Selective Worsening of Brain Injury Biomarker Abnormalities in Cognitively Normal Elderly Persons With β-Amyloidosis

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IMPORTANCE The appearance of β-amyloidosis and brain injury biomarkers in cognitively normal (CN) persons is thought to define risk for the future development of cognitive impairment due to Alzheimer disease (AD), but their interaction is poorly understood.

OBJECTIVE To test the hypothesis that the joint presence of β-amyloidosis and brain injury biomarkers would lead to more rapid neurodegeneration.

DESIGN Longitudinal cohort study.


PARTICIPANTS One hundred ninety-one CN persons (median age, 77 years; range, 71-93 years) in the Mayo Clinic Study of Aging who underwent magnetic resonance, fludeoxyglucose F 18 (FDG) positron emission tomography (PET), and Pittsburgh Compound B (PiB) PET imaging at least twice 15 months apart. Participants were grouped according to the recommendations of the National Institute on Aging-Alzheimer Association preclinical AD criteria based on the presence of β-amyloidosis, defined as a PiB PET standardized uptake value ratio (SUVr) greater than 1.5, alone (stage 1) or with brain injury (stage 2 + 3), defined as hippocampal atrophy or FDG hypometabolism. We also studied a group of patients with mild cognitive impairment (n = 17) or dementia (n = 9) from the Mayo Clinic Study of Aging or the Mayo Alzheimer Center with similar follow-up times who had undergone comparable imaging and had a PiB PET SUVr greater than 1.5.

MAIN OUTCOMES AND MEASURES Rate of change of cortical volume on volumetric magnetic resonance images and rate of change of glucose metabolism on FDG PET scan results.

RESULTS There were 25 CN participants with both high PiB retention and low hippocampal volume or FDG hypometabolism at baseline (preclinical AD stages 2 + 3). On follow-up scans, the preclinical AD stage 2 + 3 participants had greater loss of medial temporal lobe volume and greater glucose hypometabolism in the medial temporal lobe compared with the other CN groups. The changes were similar to those in the cognitively impaired participants. Extratemporal regions did not show similar changes.

CONCLUSIONS AND RELEVANCE Higher rates of medial temporal neurodegeneration occur in CN individuals who, on their initial scans, had abnormal levels of both β-amyloid and brain injury biomarkers. Although preclinical AD is currently only a research topic, the description of its brain structural changes will be critical for trials designed to prevent or forestall dementia due to AD.

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Studies that use imaging and cerebrospinal fluid biomarkers to explore the pathogenesis of Alzheimer disease (AD) have focused on 2 processes: the accumulation of β-amyloid and the appearance of markers of neuronal death and synaptic dysfunction, ie, brain injury. Accumulation of abnormal β-amyloid begins many years before cognitive dysfunction appears.3-5 β-Amyloid may reach levels seen in dementia while persons are still cognitively normal (CN), implying that elevated levels of β-amyloid are not sufficient to cause overt cognitive symptoms.6 However, biomarkers of brain injury are more closely correlated with clinical symptoms: the greater the burden of brain injury, the more severe the symptoms.3,4 6 The model of AD evolution adopted by the National Institute on Aging–Alzheimer Association workgroups for the diagnosis of AD assumes that excess β-amyloid causes brain injury,7-8 although data were not available at the time that the model was developed to specify when or how that interaction occurred.

Recent observations led us to speculate that brain injury and β-amyloid biomarker changes began independently of one another long before we first observed them.9 We found that CN individuals who had both abnormal β-amyloidosis and brain injury were more likely to develop cognitive impairment.9 Furthermore, brain injury biomarker abnormalities were far more extensive in symptomatic individuals.5-11 Therefore, we hypothesized that excess β-amyloid accumulation induces an acceleration of brain injury in the period of transition from cognitive normality to impairment. However, greater changes in brain injury biomarkers would occur only in individuals with excess β-amyloid who already had evidence of brain injury. We sought to test this hypothesis in CN persons with serial Pittsburgh Compound B (PiB) positron emission tomography (PET), fludeoxyglucose F 18 (FDG) PET, and structural magnetic resonance (MR). Based on the National Institute on Aging–Alzheimer Association preclinical AD (preclinAD) model, we grouped our CN participants according to β-amyloidosis status (normal vs abnormal) and brain injury biomarker status (normal vs abnormal).10,12 Although we did not have enough observations to measure acceleration formally, we were able to determine whether 1 or more preclinAD stage had greater loss of brain volume or greater metabolic declines compared with CN participants without abnormal biomarkers.

