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# 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's 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 from the *Alzheimer's 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 respectively 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's-signature areas; while longitudinal links were assessed in IMAP+ with linear mixed-effects models.

**Results:** 110 IMAP+ participants were included, including 32 cognitively unimpaired elders (controls, age: 70.91±6.57, female:50%), 25 patients with subjective cognitive decline (SCD, 65.88±6.64, 40%), 35 with mild cognitive impairment (MCI, 72.49±7.5, 34%) and 18 with Alzheimer's-type dementia (AD dementia, 68.17±8.59, 28%). 731 ADNI participants were included, including 157 controls (74.21±5.95, 55%), 84 SCD (72.00±5.41, 63%), 369 MCI (71.84±7.4, 44%) and 121 AD dementia (74.29±7.75, 40%). In IMAP+, higher informant-report strongly correlated to greater amyloid-PET specifically in MCI patients ($\beta$=0.48, p=.003), and to lower cognitive performance in SCD (global cognition, $\beta$=-0.41, p=.04) and MCI patients (memory, $\beta$=-0.37, p=.03). Findings in MCI patients were replicated in ADNI (amyloid-PET, $\beta$=0.25, p<.001; memory, $\beta$=-0.22, p<.001), and extended to neurodegeneration in AD signature areas ($\beta$=-0.2, p<.001). Longitudinal analyses in IMAP+ showed links with global cognitive decline over time in MCI (est. -0.74, SE 0.26, p=.005) and in SCD (est. -0.36, SE 0.26, p=.02) patients where higher baseline informant-report also predicted increased amyloid-PET over time (est. 0.008, SE 0.003, p=.02).


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

**Trial registration information:** ClinicalTrials.gov Identifier: NCT01638949

**Keywords:** Informant-reported subjective memory decline; Alzheimer's disease clinical continuum; amyloid; neurodegeneration; cognitive performances.

**Abbreviations:** ADNI = Alzheimer's Disease Neuroimaging Initiative; APOE4 = allele e4 of Apolipoprotein; CDS = Cognitive Difficulties Scale; CU = Cognitively Unimpaired elders; ECog = Everyday Cognition Questionnaire; ESR = Encoding, Storage and Retrieval; FDG = 18F-Fluorodeoxyglucose; FDR = False Discovery Rate-Correction; GM = Grey Matter volume; IMAP+ = Imagerie Multimodale de la maladie d'Alzheimer à un stade Précoce; I-SMD = Informant-reported Subjective Memory Decline; MCI = patients with Mild Cognitive Impairment; MMSE = Mini Mental State Examination; PVE = Partial Volume Effects-corrected; RAVLT = Rey Auditory Verbal Learning Test; ROI = Regions Of Interest; SCD = patients with Subjective Cognitive Decline; Self-SMD = Self-reported Subjective Memory Decline; SPM12 = Statistical Parametric Mapping software; STROBE = Strengthening the Reporting of Observational Studies in Epidemiology; SUVr = global neocortical standardized uptake value ratio

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# Introduction

Subjective cognitive decline 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).[1] The interest of the self-report for clinical practice and research is now well documented.[1,2] Research on the informant-report is more recent but promising as some studies suggest its clinical interest might exceed that of the self-report in certain circumstances,[3-5] although findings remain discrepant. Several studies showed that higher informant-report was linked to greater cognitive deficits and longitudinal

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cognitive or clinical decline in cognitively unimpaired elders (CU)[5-9] and patients with mild cognitive impairment (MCI)[5,9-11] or Alzheimer's-type dementia (AD dementia)[11]; while other studies found no link between the informant report and the risk of cognitive or clinical decline in various settings.[6,10,12] 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.[13] Studies are sparse regarding the association between the informant-report and Alzheimer's disease biomarkers; overall they reported a link between higher informant-report and lower Aβ42, higher p-tau/t-tau CSF levels,[4,14,15] higher global amyloid-PET[4] and parietal tau-PET,[16] and lower hippocampal volume[4,17] and temporo-parietal glucose metabolism.[18,19] However, the settings in which these associations were found varied greatly from one study to another, as most studies assessed only one clinical group or a mixed population merging several clinical groups. Only two studies assessed this link in several groups separately, but none of them included patients with isolated subjective cognitive decline (SCD).[4,19]

We proposed to assess the links between the informant-report and Alzheimer's disease-related markers/measures within each clinical group of the Alzheimer's 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 two independent cohorts (the IMAP+ primary and the ADNI replication cohorts). Our secondary objectives were i) to assess the links with neurodegeneration imaging markers at baseline; ii) to test these associations over time, i.e., between changes in informant-report and changes in amyloid-PET and cognition; and iii) to assess the specificity of these links with the informant-report by replicating all analyses correcting for the self-report.

