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## Subtle Cognitive Decline and Biomarker Staging in Preclinical Alzheimer's Disease

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### Abstract

The NIA-AA criteria for “preclinical” Alzheimer's disease (AD) propose a staging method in which AD biomarkers follow an invariable temporal sequence in accordance with the amyloid cascade hypothesis. However, recent findings do not align with the proposed temporal sequence and “subtle cognitive decline,” which has not been definitively operationalized, may occur earlier than suggested in preclinical AD. We aimed to define “subtle cognitive decline” using sensitive and reliable neuropsychological tests, and to examine the number and sequence of biomarker abnormalities in the Alzheimer's Disease Neuroimaging Initiative (ADNI). 570 cognitively normal ADNI participants were classified based on NIA-AA criteria and separately based on the number of abnormal biomarkers/cognitive markers associated with preclinical AD that each individual possessed. Results revealed that neurodegeneration alone was 2.5 times more common than amyloidosis alone at baseline. For those who demonstrated only one abnormal biomarker at baseline and later progressed to mild cognitive impairment/AD, neurodegeneration alone was most common, followed by amyloidosis alone or subtle cognitive decline alone, which were

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<sup>1</sup>Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (<http://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 article. A complete listing of ADNI investigators can be found at [http://adni.loni.usc.edu/wp-content/uploads/howtoapply/ADNI\\_Acknowledgement\\_List.pdf](http://adni.loni.usc.edu/wp-content/uploads/howtoapply/ADNI_Acknowledgement_List.pdf).

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equally common. Findings suggest that most individuals do not follow the temporal order proposed by NIA-AA criteria. We provide an operational definition of subtle cognitive decline that captures both cognitive and functional decline. Additionally, we offer a new approach for staging preclinical AD based on number of abnormal biomarkers, without regard to their temporal order of occurrence. This method of characterizing preclinical AD is more parsimonious than the NIA-AA staging system and does not presume that all patients follow a singular invariant expression of the disease.

### Keywords

Alzheimer's disease; Alzheimer's Disease Neuroimaging Initiative; amyloid; biomarkers; cerebrospinal fluid; dementia; neurodegeneration; neuropsychology; preclinical Alzheimer's disease; subtle cognitive decline

## INTRODUCTION

The pathogenesis of Alzheimer's disease (AD) is believed to begin many years prior to clinical diagnosis, and there is a great need to better detect and characterize the earliest phases of the disease process. The National Institute on Aging and the Alzheimer's Association (NIA-AA) published research criteria for "preclinical" AD [1], an asymptomatic phase in which individuals are classified as cognitively normal but have biomarkers associated with AD (i.e., evidence of amyloid- $\beta$  or tau protein alterations) and possible evidence of "subtle cognitive decline," which has yet to be definitively operationalized. The criteria propose a staging method based on the notion that biomarkers of AD follow an invariable temporal sequence in accordance with the amyloid cascade hypothesis [2, 3]. In Stage 1, individuals show biomarker evidence of cerebral amyloid accumulation. Stage 2 is characterized by amyloid positivity plus evidence of neuronal injury or neurodegeneration. Stage 3 involves these two criteria plus evidence of subtle cognitive decline. However, this temporal sequence has been called into question [4, 5], as studies have shown that biomarkers of neurodegeneration can occur before amyloidosis and many individuals who progress to AD demonstrate a pattern of biomarker abnormalities that fail to conform to the amyloid cascade hypothesis [6–13]. In addition, several studies have shown that cognitive decline, reflected by sensitive episodic memory measures, is at least as sensitive as, and sometimes superior to, cerebrospinal fluid (CSF) and imaging biomarkers in predicting the development of AD [14–17]. Our studies in mild cognitive impairment (MCI) have shown significant heterogeneity in cognitive profiles associated with early stages of AD beyond the typical "amnestic" profile [18–22]. Thus, it is plausible that there are different neurobiological pathways to AD [23].

Previous studies have demonstrated the imprecision of the conventional MCI diagnosis, including its instability over time (e.g., high rates of reversion to cognitive normalcy) [24–26] and a high rate of false positive diagnostic errors [20–22]. Such imprecision in diagnosis will likely become even more pronounced as studies attempt to identify "subtle cognitive decline," which according to the NIA-AA criteria [1] "may include slightly abnormal performance on sensitive cognitive measures, self-complaint of memory decline, or subtle

neurobehavioral changes.” We aimed to operationalize subtle cognitive decline within the same conceptual framework we have previously used to define MCI and to examine associated CSF biomarker abnormalities within the Alzheimer’s Disease Neuroimaging Initiative (ADNI) cohort.

## METHODS

Data were obtained from the ADNI database (<http://adni.loni.usc.edu>). ADNI was launched in 2003 by the National Institute on Aging, National Institute of Biomedical Imaging and Bioengineering, Food and Drug Administration, private pharmaceutical companies, and non-profit organizations. The primary goal of ADNI is to test whether neuroimaging, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. ADNI is the result of efforts of many co-investigators from a range of academic institutions and private corporations. This study was approved by an ethical standards committee on human experimentation at each institution. Written informed consent was obtained from all participants or authorized representatives participating in the study. For more information, including criteria for eligibility, see <http://www.adni-info.org>.