Methods

Participants
Participants in the study were CN individuals from the Mayo Clinic Study of Aging who had undergone serial brain imaging with MR and PET beginning March 28, 2006, and continuing to the present at intervals of approximately 15 months.8,10,12 One hundred ninety-one individuals had serial MR and PET scanning: 166 had 2 scans, 24 had 3 scans, and 1 had 4 scans. Data on recruitment,13 prevalence,14 and incidence15 of mild cognitive impairment (MCI) for the parent study have been published.

We also selected 17 individuals from the Mayo Clinic Study of Aging who met diagnostic criteria for MCI16 due to AD by clinical criteria and had abnormal PiB PET scan results (standardized uptake value ratio [SUVr], >1.5) and serial imaging at intervals of approximately 15 months. Of the 17 MCI patients, 13 had 2 scans and 4 had 3 scans.

From patients enrolled in the Mayo Alzheimer Disease Research Center (ADRC or Mayo Clinic Study of Aging), we identified individuals older than 70 years who underwent serial MR and PET scanning who met diagnostic criteria for dementia due to AD by clinical criteria17 and had abnormal PiB PET scan results. The ADRC visits were approximately 12 months apart. Of the 9 AD participants, 5 had 2 scans, 2 had 3 scans, and 2 had 4 scans.

Human Participant Protection
All study protocols were approved by the Mayo Clinic and Olmsted Medical Center institutional review boards, and all CN individuals provided written informed consent to participate in the study and in the imaging protocols. Participants with cognitive impairment and their accompanying family member jointly provided consent.

Assessments
The participants in this study were identified as being CN or having MCI or dementia through a consensus process that used information from 3 sources: mental status examinations performed by study physicians (D.S.K., B.F.B., and R.C.P.), Clinical Dementia Rating completed by trained study coordinators that included interview of an informant as well as the participant, and a psychometric battery previously described for the CN group13-15 and for the Mayo ADRC.18

Imaging Methods
Imaging methods for structural MR, FDG PET, and PiB PET were identical to those described previously.10,12,19 We used these imaging modalities to operationalize the preclinAD groupings: PiB PET imaging for defining abnormal brain β-amyloidosis and structural MR measurement of hippocampal atrophy or FDG PET for glucose hypometabolism for defining abnormal neurodegeneration.

Amyloid PET images were acquired using a PET/computed tomography scanner (Discovery RX; GE Healthcare). Participants are injected with 292 to 729 MBq 11C PiB. The PiB PET scan, consisting of four 5-minute dynamic frames, was acquired 40 minutes after injection.20,21 The FDG PET images were obtained on the same day 1 hour after the PiB PET scan. A computed tomography image was obtained for attenuation correction. Participants were injected with 366 to 399 MBq of FDG, and imaging was performed after 30 to 38 minutes, resulting in an 8-minute image acquisition consisting of four 2-minute dynamic frames.

Quantitative image analysis for PiB PET and FDG PET were performed using our in-house fully automated image processing pipeline.19,22 Statistics on image voxel values were extracted from automatically labeled cortical regions of interest (ROIs) using an atlas23 modified in-house. A cortical PiB PET SUVr was formed by combining the prefrontal, orbitofrontal, parietal, temporal, anterior cingulate, and posterior cingulate/precuneus ROI values normalized by the cerebellar gray matter (GM) ROI of the atlas. The FDG PET scan results were analyzed in a similar manner using angular gyrus, posterior cingulate, and inferior temporal cortical ROIs to define an Alz-
In addition to this AD composite ROI, we examined individual FDG PET ROIs defined by the atlas.

All individuals underwent MR scanning at 3 T with a standardized protocol that included a 3-dimensional magnetization-prepared 180° radiofrequency pulses and rapid gradient-echo (MPRAGE) sequence. The MPRAGE images were corrected for image distortion and bias field as previously described. For preclinical staging purposes, hippocampal volume was measured with FreeSurfer software (version 4.5; https://surfer.nmr.mgh.harvard.edu), and each participant’s raw hippocampal volume was adjusted by his or her total intracranial volume. We examined annual change in FreeSurfer hippocampal volume as well as annual change in regional GM volumes from the in-house atlas described above.