# Materials and methods

## Study setting

This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline. Data were obtained from the observational *Imagerie Multimodale de la maladie d'Alzheimer à un stade Précoce* (IMAP+) study. IMAP+ participants have been evaluated at a single center (Cyceron, Caen, France), scanned on the

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same magnetic resonance imaging (MRI) and positron emission tomography (PET) cameras, and followed up every 18 months, over 36 months. Scans used in the current study were performed from January 24, 2008, to March 22, 2019. For replication and validation, the *Alzheimer's Disease Neuroimaging Initiative* (ADNI) was used as an independent multicenter cohort with a larger sample size and participants included from more than 50 sites throughout the United States and Canada (http://www.adni-info.org). For the present study, data accessed from the ADNI database on October 18, 2018 (ADNI2, ADNIGO and ADNI3 phases) was used, with scans performed from June 17, 2010, to May 19, 2014 (http://adni.loni.usc.edu). Analyses were conducted from June 6, 2019 to December 07, 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 (CPP Nord-Ouest III) and registered at http://clinicaltrials.gov (nb. NTC01638949). 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 (IMAP+)

### 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)[20] and structural MRI, fluorine 18-labeled Fluorodeoxyglucose (FDG), and Florbetapir-PET, were available at baseline in all participants. IMAP+ inclusion and exclusion criteria have been described elsewhere.[21-24] Briefly, participants were all aged between 51-88 years, had at least 7 years of education, had no clinically significant psychiatric (including alcohol or drug abuse) or neurologic disease other than Alzheimer's disease, had no significant white matter T2-

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FLAIR-weighted hyperintensities, and a modified Hachinski ischemic score ≤ 2[25]). They were recruited from two 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),[1] amnestic MCI[26] and probable Alzheimer's disease,[27] but did not rely on neuroimaging biomarkers (i.e., ATN classification). Controls participants and SCD patients had MMSE scores of 26 or higher; MCI patients had MMSE scores of 22 or higher; and AD dementia patients had MMSE scores of 12 to 26.

## Cognitive and Behavioral Assessment

The detailed neuropsychological evaluation encompassed subjective cognitive decline using the Cognitive Difficulties Scale (CDS, 39 items on a 5-point scale, total possible range: 0-156)[28]. 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's disease than subjective decline in other domains of cognition,[1,29,30] 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.[31] This results in two scores, the 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).[20] Verbal episodic memory was assessed using the Encoding, Storage and Retrieval free recall measure (ESR, 0-16).[32] Higher scores indicate better performances for all tests.

In the current study, we 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).

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## Neuroimaging Examinations

All participants underwent a Florbetapir-PET scan with a 20-minute late acquisition (beginning 50-minute after injection) that reflected amyloid deposition, together with a high-resolution T1-weighted anatomical imaging to measure grey matter (GM) volume and an FDG-PET scan to measure brain glucose metabolism. The detailed acquisition and preprocessing procedures[33,34] are available in **eMethods 1 in the Supplement**. Briefly, MRI images were segmented and normalized to the Montreal Neurological Institute space, PET images were preprocessed using MRI for co-registration and normalization, a standardized uptake value ratios (SUVr) were calculated using a neocortex mask on Florbetapir-PET images, and Florbetapir- and FDG-PET images were corrected for partial volume effects (PVE) using the 3-compartmental voxelwise Müller-Gärtner method[35] and used for voxelwise statistical analyses.

In the current study, we used neuroimaging data acquired at baseline in all participants (main objective). We also used the follow-up data collected 18-month and/or 36-month 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, SCD, MCI (early- and late-MCI merged) and AD dementia patients using cross-sectional I-SMD (8 memory items of Everyday Cognition Questionnaire - Ecog)[36], cognitive testing (assessing global cognition, MMSE[20], and immediate recall verbal episodic memory, Rey Auditory Verbal Learning Test - RAVLT[37]), and multimodal neuroimaging (structural MRI, FDG- and Florbetapir-PET; and global Florbetapir SUVr), within 90 days around the MRI date. Replication cohort description can be found in **eMethods 2 in the Supplement**. Baseline data were used to replicate the main analyses.

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## Statistical analyses

To aid comparability between scores and cohorts, I-SMD, objective cognitive or memory raw scores, and global Florbetapir SUVr described above were transformed into w-scores; i.e., age-, sex- and education-adjusted z-scores relative to controls at baseline.[38,39]

Baseline differences in demographic, clinical and cognitive features across clinical groups were analyzed using analysis of variance (ANOVA) 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's-signature areas as previously defined[34] (i.e., regions of interest (ROI) corresponding to areas of greatest neurodegeneration in Alzheimer's 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 i) the links between baseline I-SMD (independent variable) and changes over time in global amyloid-PET load and cognition, and ii) 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, as well as their interactions with time (in months after the baseline visit). Finally, iii) 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 also 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; https://cran.r-project.org/bin/windows/base/old/4.0.3/) and Statistical Parametric Mapping software (SPM12; Wellcome Centre for Human Neuroimaging, UCL Queen Square Institute of Neurology). $P<.05$ was considered statistically significant after applying a false discovery rate-correction (FDR) for multiple comparisons, and voxelwise analyses were carried out with a full factorial design and an uncorrected cluster-level threshold of $p<.001$ combined with a minimum cluster size determined by Monte-Carlo simulation using the Cluster-Sim

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program to achieve a statistical significance corrected for multiple comparisons of $p<.05$. 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. On 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 subjective cognitive decline scores, as well as corresponding baseline between-group differences are provided in **Table 1**. SCD patients were younger than controls and MCI patients. AD dementia and MCI patients include more APOE4 carriers and have higher global amyloid load and lower cognitive scores than controls and SCD patients. I-SMD significantly increased from one clinical stage to another, except between SCD and MCI patients, whereas the self-SMD was higher in all patient groups compared to controls, and did not differ between patient groups.

