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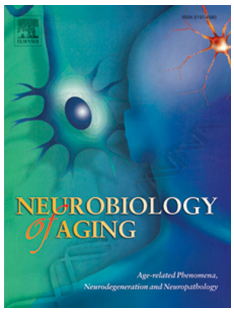

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NIA-AA Staging of Preclinical Alzheimer Disease: Discordance and Concordance of CSF and Imaging Biomarkers

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Abstract

The National Institute of Aging and Alzheimer's Association (NIA-AA) criteria for Alzheimer disease (AD) treat neuroimaging and cerebrospinal fluid (CSF) markers of AD pathology as if they would be interchangeable. We tested this assumption in 212 cognitively normal participants who have both neuroimaging and CSF measures of β-amyloid (CSF $A\beta_{1-42}$ and PET imaging with Pittsburgh Compound B) and neuronal injury (CSF t-tau and p-tau and structural MRI) with longitudinal clinical follow-up. Participants were classified in preclinical AD Stage 1 (β-amyloidosis) or preclinical AD Stage 2+ (β-amyloidosis and neuronal injury) using the NIA-AA criteria, or in the normal or suspected non-Alzheimer pathophysiology group (SNAP; neuronal injury without β-amyloidosis). At baseline, 21% of participants had preclinical AD based on CSF and 28% based upon neuroimaging. Between modalities, staging was concordant in only 47% of participants. Disagreement resulted from low concordance between biomarkers of neuronal injury. Still, individuals in Stage 2+ using either criterion had an increased risk for clinical decline. This highlights the heterogeneity of the definition of neuronal injury, and has important implications for clinical trials utilizing biomarkers for enrollment or as surrogate endpoint measures.

Key words

Alzheimer's disease, amyloid, neuronal injury, cerebrospinal fluid, neuroimaging, comorbidities, aging, diagnosis, prognosis, biomarkers, PET, MRI

1. Introduction

Cerebrospinal fluid (CSF), magnetic resonance imaging (MRI), and positron emission tomography (PET) biomarkers can identify preclinical Alzheimer disease (AD), where brain pathology begins to accumulate but cognition is still unimpaired. This preclinical period can begin decades before the onset of clinical symptoms (Bateman et al., 2012; Jack et al., 2013; Sutphen et al., 2015) and provides a promising window for clinical trials (Aisen et al., 2013). Recently proposed AD criteria allow imaging and CSF measures to be used interchangeably to identify underlying AD pathological processes.

In 2011, the National Institute of Aging and Alzheimer's Association (NIA-AA) working group proposed research criteria for preclinical AD where Stage 1 is characterized by the presence of β-amyloidosis alone, and Stages 2 and 3 by the presence of both β-amyloidosis and neuronal injury (Sperling et al., 2011). AD pathology can be assessed by either CSF or imaging biomarkers. Since the initial introduction of the criteria additional suggestions have been proposed to incorporate individuals with no abnormal biomarkers (normal individuals or Stage 0), and those with evidence of neuronal injury in the absence of β-amyloidosis, so-called suspected non-Alzheimer pathophysiology (SNAP) (Jack et al., 2012). Although there is a clear utility in using a simplified staging system, CSF and imaging measures may reflect different components of AD pathophysiology or may become abnormal at different stages of the disease.

Prior work has shown good agreement between different biomarkers of β-amyloid (Fagan et al., 2006; Mattsson et al., 2014; Toledo et al., 2015) and less agreement between neuronal injury biomarkers (Alexopoulos et al., 2014; Toledo et al., 2014; Jack et al ., 2015). Previous work using the NIA-AA-defined preclinical AD framework has examined only imaging measures (Ivanoiu et al., 2015; Jack et al., 2015, 2012; Knopman et al., 2012; Mormino et al., 2014), only CSF measures (Roe et al., 2013; Van

Harten et al., 2013; Vos et al., 2013), or an incomplete integration, with multimodal measure of neuronal injury (CSF tau and fludeoxyglucose PET) but not β-amyloid (Toledo et al., 2014). Crucially, no prior work has done head-to-head comparisons of CSF and neuroimaging markers of both β-amyloidosis and neuronal injury in the same clinical cohort. Directly evaluating these biomarkers in the same cohort is imperative as markers of preclinical AD are being used in both clinical and research settings. The aims of our study were to use a large cohort of cognitively normal elderly individuals to directly compare the relationship between CSF and imaging biomarkers of β-amyloid and neuronal injury as well as contrast the measures' performance in identifying the prevalence of preclinical AD and predicting clinical outcome. Understanding the similarities, and differences, in AD staging and classification across modalities is essential for future research, clinical trials, and patient care, as these are already incorporated into clinical practice in many settings.