## Definitions of PreclinAD Stages and Suspected Non-AD Pathophysiology Group

As previously described, we chose the cut points for each imaging biomarker that corresponded to 90% sensitivity in individuals with a clinical diagnosis of AD dementia from the Mayo ADRC. For abnormal brain β-amyloidosis, a requirement for all stages of the preclinical criteria, we used the cut point for the PIB PET global cortical ratio of 1.5. For the markers of brain injury required for stages 2 and 3, participants were classified as having brain injury if they had abnormal hippocampal atrophy or abnormal FDG PET hypometabolism. The 90% sensitivity cut point for hippocampal volume adjusted for total intracranial volume was −0.70 cm³, which is interpreted as 0.7 cm³ below the normative average after accounting for head size. For the FDG PET glucose metabolism ratio of the AD signature composite, the cut-point value for hypometabolism was 1.31.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Stage 0 (n = 90)</th>
<th>Stage 1 (n = 32)</th>
<th>Stages 2 + 3 (n = 25)</th>
<th>CN sNAP (n = 44)</th>
<th>MCI-AD (n = 17)</th>
<th>Dementia-AD (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hippocampal volume, cm³</td>
<td>7.6 (7.1 to 7.9)</td>
<td>7.4 (7.1 to 7.8)</td>
<td>6.5 (6.1 to 7.0)</td>
<td>6.5 (5.9 to 7.1)</td>
<td>6.3 (6.1 to 6.9)</td>
<td>5.3 (5.0 to 6.4)</td>
</tr>
<tr>
<td>FDG uptake, SUVr</td>
<td>1.48 (1.39 to 1.55)</td>
<td>1.41 (1.39 to 1.49)</td>
<td>1.26 (1.21 to 1.30)</td>
<td>1.28 (1.24 to 1.32)</td>
<td>1.32 (1.27 to 1.42)</td>
<td>1.21 (0.98 to 1.33)</td>
</tr>
<tr>
<td>Annual rates of change</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hippocampal volume, cm³/y</td>
<td>−0.08 (−0.19 to 0.02)</td>
<td>−0.10 (−0.21 to 0.04)</td>
<td>−0.21 (−0.35 to −0.10)</td>
<td>−0.08 (−0.20 to 0.00)</td>
<td>−0.19 (−0.28 to −0.14)</td>
<td>−0.14 (−0.19 to −0.02)</td>
</tr>
<tr>
<td>Hippocampal volume annual % change</td>
<td>−1.0 (−2.7 to 0.3)</td>
<td>1.3 (−2.8 to 0.6)</td>
<td>−3.5 (−5.6 to −1.8)</td>
<td>−1.2 (−3.2 to 0.0)</td>
<td>−3.6 (−4.9 to −2.0)</td>
<td>−2.3 (−3.5 to −0.4)</td>
</tr>
<tr>
<td>FDG uptake, SUVr/y</td>
<td>−0.015 (−0.055 to 0.017)</td>
<td>−0.023 (−0.047 to 0.000)</td>
<td>−0.010 (−0.024 to 0.005)</td>
<td>−0.008 (−0.031 to 0.015)</td>
<td>−0.032 (−0.060 to −0.007)</td>
<td>−0.058 (−0.075 to −0.049)</td>
</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer disease; APOE, apolipoprotein E gene; CN, cognitively normal; FDG, fludeoxyglucose F 18; IQR, interquartile range; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination (maximum score, 30); sNAP, suspected non-Alzheimer pathophysiology; SUVr, standardized uptake value ratio.