Baseline informant-report information are provided in **eTable 1.** Briefly, 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.

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# 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 2–3.** A significant interaction with the clinical group was found (*F value* 4.67, $p_{unadjusted}$=.004), with higher I-SMD being associated with higher global amyloid load only in MCI patients ($p_{FDR}$=.02) and with Florbetapir-PET in extended brain areas including frontal, medial parietal, and lateral temporo-parietal areas.

Results of general linear models exploring the association between I-SMD and cognition are presented in **Figure 2** and detailed in **eTable 2**. In SCD patients, higher I-SMD was associated with lower global cognition w-scores. In MCI patients, 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 $p_{FDR}$>.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 in **eTables 4–6**. Substrates of I-SMD resembled those found in IMAP+, including the strong association with global amyloid load in MCI patients only ($p_{FDR}$<.001; interaction with the clinical group, *F value* 2.26, $p_{unadjusted}$=.08), and the voxelwise correlations including the same brain regions and extending to almost the entire cortex (**Figure 3, A–B**). An association with the memory w-score ($p_{FDR}$<.001), and as a trend for the global cognition w-score ($p_{FDR}$=.21), was found in MCI patients only (**Figure 3, C–D**).

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## Links between I-SMD and neurodegeneration at baseline in both cohorts

In IMAP+, no significant associations were found with glucose metabolism or GM volume in Alzheimer's-signature areas (i.e., the medial temporal lobe; and the temporo-parietal and precuneus/posterior cingulate cortex, respectively) in any clinical group; while in ADNI, higher I-SMD was related to lower glucose metabolism ($p_{FDR}$<.001; **Figure 4A**) and GM volume ($p_{FDR}$=.004; **Figure 4B**) in Alzheimer's-signature areas in MCI patients only (detailed in **eTable 2)**.

## 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, $p_{unadjusted}$=.001, and $p_{FDR}$=.01) and increase over time in I-SMD (*estimate* 0.02, *SE* 0.007, *t value* 3.72, $p_{unadjusted}$=.001, and $p_{FDR}$=.01) were found in MCI patients; surviving FDR correction. No other significant changes over time were found (**eTable 2)**.

Higher baseline I-SMD was associated with increased global amyloid load over time in SCD patients (*estimate* -0.008, *SE* 0.003, *t value* 2.69, $p_{unadjusted}$=.02, and $p_{FDR}$=.14), but not surviving FDR correction. No other significant associations were found (**eTable 2)**.

Finally, increased I-SMD over time was associated with decreased global cognition (*estimate* -0.36, *SE* 0.14, *t value* -2.52, $p_{unadjusted}$=.02, and $p_{FDR}$=.05) in SCD patients, and with decreased global cognition (*estimate* -0.74, *SE* 0.26, *t value* -2.88, $p_{unadjusted}$=.005, and $p_{FDR}$=.03) and memory (*estimate* -0.26, *SE* 0.10, *t value* -2.79, $p_{unadjusted}$=.007, and $p_{FDR}$=.03) in MCI; all surviving FDR correction. No other significant associations were found (**eTable 2)**.

## Correcting for self-reported subjective memory decline, depressive symptoms and cardiovascular disease

Results of models exploring the associations between baseline I-SMD and SMD are detailed in **eTable 2;** and those between baseline I-SMD and multimodal Alzheimer's disease

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biomarkers or cognition, independently of the effect of the self-SMD measure, depressive symptoms and the presence of concomitant cardiovascular disease, are detailed in **eFigure 1** and **eTable 6 in the Supplement**. 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, $p_{unadjusted}$=.22) or memory w-scores (MCI, *estimate* -0.20, *SE* 0.32, *t value* 0.64, $p_{unadjusted}$=.53). Only the links with global amyloid load, memory w-scores and Alzheimer's-like neurodegeneration in ADNI MCI patients survived the FDR correction (all $p_{FDR}$<.03); and 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 the present 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's-type dementia stages. We found that I-SMD was strongly associated with amyloid deposition, and slightly with cognition and neurodegeneration, in MCI patients. 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's disease clinical continuum contrasts with the similar level of self-SMD between SCD, MCI and Alzheimer's-type dementia patients. 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[3,9,40-42] or sensitivity/specificity analyses.[4,43] This might reflect the fact that, as the disease progresses, patients are less aware of their cognitive deficits due to increasing levels of anosognosia,

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leading to unreliable self-report. In contrast, the I-SMD seems to be more closely linked to the increasing level of the patient's cognitive impairment.