2. Methods

2.1 Participants

212 cognitively normal volunteers (age range 45-88 years) were enrolled in longitudinal studies of memory and ageing at the Knight Alzheimer's Disease Research Center (ADRC), St. Louis, MO, USA. Details of recruitment and assessment have been published elsewhere (Berg et al., 1998). Participants underwent clinical assessment annually (individuals 65 years and older) or every 3 years (individuals below 65 years). Participants were selected from the larger ADRC cohort based on the following criteria: baseline cognitive, CSF, and imaging assessment within 12 months; baseline clinical dementia rating (CDR) score of 0; at least one clinical follow-up assessment; and good general health. The Human Research Protection Office at Washington University School of Medicine approved the ADRC studies. Written informed consent was

obtained from all participants. Compared to our previous study (Vos et al., 2013), we also included individuals below 65 years (33%), and participants were required to have both CSF and imaging data available.

2.2 Cognitive assessment

At baseline and follow-up participants underwent cognitive assessment, which included CDR and CDR sum of boxes (CDR-SB) (Morris, 1993), Mini-Mental State Examination (MMSE), and a psychometric test battery (Johnson et al., 2008; Pizzie et al., 2014; Hassenstab et al., 2016 (in press)). Baseline CDR score and diagnosis were assigned by trained clinicians and were based on the cognitive assessment closest to the time of biomarker assessment. Individuals with a CDR > 0 received a symptomatic AD diagnosis if given a CDR score of at least 0.5 for memory and at least one other domain and the clinician deemed the cognitive impairments to be due to AD (McKhann et al., 1984). A cognitive composite score was created based on the selective reminding task, animal fluency test, and trail making test part A, as these tests were available in all participants. Scores from each test were converted to *Z* scores relative to overall cohort performance and averaged to create a cognitive composite score.

2.3 CSF assessment

Samples (20–25 mL) were collected after overnight fasting by lumbar puncture, gently inverted to avoid possible gradient effects, briefly centrifuged at low speed, and aliquoted (0.5 mL) into polypropylene tubes before being frozen at −84°C. Samples were analyzed for β-amyloid ($A\beta_{1–42}$), total tau (t-tau), and phosphorylated tau_{181} (p-tau) by ELISA (Innotest; Fujirebio formerly Innogenetics, Ghent, Belgium). As previously published, CSF markers were defined as normal or abnormal based on cutoffs that could best differentiate participants who had CDR 0 at baseline from those in an independent

cohort who had CDR 0.5 symptomatic AD, on the basis of the Youden index (Vos et al., 2013). Abnormality was defined as $A\beta_{1-42}$ <459 pg/mL, t-tau >339 pg/mL, and p-tau >67 pg/mL. Cases were considered positive for β-amyloid if $A\beta_{1-42}$ was abnormal. As levels of t-tau and p-tau have been shown to be highly correlated in the literature as well as in our own sample (rho=0.848, p<0.001) participants were considered positive for neuronal injury if either t-tau or p-tau was abnormal.

2.4 Imaging assessment

Hippocampal volume (HCV) was used as the imaging biomarker of neuronal injury (Caroli et al., 2015; Jack et al., 2014, 2012; Knopman et al., 2012; Mormino et al., 2014; Petersen et al., 2013). High-resolution structural magnetic resonance imaging (MRI) was performed at 1.5 Tesla (n=26, Siemens Vision, Erglangen, Germany) or 3T (n=186, Siemens TIM Trio) using a magnetization-prepared rapid gradient echo (MPRAGE) sequence. HCVs were obtained from FreeSurfer (Fischl et al., 2004), adjusted for total intracranial volume (Buckner et al., 2004), and summed across hemispheres. Volumes were converted to age-adjusted z-scores relative to a normative cohort of 196 individuals who were biomarker negative and remained cognitively normal for at least three years (mean age 64.8 (range 43-90) years, 128 (65%) female, 45 (23%) *APOE* ε4 carriers, 1.5T=87, 3T=109). HCV was defined as normal or abnormal based on cutoffs that could best differentiate participants who had CDR 0 at baseline from those in an independent cohort who had CDR 0.5 symptomatic AD (n=141), on the basis of the Youden index. Abnormality was defined as HCV Z-score <-0.3023.