* Patients with AD dementia did not have the identical neuropsychological test battery as the other participants, and therefore their cognitive test scores cannot be reported in the same z-score frame of reference.
The CN individuals were divided into 4 groups on the basis of the biomarker cut points described above: all biomarkers normal (stage 0), abnormal brain β-amyloidosis only (preclinAD stage 1), abnormal brain β-amyloidosis and brain injury without regard to cognitive test scores (preclinAD stage 2 + 3), and normal brain β-amyloidosis with brain injury without regard to cognitive test scores (suspected non-AD pathophysiology [sNAP] group). A small group of participants (n = 5) not classified as stage 0, preclinAD stages 1 to 3, or sNAP were excluded from analyses.12

Statistical Analysis
We fit linear regression models within each participant to estimate the annual change in GM volumes and FDG metabolism using all available time points. Using all available time points in participants with more than 2 scans provides more stable estimates of rates of change. Wilcoxon rank sum tests were used to assess pairwise differences in annual change between the biomarker-defined groups. We report differences in regional volumes in cubic centimeters and in glucose metabolism in SUVr. We did not adjust P values for multiple testing.

Results
The demographic features of the 191 CN participants (median age, 77 years; range, 71-93 years) are reported in the Table by preclinAD stage and sNAP group. Seventeen participants with MCI due to AD and 9 with AD dementia are also listed in the Table. The ages of all groups except CN stage 0 were comparable, and there was a higher proportion of apolipoprotein E ε4 genotype in preclinAD stages 1 and 2 + 3 compared with CN stage 0 and sNAP. The lower baseline hippocampal volumes and glucose metabolic rates in the AD signature regions in the CN preclinAD stages 2 + 3 and sNAP groups were by design based on how those groups were defined. The comparable or lower values in the MCI and dementia groups were expected.5 Compared with CN participants who were part of the study group with imaging at baseline as previously reported,10 the current group (the vast majority of whom were included in the prior study) had a comparable overall rate of decline to MCI (13% vs 10%). Rates of MCI conversion were estimated using only the next follow-up visit, which was conducted approximately 15 months after the baseline visit. In the current group, the rate of conversion to MCI among preclinAD stages 2 + 3 (21%) was higher than that of the biomarker-negative group (stage 0, 7%), but was not significantly different from the preclinAD stage 1 (19%) or the sNAP (16%) group.

We evaluated the annual change in GM volume for the hippocampal formations in each group. As can be seen in Figure 1, the annualized rate of volume loss in the hippocampal formations in preclinAD stages 2 + 3 exceeded that of the stage 0 (P = .001), stage 1 (P = .005), and sNAP (P = .003) groups by approximately 0.1 cm³/y on average. The rate of change in GM volume for the hippocampal formations in preclinAD stages 2 + 3 was comparable and not significantly different from that seen in participants with MCI. The rate of change in the preclinAD stages 2 + 3 was greater than that in the group with dementia presumed due to AD, although this difference was not significant (P = .10). There were no significant differences in annual rate of change between stages 0, preclinAD stage 1, and the sNAP group. Although there were group differences in baseline hippocampal volume by design, even after adjusting for baseline differences in hippocampal volume and age, we still noted a greater rate of volume loss in the preclinAD stages 2 + 3 group compared with the other CN groups (Table).

We also examined GM volume loss in 19 other ROIs and selected 6 regions for display in Figure 2. The medial temporal region showed results similar to those of the hippocampus alone, with the expected greater rate of volume loss in the preclinAD stages 2 + 3 compared with stage 0 (P = .004), stage 1 (P = .02), and sNAP (P = .03). A lateral temporal ROI had a significantly greater rate of volume loss in preclinAD stages 2 + 3 compared with stage 0 (P = .008) and the sNAP group (P = .02) but not preclinAD stage 1 (P = .19). In the insula (P = .007) and primary visual cortex (P = .04), the sNAP group had a lower rate of volume loss than did the preclinAD stages 2 + 3 group. None of the other regions showed significant differences between any CN groups.

Examination of differences in annual rate of change in glucose use in the AD signature ROI (Figure 3) failed to show any significant group differences in the AD signature region in the CN participants, although greater declines in glucose use were seen in this group of ROIs in the MCI and dementia participants. However, in examining individual brain regions (6 selected regions are shown in Figure 4), we found greater decline in glucose metabolism in the medial temporal region in preclinAD stages 2 + 3 compared with stage 0 (P = .02) and sNAP (P = .01), with a nonsignificant difference from stage 1 (P = .10). None of the other 18 regions showed significant differences in the rate of change in FDG metabolism between preclinAD stages 2 + 3 and the other CN groups.
Although all of our biomarker-defined subgroups of CN persons experienced some worsening of brain injury imaging biomarkers, it was only in those who had levels of both β-amyloidosis and brain injury (preclinAD stages 2 + 3) meeting criteria for Alzheimer-like at baseline that greater brain atrophy and glucose hypometabolism occurred. The structural and metabolic changes were limited to the medial temporal lobe. Interactions between β-amyloid and neurodegenerative changes in the medial temporal lobe might represent an im-