The current study also reveals a strong association between the I-SMD and amyloid deposition in MCI patients only. This finding is consistent with a previous study showing a correlation between higher I-SMD measure and higher global amyloid load in late-MCI patients.[4] Beyond, our findings show (i) the specificity of this association to the MCI stage as it was not found in other clinical groups (i.e., CU, SCD and Alzheimer's-type dementia), ii) the value of this information beyond self-reported subjective memory decline, participant's depressive symptoms and concomitant cardiovascular disease, (ii) the topography of the links with the voxelwise correlations, and (iii) the strength and reliability of this result as it was found in two independent samples and survived the FDR correction. Interestingly and consistently with previous studies,[4,17,19] this association in MCI patients extended to lower GM volume (i.e., medial temporal lobe) and glucose metabolism (i.e., precuneus/posterior cingulate cortex and angular gyrus) in ADNI; and was also found in IMAP+ at a more permissive threshold (see **eFigure 2 in the Supplement**). The report by a close relative thus appears to be particularly meaningful at the MCI stage, where a higher score is indicative of greater amyloid deposition and Alzheimer's-like neurodegeneration.

Our findings also highlight a link between the I-SMD and cognition in MCI patients from both cohorts, and in SCD patients in IMAP+. In IMAP+, these links were also found longitudinally in both clinical groups, with increased I-SMD over time associated with cognitive decline. Those findings are in line with previous studies showing that higher I-SMD measure was associated with poorer global cognitive/memory performances and faster rate of cognitive/memory decline in SCD patients,[7,8,11] and in MCI patients.[5,9-11,44,45] Note that data in ADNI for SCD patients 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 ADNI SCD patients, together with the fact that they were recruited from the community and not from a memory clinic as in IMAP+.[22,46]

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 IMAP+ SCD patients. Although weak (not surviving FDR correction), this relationship suggests that patients combining a significant

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concern about their memory (i.e., SCD patients) and a high I-SMD level could be at 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 to previous studies that highlighted such an association.[6,9,47]

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 two 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 MCI patients. However, this study has some limitations. Our findings may not be generalized to all MCI subtypes as patients were selected based upon 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 as all individuals were selected to have no severe brain lesions on T2-weighted or FLAIR MRI scans, and a modified Hachinski ischemic score $\leq 2$[24]. Additionally, potential confounds such as the nature of the relationship between the informant and the patient, the informant's cognitive status and psychological burden[48] 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 as it strongly correlates to higher amyloid deposition, and slightly to worse cognition and greater Alzheimer's-like neurodegeneration. I-SMD thus appears to be clinically useful to screen MCI patients with increased likelihood of Alzheimer's disease. It could also be helpful in

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SCD patients to screen those with higher Alzheimer's disease risk, as it correlates to worse cognition and predicts increased global amyloid load over time.

**WNL-2023-000205_sup ---http://links.lww.com/WNL/C777**

**WNL-2023-000205_coinvestigator_appendix --- http://links.lww.com/WNL/C778**

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# Figure legends

**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

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I-SMD w-scores and either the global Florbetapir SUVr across the different stages of the Alzheimer's disease clinical continuum (**A.** $p_{unadjusted}$<.05 in purple) or the Florbetapir-PET in the group of MCI patients (**B.** thresholded at p<.001 with a cluster-level correction for multiple comparisons; k>582 voxels; no significant association was found in the other groups). Abbreviations: AD, Alzheimer's Disease; CDS, Cognitive Difficulties Scale; I-SMD, informant-reported subjective memory decline; MCI, Mild Cognitive Impairment; PET, positron emission tomography; SCD, Subjective Cognitive Decline; SUVr, standardized uptake value ratio.

