneration. I-SMD thus seems to be clinically useful to screen patients with MCI with an increased likelihood of Alzheimer disease. It could also be helpful in patients with SCD to screen those with higher Alzheimer disease risk because it correlates to worse cognition and predicts increased global amyloid load over time.

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<b>Audrey Perrotin, PhD</b>	Normandie Univ, UNICAEN, INSERM, U1237, PhIND "Physiopathology and Imaging of Neurological Disorders," Institut Blood and Brain @ Caen-Normandie, Cyseron, France	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; and study concept or design
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## Appendix 1 (continued)

Name	Location	Contribution
<b>Gaël Chételet, PhD</b>	Normandie Univ, UNICAEN, INSERM, U1237, PhIND "Physiopathology and Imaging of Neurological Disorders," Institut Blood and Brain @ Caen-Normandie, Cyseron, France	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data

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Coinvestigators are listed at [links.lww.com/WNL/C778](http://links.lww.com/WNL/C778).

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