**Figure 2. Annualized Rate of Change in Gray Matter (GM) Volume**

- **Cingulate Precuneus**
  - Annual Change in GM Volume, cm³/y
  - Stage 0, Stage 1, Stage 2 + 3, sNAP

- **Insula**
  - Annual Change in GM Volume, cm³/y
  - Stage 0, Stage 1, Stage 2 + 3, sNAP

- **Medial Temporal**
  - Annual Change in GM Volume, cm³/y
  - Stage 0, Stage 1, Stage 2 + 3, sNAP

- **Parietal**
  - Annual Change in GM Volume, cm³/y
  - Stage 0, Stage 1, Stage 2 + 3, sNAP

- **Prefrontal**
  - Annual Change in GM Volume, cm³/y
  - Stage 0, Stage 1, Stage 2 + 3, sNAP

- **Lateral Temporal**
  - Annual Change in GM Volume, cm³/y
  - Stage 0, Stage 1, Stage 2 + 3, sNAP

Annualized rate of change in GM volume in selected cortical regions in the cognitively normal groups. The preclinical Alzheimer disease (preclinAD) stages 2 + 3 group differed significantly from the stage 0 (*P* = .004 medial temporal; *P* = .008 lateral temporal) and suspected non-AD pathophysiology (sNAP) (*P* = .03 medial temporal; *P* = .02 lateral temporal) groups in GM loss in both the medial temporal region of interest (ROI) and the lateral temporal ROI. For the medial temporal ROI, the preclinAD stages 2 + 3 group also differed significantly from the preclinAD stage 1 group (*P* = .02). The individual regions included in the medial temporal ROI included the hippocampus, parahippocampal gyrus, entorhinal cortex, and the amygdala. The individual regions in the lateral temporal ROI included the superior temporal gyrus (mid- and polar portions), middle temporal gyrus (mid- and polar portions), inferior temporal gyrus, Heschl gyrus, and fusiform gyrus. Graph elements are defined in the legend to Figure 1.
portant antecedent event to the transition from cognitive normality to overt cognitive impairment in AD. In contrast, extratemporal regions were not changing at this stage of AD pathophysiology.

Our observations are consistent with the hypothesis that β-amyloidosis accelerates neurodegenerative changes in elderly CN individuals who already have some degree of brain injury. As we suggested recently and others have postulated, neurodegenerative changes (including but not limited to tauopathy) arise independently of β-amyloidosis, but β-amyloidosis may be necessary to transform the neurodegeneration into a self-propagating process. The presence of abnormal levels of β-amyloid alone (preclinAD stage 1) did not result in greater hippocampal atrophy or glucose hypometabolism than in CN participants in stage 0. Perhaps if we had much longer observation periods or if we had studied persons with dominantly inherited AD, the relationship might be seen differently. The presence of brain injury alone, as occurred in the CN sNAP group, was also not associated with a higher rate of brain atrophy or glucose hypometabolism.

The annual percentage changes in hippocampal volume that we observed in the preclinAD stages 2 + 3 group (~3.5%) and the MCI groups (~3.6%) were nearly identical to those reported in MCI participants in the Alzheimer’s Disease Neuroimaging Initiative (ADNI) and in prior work. Our small group of patients with AD dementia showed a lower rate of hippocampal volume loss than expected despite the fact that they all had elevated PiBSUVr, low baseline glucose hypometabolism, and a large decline in glucose metabolism during the follow-up period.

More than 25% of our CN participants had glucose hypometabolism of a magnitude seen in patients with typical AD dementia (a value in line with 2 other large studies). Although we did not observe excess declines in glucose metabolism in the AD signature composite region, our follow-up analyses revealed excess hypometabolic changes in the medial temporal lobe in the preclinAD 2 + 3 group compared with the sNAP and stage 0 groups. Just like the structural imaging findings, changes in FDG PET were regionally circumscribed.