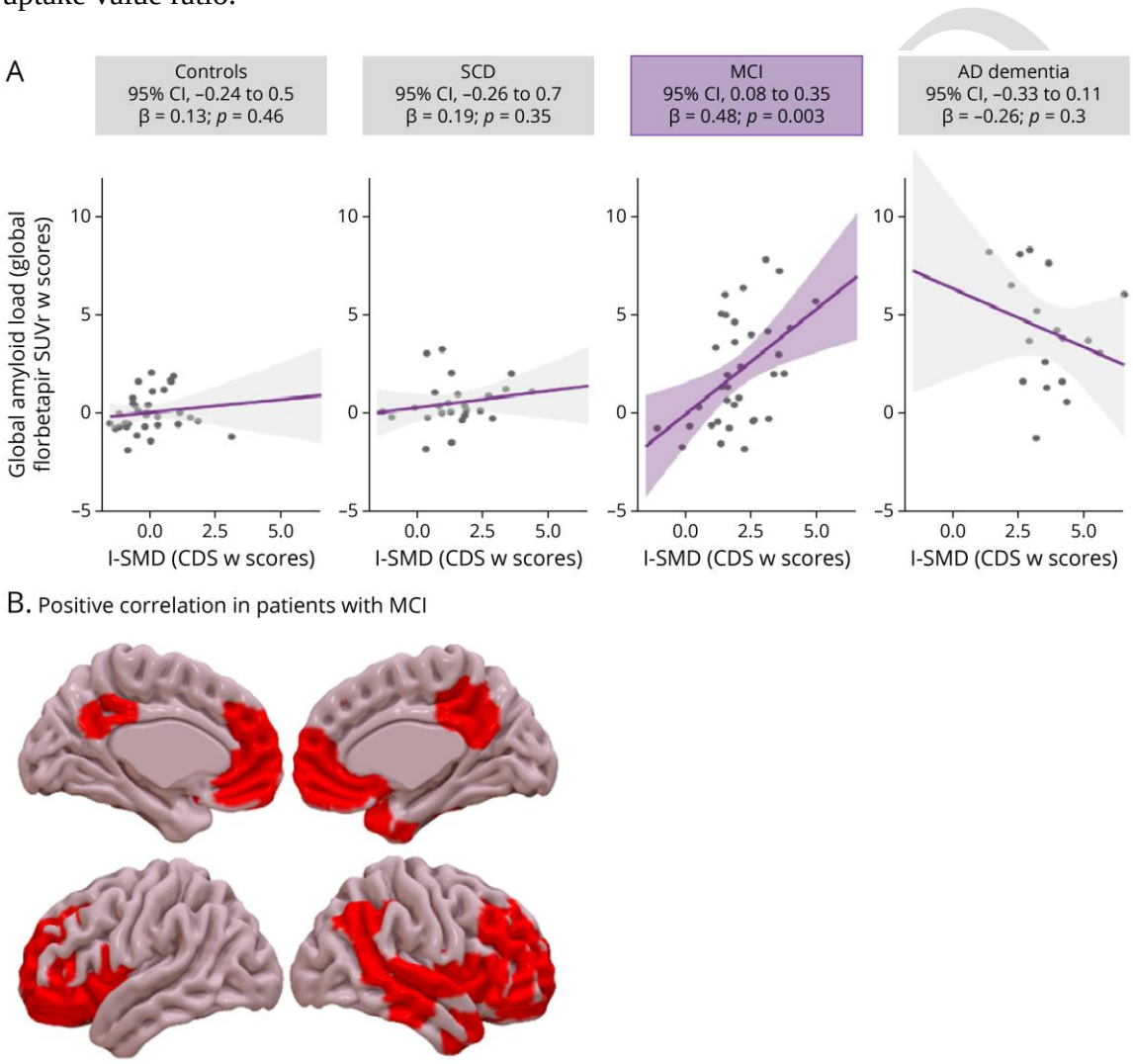


**Figure 2. Relationships at baseline between the I-SMD and objective cognitive or memory performances across the different stages of the Alzheimer's disease clinical continuum**. Graphs illustrate the results of general linear models for the correlations between I-SMD w-scores and either global cognition (**A.** MMSE w-scores) or verbal episodic memory (**B.** ESR free recall w-scores) at baseline. $p_{unadjusted}$<.10 in pink and $p_{unadjusted}$<.05 in purple. Abbreviations: AD, Alzheimer's Disease; CDS, Cognitive Difficulties Scale; ESR, Encoding,

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Storage and Retrieval; I-SMD, informant-reported subjective memory decline; MCI, Mild Cognitive Impairment; MMSE, Mini Mental State Examination; SCD, Subjective Cognitive Decline.