### Participants

Participants were 570 cognitively normal ADNI participants drawn from the pool of 1,381 non-demented participants who completed a baseline neuropsychological evaluation. We included non-demented participants who were determined to be “cognitively normal” based on an actuarial neuropsychological method put forward by Jak and Bondi [22, 27] as applied to participants’ baseline neuropsychological data. Six neuropsychological scores were examined; two measures of language: Animal Fluency (total score) and 30-item Boston Naming Test (total score); two scores from a measure of attention/executive function: Trail Making Test, Parts A & B (time to completion); and two scores from a measure of memory: Rey Auditory Verbal Learning Test (AVLT) 30-minute delayed free recall and AVLT recognition. Non-demented participants were diagnosed with MCI and therefore excluded from the study sample if any of the following three criteria were met: (1) they had an impaired score, defined as >1 standard deviation (SD) below the age-corrected normative mean, on two measures within at least one cognitive domain (i.e., memory, language, or attention/executive function), (2) they had an impaired score, defined as >1 SD below the age-corrected normative mean, in each of the three cognitive domains sampled, or (3) they had a score on the Functional Assessment Questionnaire (FAQ)  $\geq 9$  indicating dependence in three or more daily activities [22, 27]. This actuarial definition of MCI does not rely on clinical judgment or include subjective cognitive complaints as a criterion for MCI. Four-hundred-one of the 1,381 individuals (29.0%) met the above MCI criteria and were removed from further study. Of the 980 participants who were considered cognitively normal, 570 (58.2%) had undergone lumbar puncture and had at least one year of follow-up data available (range 12–96 months), and were thus included in our sample; the remaining 410 were excluded. The included 570 participants were younger ( $t(978) = 3.1, p = 0.002, \eta_p^2 = 0.01$ ) and performed better on the Trail Making Test, Part A ( $t(761.4) = 3.2, p = 0.001, \eta_p^2 =$

0.01) relative to the 410 excluded participants; there were no other differences in demographics or performance on neuropsychological testing.

## Materials

The same six neuropsychological scores (described above) used to diagnose MCI were also used to classify whether participants demonstrated evidence of “subtle cognitive decline.” CSF measures included concentrations of amyloid- $\beta$  ( $A\beta_{1-42}$ ), tau, and hyperphosphorylated tau (p-tau<sub>181p</sub>). Apolipoprotein E (APOE) genotype was available for all participants.

## Procedure

Each neuropsychological score was converted to a standard score using published normative data. Age-adjusted norms from the Mayo Older Americans Normative Study [28] were applied to Rey AVLT scores. Age-adjusted norms from the National Alzheimer’s Coordinating Center [29, 30] were applied to the remaining neuropsychological measures. To operationalize the NIA-AA criterion of subtle cognitive decline, cognitively normal participants were considered to have *subtle cognitive or functional decline* if (1) they had impaired scores, defined as  $>1$  SD below the age-corrected normative mean, on two of the six neuropsychological measures in different cognitive domains, or (2) they had an FAQ score of 6–8 (indicating some dependence in daily activities). These criteria were selected because they are based on the same conceptual framework we have used to define MCI, capturing both the breadth and depth of cognitive impairments (see Fig. 1). The criteria are designed to balance sensitivity (impairment defined as below  $-1$  SD as opposed to  $-1.5$  or  $-2$  SDs) and reliability (two impaired scores required as opposed to a single impaired score) [27, 22]. Specifically, we required two tests to fall below 1 SD, rather than just one test, given the high base rates of an isolated low score in neurologically normal older adults [31, 32]. For example, Brooks and colleagues [31] found that 55.5% of healthy older adults had at least one memory score 1 SD below the mean, and Palmer and colleagues [32] found 73% of healthy older adults showed at least one borderline score while 37% demonstrated at least one impaired score. Further, we required that the two low scores be within different cognitive domains for a classification of subtle cognitive decline, rather than in the same domain, as an individual with two impaired scores in the same domain would meet our criteria for MCI (see Fig. 1). This distinction is based on research showing that  $>20\%$  of healthy older adults obtain one impaired score in two different cognitive domains, but far fewer ( $<5\%$ ) earn two or more impaired scores within the same cognitive domain [32]. The criteria for subtle cognitive decline that we propose are likely to provide a relatively conservative estimate of subtle cognitive decline, as some individuals may have experienced a decline in their cognitive abilities but are nonetheless still performing in the normal range on neuropsychological testing. However, by requiring performance to be in the “impaired” range, the criteria can be more reliably and consistently applied.

Per cut-offs specified in Shaw et al. [33], the presence of cerebral amyloid accumulation (Stage 1 of preclinical AD based on the NIA-AA criteria [1]) was determined by an abnormally low  $A\beta_{1-42}$  level, while neurodegeneration (Stage 2) was determined by

abnormally high levels of tau or p-tau<sub>181p</sub>. Specific cut-off values were as follows: 192 pg/ml for A $\beta$ <sub>1-42</sub>, 93 pg/ml for tau, and 23 pg/ml for p-tau<sub>181p</sub>.

After characterizing the 570 participants with regard to subtle cognitive decline, amyloidosis, and neurodegeneration, we then applied two classification procedures. The first was based on the NIA-AA criteria [1], and the second involved simply a tally of the number of abnormal biomarkers (i.e., amyloidosis, neurodegeneration) or cognitive markers (i.e., subtle cognitive decline) associated with preclinical AD that each individual possessed without regard for the temporal order of occurrence.

### Statistical analyses

Differences between groups were examined separately for each classification method using a series of ANOVAs with *post-hoc t*-tests, and chi-squares. Bonferroni correction was used to adjust for multiple comparisons. Hazard curves were used to explore rates of progression to MCI/AD.