Our findings, using imaging to define risk status in CN participants, replicated and expanded an analysis in which cerebrospinal fluid (CSF) β-amyloid 1-42 and tau were used for defining risk groups. Among 107 CN participants in the ADNI, entorhinal cortex atrophy occurred when there was low CSF β-amyloid 1-42 together with elevations of phosphorylated tau protein. The same result could be inferred from a prior ADNI analysis. One other study of note stratified participants only by amyloid status and did not provide data on brain injury biomarker status. An analysis of 74 elderly individuals (mean age, 76.6 years) from the Australian Imaging Biomarkers and Lifestyle study found that atrophy rates in cortical regions, including the temporal lobe and posterior cingulate-precuneus, were higher in those who had a PiB SUVr greater than 1.4.

Reductions in hippocampal volume occur in CN persons destined to develop MCI or in those with MCI that progresses to dementia. In persons with dominantly inherited AD, atrophy in the hippocampus occurs years before clinical symptoms appear and precedes changes in the isocortex. Other biomarkers, such as CSF tau protein levels, might change even earlier than hippocampal volume, but we lacked CSF analyses in our cohort. Our findings extend prior observations by showing that the rate of medial temporal atrophy in CN individuals was greater in one biomarker-defined subgroup: those with both β-amyloidosis and brain injury.

We are not aware of any prior longitudinal studies of FDG PET in CN individuals in whom amyloid biomarkers were used for stratification. However, the findings from other cohorts support the claim that larger changes in FDG PET in extratemporal regions occur only after persons become symptomatic. In the ADNI cohort, the rate of change of hypometabolism in the AD signature region was highest in dementia due to AD and least in CN participants. To be sure, there were declines in the CN group in ADNI, but their rate was less than one-fifth of that seen in AD dementia. Another study noted that worsening FDG hypometabolism can be detected in persons with MCI who progressed to dementia in contrast to those with stable MCI, but without knowledge of amyloid status, we cannot directly compare our findings.

The mechanism by which β-amyloidosis induces neurodegeneration is a matter of intense debate, and speculation is beyond the scope of this report. Many possibilities are on the table, but defective clearance seems most plausible. The joint presence of high levels of β-amyloid and tau in the entorhinal cortex or adjacent inferior temporal isocortex might overwhelm the ubiquitin-proteosomal and lysosomal-autophagy systems. Such a failure would allow damaged proteins to remain in the neuronal cytoplasm, thus enabling aggregation of tau into insoluble polymers.
In the sNAP group, 2 regions (insula and primary visual cortex) showed less longitudinal decline in volume compared with preclinAD stages 1 and 2 + 3. We are uncertain of the implications of resistance to brain atrophy in these regions in non-AD pathophysiologies, but the slower changes are in contrast to the lack of difference compared with preclinAD in baseline GM volumes in these regions that we observed previously in the sNAP group.9

Limitations of our study should be noted. The number of individuals in preclinAD stages 2 + 3 was small, and the median follow-up was only 1.3 years. There should be caution in drawing comparisons between different types of biomarkers for hippocampal atrophy and isocortical hypometabolism. The 2 biomarkers were related cross-sectionally (Spearman $r = 0.44$), but the correlation between rate of change of the 2 biomarkers was low (Spearman $r = 0.10$). We have previously detailed a num-

Annualized rate of change in glucose metabolic rate from fludeoxyglucose F 18 positron emission tomography (FDG PET) in selected cortical regions in the cognitively normal groups. The preclinical Alzheimer disease (AD) stages 2 + 3 group differed significantly from stage 0 ($P = .02$) and suspected non-AD pathophysiology (sNAP) ($P = .01$) groups in glucose hypometabolism in the medial temporal regions of interest (hippocampus, parahippocampal gyrus, entorhinal cortex, and the amygdala) and showed a trend toward a difference from preclinical AD stage 1. Graphelements are defined in the legend to Figure 1. SUVr indicates standardized uptake value ratio.
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number of concerns with operationalizing the National Institute on Aging–Alzheimer Association model of preclinical AD\textsuperscript{10,12} but to date, those concerns are mainly quantitative (i.e., selecting bio-
marketers and defining cut points) rather than conceptual. None-
theless, our observations are consistent with predictions from
our sequential model of AD pathophysiology.\textsuperscript{7}

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