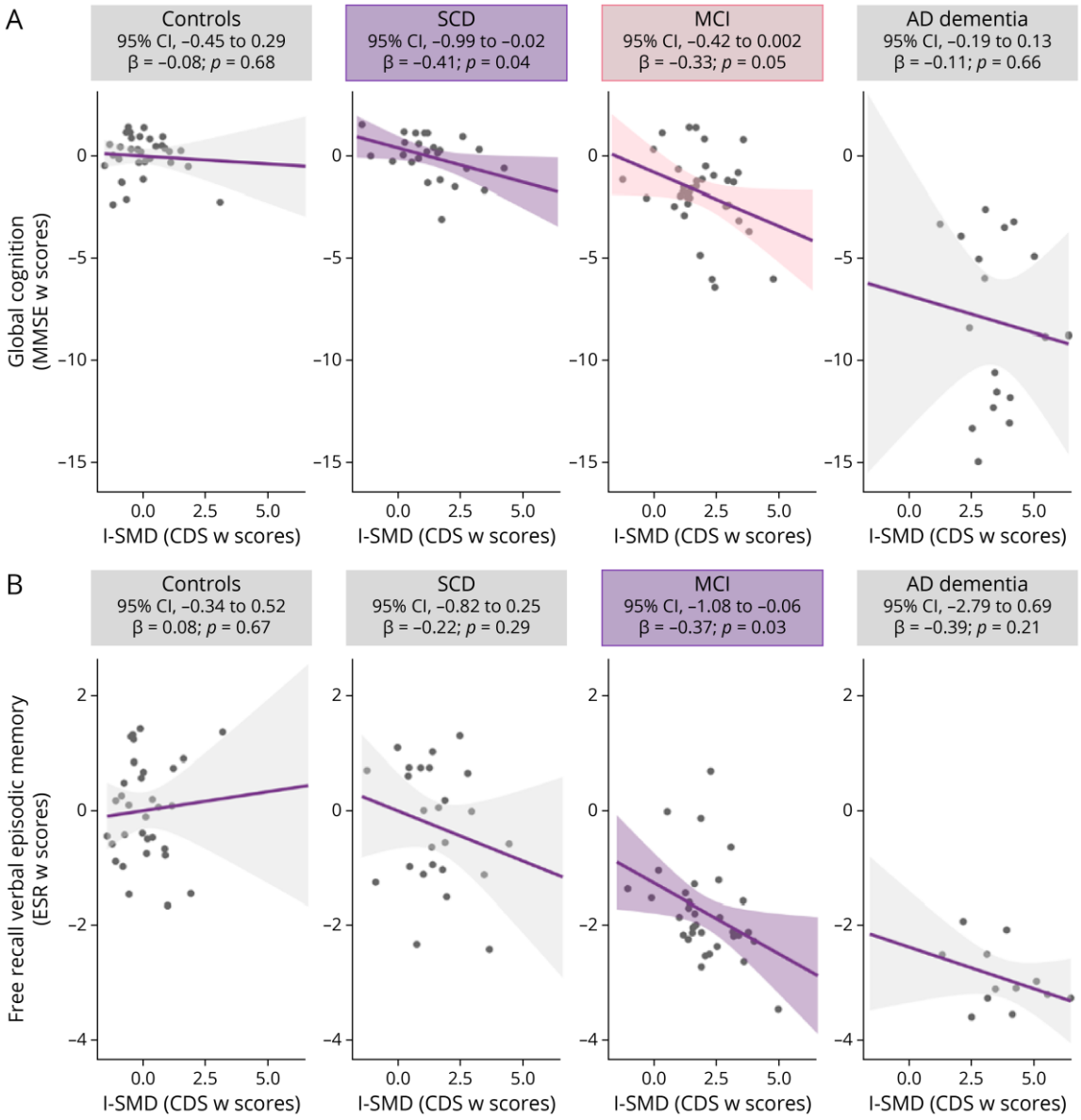


**Figure 3. Relationships at baseline between I-SMD and amyloid deposition and objective cognitive or memory performances within the ADNI replication cohort.** Graphs illustrate the results of general linear models for the cross-sectional correlations between the I-SMD w-scores and either the global Florbetapir SUVr across the different stages of the Alzheimer's disease clinical continuum (**A.** $p_{unadjusted}<.05$ in purple), the Florbetapir-PET in the group of MCI patients (**B.** thresholded at $p<.001$ with a cluster-level correction for multiple comparisons (red) and at $p_{FWE}<.05$ with a $k>200$ voxels (orange); no significant association was found in the other groups), global cognition (**C.** MMSE w-scores)

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or verbal episodic memory (**D.** RAVLT immediate recall w-scores) at baseline. $p_{unadjusted}$<.10 in pink and $p_{unadjusted}$<.05 in purple. Abbreviations: AD, Alzheimer's Disease; ADNI, Alzheimer's Disease Neuroimaging Initiative; CDS, Cognitive Difficulties Scale; Ecog, Everyday Cognition; I-SMD, informant-reported subjective memory decline; MCI, Mild Cognitive Impairment; MMSE, Mini Mental State Examination; PET, positron emission tomography; RAVLT, Rey Auditory Verbal Learning Test; SCD, Subjective Cognitive Decline; SUVr, standardized uptake value ratio.