## RESULTS

At baseline, 48.9% of the sample ( $n = 279$ ) was positive for amyloidosis, 63.3% ( $n = 361$ ) for neurodegeneration, and 13.3% ( $n = 76$ ) for subtle cognitive decline. There was no difference in age, education, or gender between individuals who demonstrated subtle cognitive decline and those who did not (all  $p$ -values  $>0.05$ ). Of the 76 participants who demonstrated subtle cognitive decline, 65 had impaired scores on two of the six neuropsychological measures in different cognitive domains (criterion 1 of our operational definition), and 11 had an FAQ score between 6–8 but no impairment on neuropsychological testing (indicating functional decline; criterion 2 of our operational definition). Comparison of those who met criteria for subtle cognitive decline based on cognitive performance versus functional performance showed no significant differences in age, education, gender, amyloid positivity, neurodegeneration, APOE status, or rates of progression to AD or MCI (all  $p$ -values  $>0.05$ ).

Forty-four of the 570 participants (7.7%) progressed to dementia at a subsequent follow-up visit (mean time of diagnosis = 31.4 months, SD = 23.1). Of these, 43 met the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS/ ADRDA) criteria for AD. The remaining participant was diagnosed with progressive supranuclear palsy and was therefore excluded from the progression analyses. One-hundred-thirty four additional participants (23.5%) progressed to diagnosis of MCI (mean time of diagnosis = 18.5 months, SD = 21.3) based on the actuarial neuropsychological criteria.

### Preclinical AD stages based on the NIA-AA criteria [1]

As shown in Table 1, 24.9% ( $n = 142$ ) of the sample did not meet criteria for preclinical AD (Stage 0), 8.4% ( $n = 48$ ) showed evidence of amyloidosis based on low CSF A $\beta$ <sub>1-42</sub> (Stage 1), 30.4% ( $n = 173$ ) showed amyloidosis and neurodegeneration based on high CSF tau or p-tau<sub>181p</sub> (Stage 2), and 8.8% ( $n = 50$ ) showed abnormalities on all three markers (i.e., amyloidosis, neurodegeneration, and subtle cognitive decline; Stage 3). An additional 24.2%

( $n = 138$ ) of the sample showed normal amyloid levels but abnormal levels on biomarkers of neurodegeneration (with or without subtle cognitive decline). This group has been referred to by Jack and others [9, 34, 35] as “suspected non-AD pathophysiology” (SNAP). The remaining 3.3% ( $n = 19$ ) were considered “Unclassified” [8] as they showed subtle cognitive decline but no evidence of neurodegeneration (with or without amyloidosis).

A Genotype (APOE- $\epsilon 4$  versus non- $\epsilon 4$ )  $\times$  Group chi-square analysis showed significant differences in the presence of the APOE- $\epsilon 4$  allele. Frequency of APOE- $\epsilon 4$  carriers was similar for the Stage 0 and SNAP groups (13–19%), similar for the Stage 1 and Unclassified groups (37–38%), and significantly higher for the Stage 2 and 3 groups (55–72%); see Table 1. Total score on the FAQ did not differ between the Stage 3 and Unclassified groups, but both had significantly higher total scores than all other groups, which did not differ from one another; see Table 1. Longitudinal data showed that the Stage 0 group had a longer period of follow-up on average (39 months) than the Stage 2 and SNAP groups (29–30 months), but there were no other significant differences in length of follow-up. Outcome (progression versus no progression)  $\times$  Group chi-square analyses revealed significant differences in prevalence of progression to MCI/AD ( $\chi^2(5) = 92.6, p < 0.001, \phi_c = 0.40$ ) and to AD ( $\chi^2(5) = 61.9, p < 0.001, \phi_c = 0.33$ ). Progression rates to MCI/AD were similar for the Stage 0, Stage 1, and SNAP groups (17–22%); moderately higher for the Stage 2 (37%;  $p < 0.01, \phi_c = 0.17$  to 0.21) and Unclassified groups (44%;  $p < 0.05, \phi_c = 0.17$  to 0.29); and higher still for the Stage 3 group (84%;  $p < 0.001, \phi_c = 0.39$  to 0.67); see Figs. 2a and 3a. For only those who progressed to a diagnosis of AD ( $n = 43$ ), progression rates were similar for the Stage 0, Stage 1, SNAP, and Unclassified groups (2–6%); somewhat higher for the Stage 2 group (9%;  $p < 0.05$  for Stage 2 versus Stage 0 and SNAP,  $\phi_c = 0.13$  to 0.15); and higher still for the Stage 3 group (34%;  $p < 0.001$  for all comparisons except  $p < 0.05$  for Stage 3 versus Unclassified,  $\phi_c = 0.28$  to 0.46); see Fig. 2a.

### Preclinical AD stages based on number of abnormal biomarkers

As shown in Table 2, 24.9% ( $n = 142$ ) of the sample had no abnormal biomarkers or cognitive markers, while 8.8% ( $n = 50$ ) showed abnormalities on all three markers at baseline; these groups are identical to Stages 0 and 3 using the NIA-AA criteria [1] described above. One-hundred-ninety participants (33.3%) had only one abnormal marker: 48 with amyloidosis, 131 with neurodegeneration, and 11 with subtle cognitive decline. Finally, 33.0% ( $n = 188$ ) had two abnormal markers: 173 with amyloidosis and neurodegeneration, 8 with amyloidosis and subtle cognitive decline, and 7 with neurodegeneration and subtle cognitive decline.