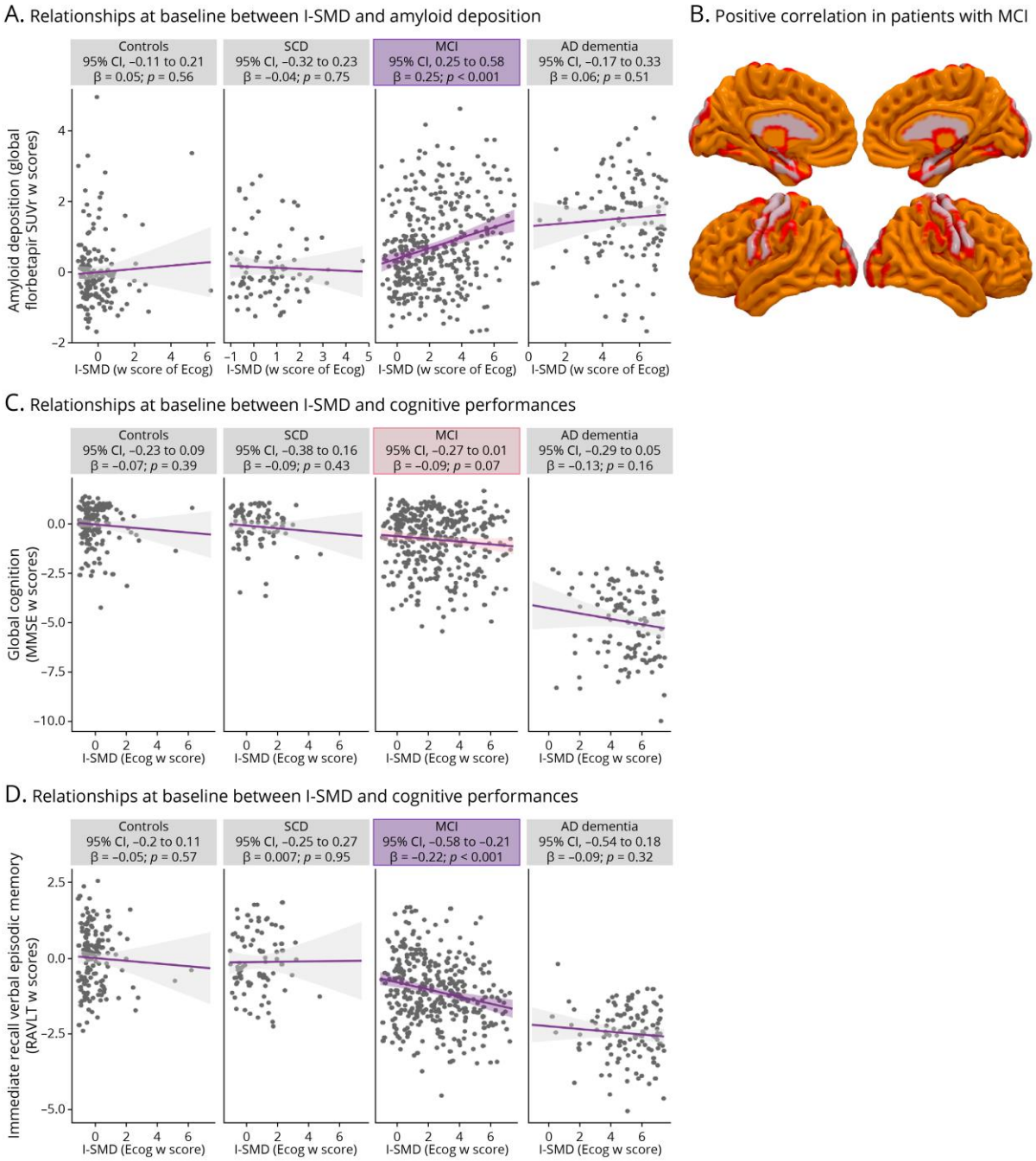


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**Figure 4. Relationships at baseline between I-SMD and glucose metabolism and grey matter volume in Alzheimer's-signature areas within the ADNI replication cohort.** Graphs illustrate the results of general linear models for the cross-sectional correlations between the I-SMD w-scores and either the glucose metabolism (**A**) and grey matter volume (**B**) in Alzheimer's-signature areas determine in a previous study across the different stages of the Alzheimer's disease clinical continuum ($p_{unadjusted}$<.05 in purple). Results of the whole brain voxelwise correlations between the I-SMD score and either glucose metabolism and grey matter volume are provided in **eFigure 1** and detailed in **eTables 3 (IMAP+) and 6 (ADNI) in the Supplement.** Abbreviations: AD, Alzheimer's Disease; ADNI, Alzheimer's Disease Neuroimaging Initiative; FDG, 18F-fluorodeoxyglucose; I-SMD, informant-reported subjective memory decline; MRI, Magnetic Resonance Imaging; PET, positron emission tomography.

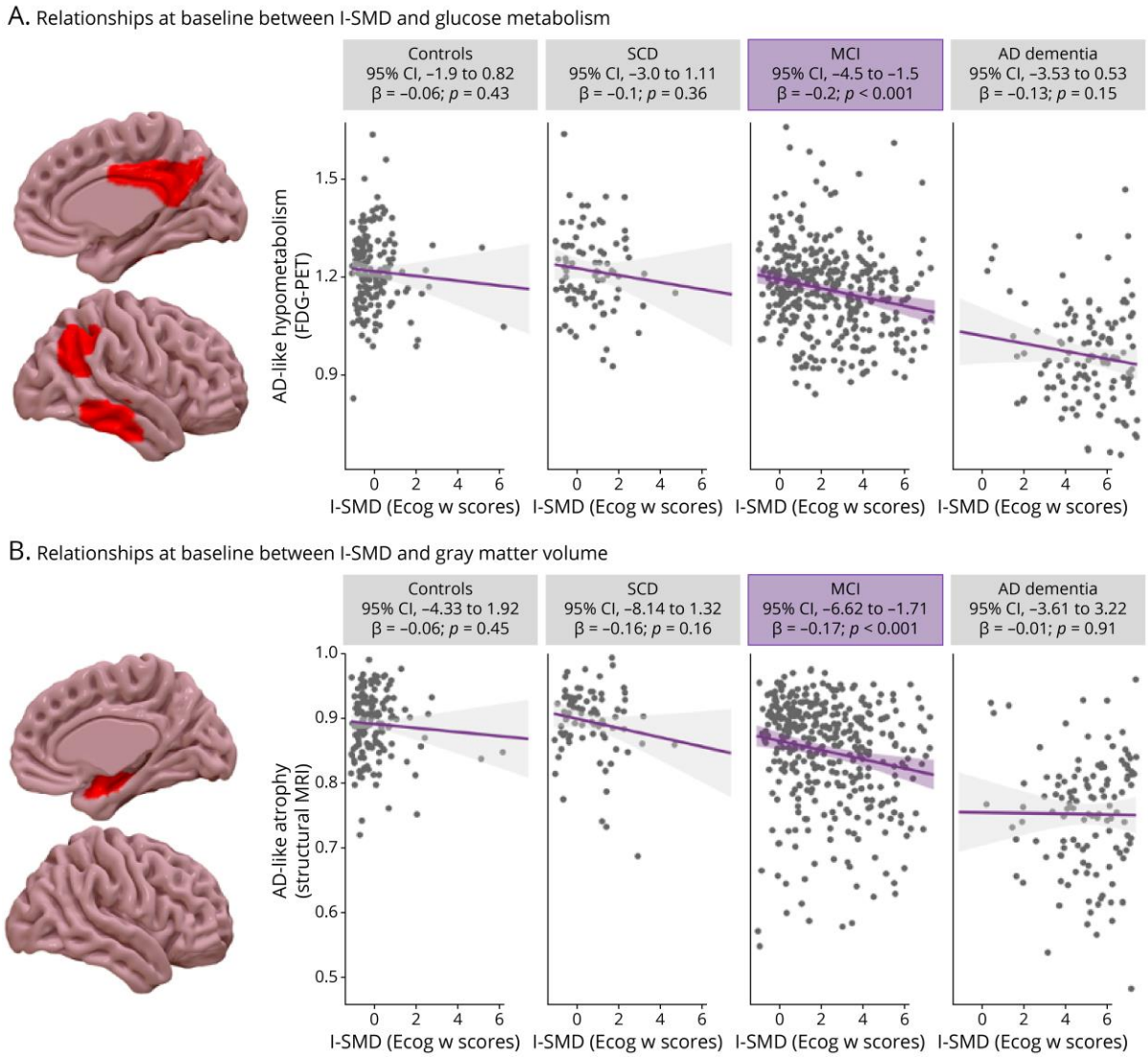


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**Table 1 Demographic and clinical features at baseline by diagnostic group**

| Characteristic | Controls | SCD | MCI | AD dementia | p value for baseline group differences (F or χ-squared) | Post hoc Tukey-test, Pairwise comparisons |
|---|---|---|---|---|---|---|
| No. of participants, No. | | | | | | |
| Baseline | 32 | 25 | 35 | 18 | | |
| Follow-up 18 months | 18 | 20 | 22 | 7 | | |
| Follow-up 36 months | 12 | 12 | 12 | 0 | | |
| Follow-up duration, mean (sd), y | 25.47 (10.02) | 25.56 (9.52) | 25.47 (9.08) | 19.29 (4.50) | .41 (0.97)[b] | |
| Female sex, No. (%) | 16 (50) | 10 (40) | 12 (34) | 5 (28) | .40 (2.92)[a] | |
| Age, mean (sd), y | 70.91 (6.57) | 65.88 (6.64) | 72.49 (7.5) | 68.17 (8.59) | **.005 (4.60)[b]** | SCD < controls (p=.05), MCI (p=.004) |
| Education, mean (sd), y | 12.22 (3.68) | 13.52 (3.25) | 11.46 (3.86) | 11.5 (3.17) | .14 (1.87)[b] | |
| APOEe4 carrier, No. (%) | 7 (22) | 4 (17) | 16 (46) | 12 (67) | **.001 (15.48)**[a] | AD dementia, MCI > controls, SCD (all p<.05 except MCI-controls, p=0.07) |
| Global amyloid load (global Florbetapir SUVr, w-score), mean (sd) | 0.99 (0.16) | 0.99 (0.15) | 1.29 (0.32) | 1.52 (0.39) | **<.001 (17.88)**[c] | Controls, SCD < MCI < AD dementia (all p<.02) |
| Global cognition (MMSE), mean (sd) | 28.69 (1.20) | 28.88 (1.13) | 26.71 (2.08) | 19.78 (4.81) | **<.001 (66.17)**[c] | Controls, SCD < MCI < AD dementia (all p<.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) | **<.001 (47.89)**[c] | Controls, SCD < MCI < AD dementia (all p<.001) |
| Self-SMD (self-report CDS), mean (sd) | 8.86 (3.65) | 12.39 (3.79) | 13.71 (4.46) | 13.44 (4.39) | **<.001 (10.02)**[c] | Controls < SCD, MCI, AD dementia (all p<.001) |
| I-SMD (informant-report CDS), mean (sd) | 6.69 (3.38) | 10.53 (4.41) | 13.47 (4.2) | 18.11 (3.78) | **<.001 (37.93)**[c] | Controls < SCD, MCI < AD dementia (all p<.001) |

[a] Based on raw data: $\chi^2$ between clinical groups (i.e., controls, SCD, MCI, AD dementia).

[b] Based on raw data: ANOVA between clinical groups (i.e., controls, SCD, MCI, AD dementia), *Post-hoc* Tukey pairwise tests.

[c] Based on w-scores: ANOVA between clinical groups (i.e., controls, SCD, MCI, AD dementia) *Post-hoc* Tukey pairwise tests.

Abbreviations: AD dementia, Alzheimer's-type dementia; APOE, apolipoprotein E; CDS, Cognitive Difficulties Scale; ESR, Encoding, Storage and Retrieval task; I-SMD, informant-reported subjective memory decline; MMSE, Mini Mental State Examination; No, sample size; sd, standardized deviation; SMD, subjective memory decline; SUVr, standardized uptake value ratio.

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

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