A Genotype (APOE- $\epsilon 4$  versus non- $\epsilon 4$ )  $\times$  Group chi-square analysis showed significant differences in the presence of the APOE- $\epsilon 4$  allele. The prevalence of APOE- $\epsilon 4$  carriers increased significantly with greater number of abnormal markers; see Table 2. Total score on the FAQ for the group with three abnormal markers was significantly higher than for all other groups, which did not differ from one another; see Table 2. Longitudinal data showed that the group demonstrating no abnormal markers had the longest period of follow-up on average (39 months), but there were no significant differences in length of follow-up for the other groups (29–30 months). Of the 177 participants who progressed to MCI/AD, 14.1% ( $n$



= 25) had no abnormal markers at baseline, 20.9% ( $n = 37$ ) had one abnormal marker (8 with amyloidosis, 24 with neurodegeneration, 5 with subtle cognitive decline), 41.2% ( $n = 73$ ) had two abnormal markers (64 with amyloidosis and neurodegeneration, 3 with amyloidosis and subtle cognitive decline, and 6 with neurodegeneration and subtle cognitive decline), and 23.7% ( $n = 42$ ) had three abnormal markers. Outcome (progression versus no progression)  $\times$  Group chi-square analyses revealed significant differences in prevalence of progression to MCI/AD ( $\chi^2(3) = 94.8, p < 0.001, \phi_c = 0.41$ ) and to AD ( $\chi^2(3) = 59.3, p < 0.001, \phi_c = 0.32$ ). Possessing one abnormal marker did not significantly increase risk for progression to MCI/AD relative to having zero (20% versus 18%, respectively), but having two abnormal markers increased risk (39%;  $p < 0.001, \phi_c = 0.22$  to 0.24), and having three increased risk even further (84%;  $p < 0.001, \phi_c = 0.36$  to 0.61); see Figs. 2b and 3b. When examining only those who progressed to a diagnosis of AD ( $n = 43$ ), a similar pattern was seen, as having one abnormal marker did not significantly increase risk for progression to AD relative to having zero (3% for both), but having two abnormal markers was associated with a moderately increased risk (9%;  $p < 0.05, \phi_c = 0.12$  to 0.13), and having three abnormal markers increased risk even further (34%;  $p < 0.001, \phi_c = 0.29$  to 0.44); see Fig. 2b.

## DISCUSSION

Using a novel operational definition of “subtle cognitive decline” that examined the performance of individual neuropsychological test scores and captured both cognitive and functional decline, we classified cognitively normal participants based on the NIA-AA criteria [1] and separately based on the number of abnormal biomarkers or cognitive markers that each individual possessed. Using the NIA-AA criteria [1], we found that Stage 2 (amyloidosis plus neurodegeneration) and SNAP (neurodegeneration with normal amyloid levels) were the most common stages in individuals who showed evidence of preclinical AD. When we used the number of biomarkers or cognitive markers without regard for their temporal order, we found that neurodegeneration alone was 2.5 times more common than amyloidosis alone at baseline. For those who demonstrated only one abnormal marker at baseline and later progressed to MCI/AD ( $n = 37$ ), it was most common to have neurodegeneration alone ( $n = 24$ ), and nearly equally common to have amyloidosis alone or subtle cognitive decline alone ( $n = 8$  versus 5) as the first sign of prodromal AD. These findings suggest that most individuals did not follow the temporal order proposed by the amyloid cascade hypothesis, which is that amyloid biomarkers become abnormal first, followed by biomarkers of neurodegeneration, and then clinical symptoms [2, 3]. Our results are consistent with research showing that biomarkers of neurodegeneration can occur before amyloidosis [10], as well as findings that individuals with subtle cognitive decline but normal neurodegeneration biomarkers (i.e., the Unclassified group) have a relatively high rate of progression to AD [36]. By presuming that all patients follow a singular invariant expression of the disease, we may be failing to identify individuals with differing initial presentations who nevertheless will progress to AD. It should be noted that the NIA-AA diagnostic criteria for AD [37] and MCI [38] are agnostic with respect to the temporal order of biomarker changes. Evidence of amyloidosis or neural injury increases diagnostic confidence to an “intermediate” likelihood, and having both increases it to a “high”



likelihood that the diagnosis of dementia or MCI is due to AD. Our method of staging preclinical AD based on the number of abnormal markers, irrespective of their order of appearance, similarly demonstrated increasing likelihood of progression.

A comparison of our findings to other studies [34–36] aimed at examining the NIA-AA criteria [1] for preclinical AD are shown in Fig. 4. Our study found relatively high rates of amyloid positivity (48.9%) and neurodegeneration (63.3%), which is reflected in the higher percentage of participants in Stage 2 and Stage 3 compared to previous studies. This discrepancy is purely the result of the way in which we defined “cognitively normal” versus “MCI.” Rather than using the diagnoses assigned by ADNI, which has been shown to produce a high rate of false positive diagnostic errors (i.e., roughly one-third of those diagnosed with MCI by ADNI actually perform normally on more extensive cognitive testing and have normal CSF biomarker levels) [21, 22], we used actuarial neuropsychological criteria [22, 27] to determine cognitively normal versus MCI classifications. Of the 570 deemed cognitively normal by the actuarial criteria and included in the current study, only 250 were also classified as normal by ADNI while the remaining 320 were diagnosed with MCI by ADNI (based on subjective memory complaints, a Clinical Dementia Rating Scale score of 0.5, and low performance on a single memory test) [39]. If our analyses are conducted only on the 250 individuals classified as cognitively normal by ADNI, the percentage of participants in each preclinical AD classification stage based on NIA-AA criteria [1] is comparable to previous studies. In particular, our results are quite similar to the Toledo et al. [36] study, which also used an ADNI sample (Stage 0 : 29% versus 32%; Stage 1 : 13% versus 15%; Stage 2 : 25% versus 22%; Stage 3 : 2% versus 3%; SNAP: 30% versus 23%; Unclassified: 2% versus 5% in the current study versus the Toledo et al. [36] study, respectively). However, the main findings of our study remain the same in this smaller sample of 250. Specifically, of the 2% ( $n = 5$ ) who progressed to dementia at follow-up, three of these five individuals had one abnormal biomarker at baseline: one with amyloidosis and two with neurodegeneration. In addition, two of the five individuals were in the SNAP category at baseline based on NIA-AA criteria [1]. Thus, the majority did not show amyloid biomarker abnormalities as the first sign of AD.

Although our findings do not abide by the amyloid cascade model [2, 3], they do concur with the theoretical notions of Braak and colleagues [4], who have proposed an alternative model to the amyloid cascade hypothesis. They propose that detectable AD pathologic markers (CSF A $\beta$  and tau pathology, neuronal loss, cognitive symptoms) all represent late-appearing and relatively simultaneous changes in the AD pathophysiologic cascade, which appear in a very narrow time sequence. The perceived differences in the sequence of biomarker abnormalities may be more a reflection of the varying sensitivity of the biomarkers or of our ability to detect change than to the timing of these neurobiological changes. The fact that subtle cognitive decline has traditionally been viewed as the last marker to be affected in preclinical AD may be due to the routine use of crude, insensitive measures of cognitive abilities (i.e., rating scales or screening measures) or variations in the way subtle cognitive decline is defined. By contrast, sensitive memory measures (e.g., Rey Auditory Verbal Learning Test) have been shown to be the earliest markers to become abnormal in the progression to AD relative to screening measures, rating scales, and

biomarkers [14], and are more robust predictors of conversion from MCI to AD than most biomarkers [15, 16].

Our novel method of staging preclinical AD is at least as predictive of progression to MCI/AD as the stages proposed by the NIA-AA criteria [1]. This approach that simply tallies the number of abnormal markers provides a more parsimonious method of characterizing preclinical AD, since the staging system described by others [9, 34, 35] results in ambiguous “SNAP” and “Unclassified” categories. In the current study, the SNAP group was similar to Stages 0 or 1 with regard to APOE- $\epsilon$ 4 frequency, FAQ total scores, and progression rates, while the Unclassified group was similar to Stages 1 or 2 with regard to APOE- $\epsilon$ 4 frequency and progression rates and similar to Stage 3 with regard to FAQ total scores. It is not clear if there is anything to be gained by creating these separate SNAP and Unclassified groups, particularly given that SNAP (i.e., suspected non-AD pathophysiology) itself has been shown to be a misnomer by research demonstrating that both amyloid-first and neurodegeneration-first biomarker profile pathways to preclinical AD exist [10].

One might argue that biological markers offer a more specific marker of AD pathophysiology than cognitive decline, which could be due to a number of other non-AD pathologies, and that elevating the notion of subtle cognitive decline to be on par with the highly specific amyloid pathology may ultimately decrease specificity of the AD diagnosis. In the current study, nearly all (43/44) of the participants who progressed to dementia met NINCDS/ADRDA criteria for a diagnosis of AD. Nonetheless, an individual who demonstrates the biomarkers and cognitive markers examined in this study may also show non-AD pathology and could go on to develop a mixed dementia syndrome. Indeed, the notion of “pure” AD pathology is increasingly thought to be far more rare than multiple underlying neuropathologies (e.g., AD, cerebrovascular disease, Lewy bodies, hippocampal sclerosis, TDP-43) [40–42] for the vast majority of late-onset AD. Thus, a combination of biomarkers and sensitive neuropsychological tests that detect these various underlying pathologies is an improvement on any individual biomarker and can substantially improve prediction of dementia risk [17].

A strength of the present study was the use of individual test scores and actuarial neuropsychological criteria to operationalize subtle cognitive decline within the same conceptual framework we have previously used to define MCI [27]. This method of defining subtle cognitive decline may improve diagnostic consistency and reliability compared to the use of “self-complaint of memory decline or subtle neurobehavioral changes,” [1] which has been shown to cloud rather than clarify diagnosis [43], or the use of composite scores [9, 34, 35] in which sensitive and insensitive test performances are averaged together, with the result that the composite score’s sensitivity to subtle cognitive decline is likely reduced. A direction for future research will be to examine individual neuropsychological markers of subtle cognitive decline against different methods of constructing composite scores (e.g., principle components analysis, item response theory) [44] to determine which method most reliably predicts progression. In addition, future studies are needed to explore the impact of using different normative reference methods (e.g., education-based norms) to define subtle cognitive decline.

One limitation of our criteria for subtle cognitive decline is that they may be too strict to capture all individuals with very early cognitive changes (i.e., those who have declined cognitively but are still performing in the normal range on neuropsychological testing or those who show only one impaired score). On the other hand, it is possible that false positive errors could result from applying our actuarial criteria for subtle cognitive decline to populations where individuals deviate from the demographic characteristics of ADNI (e.g., low education or premorbid abilities). Despite this potential risk, our previous work has demonstrated that using our actuarial criteria for MCI actually substantially *reduces* false positive diagnostic errors compared to conventional criteria that rely on subjective complaints, rating scales, and a single memory test [20, 22]. Another limitation of the current study is that ADNI participants undergo only a relatively brief battery of neuropsychological tests. A more extensive neuropsychological evaluation would enhance our ability to detect and more fully characterize subtle cognitive decline, provided that we are mindful of the possible increase in base rates of low scores with increasing numbers of tests [45, 46] and the resulting potential for misclassification [31]. By clearly defining “subtle cognitive decline” via sensitive and reliable neuropsychological test scores, and by re-exploring timelines of biomarker and cognitive changes, we hope to improve diagnostic precision of preclinical AD and sharpen our ability to identify early signs associated with different neurobiological pathways to the diagnosis of AD.

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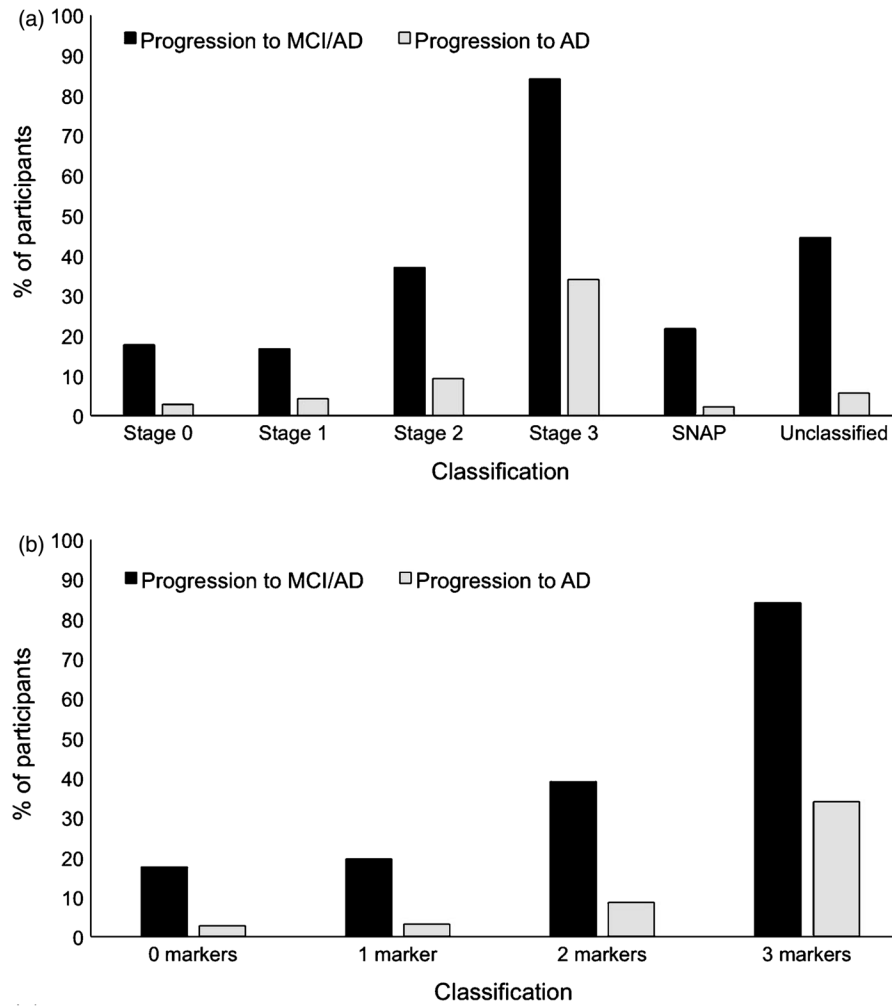
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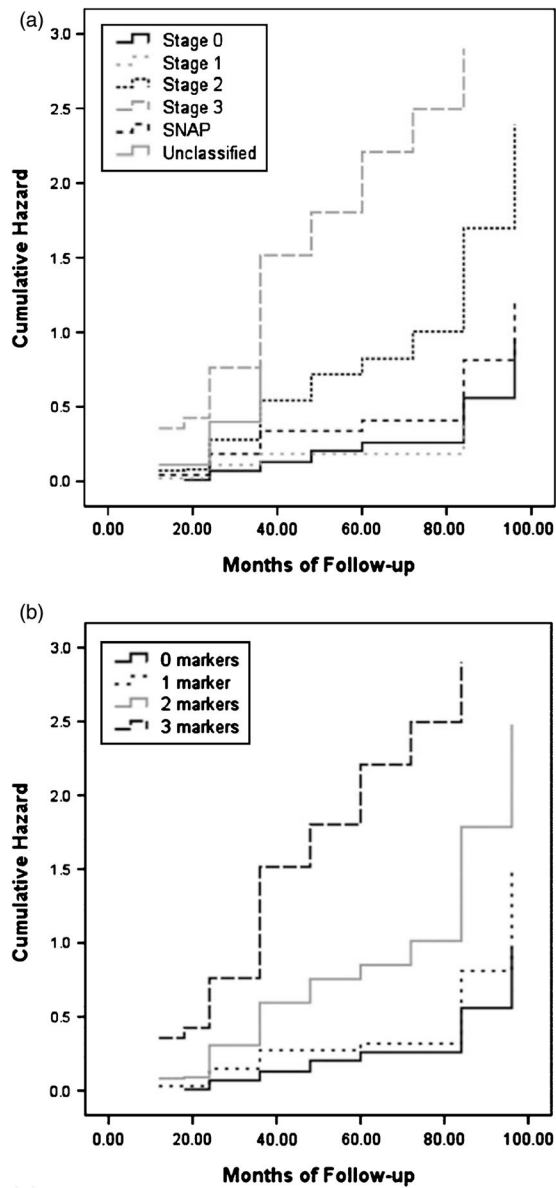
	<b>Mild Cognitive Impairment</b>	<b>Subtle Cognitive Decline</b>
<b>Neuropsychological Testing:</b>	Impaired score (>1 SD below age-corrected normative mean) on two measures in the <b>same</b> cognitive domain; <b>or</b> impaired score in each of the three cognitive domains sampled	Impaired score (>1 SD below age-corrected normative mean) on two measures in <b>different</b> cognitive domains
<b>Functional Abilities:</b>	Functional Assessment Questionnaire score: <b>≥9</b>	Functional Assessment Questionnaire score: <b>6-8</b>

**Fig. 1.** Comparison of the actuarial neuropsychological criteria for mild cognitive impairment and subtle cognitive decline. The criteria are set up along a continuum and capture both the breadth and depth of cognitive impairments.

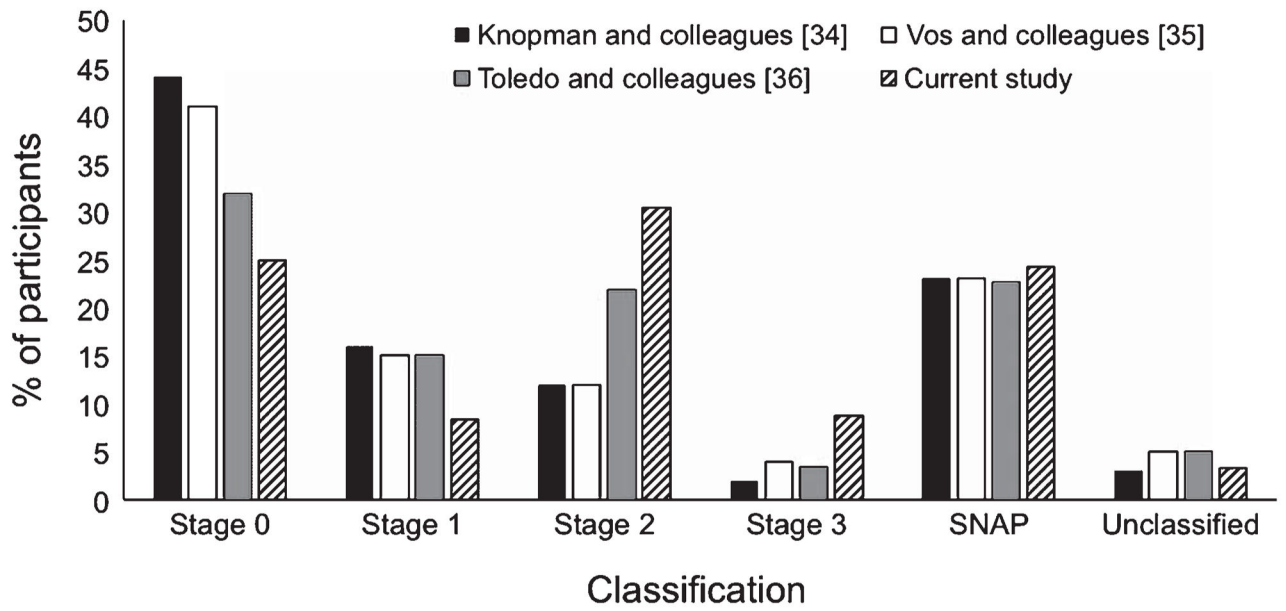




**Fig. 2.** Rate of progression to MCI/AD and to AD for each group based on a) the NIA-AA criteria [1] and b) the number of abnormal biomarkers and cognitive markers for “preclinical” AD.



**Fig. 3.** Hazard functions showing risk of progression to MCI/AD across time for each group based on a) the NIA-AA criteria [1] and b) the number of abnormal biomarkers and cognitive markers for “preclinical” AD.



**Fig. 4.** Percentage of participants in each preclinical AD classification stage based on NIA-AA criteria [1]; comparison of current study to previous studies.

Table 1

Baseline characteristics for each group based on the NIA-AA criteria [1]

	Stage 0 (n = 142)	Stage 1 (n = 48)	Stage 2 (n = 173)	Stage 3 (n = 50)	SNAP (n = 138)	Unclassified (n = 19)	F or $\chi^2$	Sig.	Effect size
<i>Demographics*</i>									
Age (y)	72.3 (6.8)	71.8 (6.7)	74.6 (6.9)	74.3 (6.1)	71.9 (7.7)	71.5 (8.5)	F = 3.6	p = 0.004	$\eta_p^2 = 0.03$
Education (y)	16.2 (2.6)	16.1 (3.0)	16.2 (2.5)	16.3 (2.8)	16.9 (2.5)	16.7 (3.0)	F = 1.6	p = 0.17	$\eta_p^2 = 0.01$
Gender (% female)	48.6%	54.2%	46.8%	44.0%	45.7%	31.6%	$\chi^2 = 3.2$	p = 0.07	$\phi_c = 0.08$
<i>Neuropsychological (raw)*</i>									
Animal Fluency	20.3 (5.0)	20.4 (5.3)	20.2 (4.7)	16.1 (3.9)	20.9 (5.1)	17.2 (5.8)	F = 8.6	p < 0.001	$\eta_p^2 = 0.07$
BNT	28.0 (1.8)	28.2 (1.7)	27.8 (2.3)	26.4 (2.6)	28.1 (2.2)	27.3 (2.4)	F = 5.5	p < 0.001	$\eta_p^2 = 0.05$
TMT, Part A (s)	31.5 (9.4)	31.6 (8.0)	34.3 (10.0)	43.8 (12.3)	31.4 (9.4)	42.2 (12.5)	F = 16.7	p < 0.001	$\eta_p^2 = 0.13$
TMT, Part B (s)	77.5 (28.1)	84.2 (40.9)	91.6 (46.6)	132.3 (61.1)	72.7 (27.0)	96.2 (27.2)	F = 19.6	p < 0.001	$\eta_p^2 = 0.15$
AVLT Recall	7.8 (3.7)	7.7 (3.5)	5.9 (3.6)	3.0 (2.9)	7.4 (4.1)	3.9 (2.3)	F = 18.6	p < 0.001	$\eta_p^2 = 0.14$
AVLT Recognition	13.0 (2.2)	13.4 (1.9)	12.7 (2.2)	11.7 (2.3)	12.8 (1.9)	11.6 (3.5)	F = 4.5	p = 0.001	$\eta_p^2 = 0.04$
<i>Clinical characteristics</i>									
APOE (% $\epsilon 4$ positive) <sup>†</sup>	18 (12.7%)	18 (37.5%)	95 (54.9%)	36 (72.0%)	26 (18.8%)	7 (36.8%)	$\chi^2 = 106.2$	p < 0.001	$\phi_c = 0.43$
FAQ total score*	0.53 (1.10)	0.50 (1.13)	0.84 (1.30)	3.10 (2.87)	0.48 (1.05)	2.1 (2.71)	F = 30.1	p < 0.001	$\eta_p^2 = 0.21$
<i>Preclinical AD criteria<sup>†</sup></i>									
% low A $\beta_{1-42}$	0 (0%)	48 (100%)	173 (100%)	50 (100%)	0 (0%)	8 (42.1%)			
% high tau/p-tau <sub>181p</sub>	0 (0%)	0 (0%)	173 (100%)	50 (100%)	138 (100%)	0 (0%)			
% subtle cognitive decline	0 (0%)	0 (0%)	0 (0%)	50 (100%)	7 (5.1%)	19 (100%)			

BNT, Boston Naming Test; TMT, Trail Making Test; AVLT, Rey Auditory Verbal Learning Test; APOE, apolipoprotein E; FAQ, Functional Assessment Questionnaire; A $\beta_{1-42}$ , amyloid-beta; p-tau<sub>181p</sub>, hyperphosphorylated tau.

\* Data are summarized as mean (standard deviation), unless otherwise indicated.

<sup>†</sup> Data are summarized as raw number of participants (% of participants).

Table 2

Baseline characteristics for each group based on the number of abnormal biomarkers and cognitive markers for preclinical AD

	0 markers (n = 142)	1 marker (n = 190)	2 markers (n = 188)	3 markers (n = 50)	F or $\chi^2$	Sig.	Effect size
<i>Demographics*</i>							
Age (y)	72.3 (6.8)	71.9 (7.4)	74.4 (7.1)	74.3 (6.1)	F = 5.2	p = 0.001	$\eta_p^2 = 0.03$
Education (y)	16.2 (2.6)	16.7 (2.6)	16.2 (2.6)	16.3 (2.8)	F = 1.5	p = 0.21	$\eta_p^2 = 0.01$
Gender (% female)	48.6%	47.9%	45.2%	44.0%	$\chi^2 = 0.6$	p = 0.89	$\phi_c = 0.03$
<i>Neuropsychological (raw)*</i>							
Animal Fluency	20.3 (5.0)	20.7 (5.2)	19.9 (4.9)	16.1 (3.9)	F = 11.8	p < 0.001	$\eta_p^2 = 0.06$
BNT	28.0 (1.8)	28.2 (1.9)	27.6 (2.4)	26.4 (2.6)	F = 9.8	p < 0.001	$\eta_p^2 = 0.05$
TMT, Part A (s)	31.5 (9.4)	31.7 (8.9)	35.0 (10.7)	43.8 (12.3)	F = 23.0	p < 0.001	$\eta_p^2 = 0.11$
TMT, Part B (s)	77.5 (28.1)	76.7 (31.9)	91.4 (45.3)	132.3 (61.2)	F = 30.2	p < 0.001	$\eta_p^2 = 0.14$
AVLT Recall	7.8 (3.7)	7.5 (3.9)	5.8 (3.5)	3.0 (2.9)	F = 28.3	p < 0.001	$\eta_p^2 = 0.13$
AVLT Recognition	13.0 (2.2)	13.0 (2.0)	12.6 (2.3)	11.7 (2.3)	F = 5.3	p = 0.001	$\eta_p^2 = 0.03$
<i>Clinical characteristics</i>							
APOE (% $\epsilon 4$ positive) <sup>†</sup>	18 (12.7%)	48 (25.3%)	98 (52.1%)	36 (72.0%)	$\chi^2 = 92.4$	p < 0.001	$\phi_c = 0.40$
FAQ total score*	0.53 (1.10)	0.53 (1.20)	0.93 (1.45)	3.10 (2.87)	F = 43.70	p < 0.001	$\eta_p^2 = 0.19$
<i>Preclinical AD criteria<sup>†</sup></i>							
% low A $\beta$ <sub>1-42</sub>	0 (0%)	48 (25.3%)	181 (96.3%)	50 (100%)			
% high tau/p-tau <sub>181p</sub>	0 (0%)	131 (68.9%)	180 (95.7%)	50 (100%)			
% subtle cognitive decline	0 (0%)	11 (5.8%)	15 (8.0%)	50 (100%)			

BNT, Boston Naming Test; TMT, Trail Making Test; AVLT, Rey Auditory Verbal Learning Test; APOE, apolipoprotein E; FAQ, Functional Assessment Questionnaire; A $\beta$ <sub>1-42</sub>, amyloid-beta; p-tau<sub>181p</sub>, hyperphosphorylated tau.

\* Data are summarized as mean (standard deviation), unless otherwise indicated.

<sup>†</sup> Data are summarized as raw number of participants (% of participants).