Pittsburgh compound B (PiB) PET (Klunk et al., 2004) was used as the imaging biomarker for β-amyloid. Participants underwent a 60-minute dynamic PET scan. Structural MRIs were parcellated using FreeSurfer to create a tissue mask. A regional

spread function (RSF) based technique (Rousset et al., 1998; Su et al., 2015) was then used to correct for partial volume effects and obtain corrected regional time-activity curves within each region. Binding potentials were calculated using Logan graphical analysis (Logan et al., 1990) with a cerebellar gray matter reference. Mean cortical binding potentials (MCBP) were calculated from regions of interest known to have high levels of deposition in AD, i.e. an average across both left and right lateral orbitofrontal, inferior parietal, precuneus, rostral middle frontal, superior frontal, superior temporal, and middle temporal regions derived from FreeSurfer (Su et al., 2015, 2013). β-amyloid-PET scans were defined as normal or abnormal based on cutoffs that could best differentiate the participants in the current sample who had CDR 0 at baseline from those in an independent cohort who had CDR 0.5 symptomatic AD (n=59), on the basis of the Youden index. Abnormality was defined as MCBP >0.2245.

2.5 NIA-AA preclinical AD classification

Figure 1 provides an overview of the classifications based on CSF biomarkers, imaging biomarkers, and a combined model using CSF and imaging biomarkers. The NIA-AA criteria include three preclinical AD stages. We did not differentiate between Stage 2 (abnormal β-amyloid and neuronal injury) and Stage 3 (abnormal β-amyloid, neuronal injury and subtle cognitive decline) as subtle cognitive deficits are not well defined in the field and proposed techniques to define Stage 3, i.e. bottom 10% based upon psychometric performance (Jack et al., 2012; Vos et al., 2013), resulted in insufficient sample sizes. At baseline, participants were classified in the normal group if β-amyloid and neuronal injury biomarkers were normal, in preclinical AD Stage 1 if β-amyloid alone was abnormal, in preclinical AD Stage 2+ if β-amyloid and neuronal injury biomarkers were abnormal without regard to psychometric performance, and in the SNAP group if the neuronal injury biomarker was abnormal and the β-amyloid biomarker normal (Jack et al., 2012). As β-amyloid biomarkers were highly correlated

and concordant (see section 3.4), in the combined model we allowed either CSF $A\beta_{1-42}$ or β-amyloid-PET to be abnormal for the β-amyloid measure while we differentiated between neuronal injury biomarkers (Figure 1).

2.6 Statistical analyses

Baseline differences in clinical and biomarker variables between NIA-AA classifications determined using CSF and imaging modalities were analyzed using a *t* test for continuous variables and χ^2 or logistic regression for categorical variables. We performed Spearman's rho correlation analyses when relating continuous CSF and imaging biomarkers levels of pathophysiology and Cohen's Kappa (*K*) to test agreement between classifications of abnormality.

When examining the NIA-AA criteria our primary outcome measures were the proportion of participants in each stage at baseline and the progression to CDR≥0.5 at follow-up. We used Cox proportional hazards models (hazard ratio, HR) to investigate the relative risk for a progression to CDR≥0.5 during the available follow-up period for each preclinical stage. In these statistical models individuals with normal biomarkers served as a reference group, and models were run both unadjusted and adjusted for baseline age, sex, education, and *APOE* genotype.

3. Results

We included 212 cognitively normal individuals with baseline clinical, CSF and imaging assessment collected within an average period of 4.4 (3.2 SD) months and a median clinical follow-up of 3.3 years (range 1-9). Table 1 lists the sample characteristics according to NIA-AA stage and Figure 1 demonstrates how data was used to designate preclinical stages.

3.1 CSF biomarkers

Using CSF biomarkers 127 (60%) participants were in the normal group, 26 (12%) in Stage 1, 19 (9%) in Stage 2+, and 40 (19%) were in the SNAP group (Table 1). The 5-year progression rate to CDR≥0.5 was 4% for the normal group, 5% for Stage 1, 46% for Stage 2+, and 21% for the SNAP group. Survival analyses adjusted for covariates showed that individuals in Stage 2+ were more likely to progress to CDR≥0.5 compared to those in the normal group (HR=9.7, p=0.001) and Stage 1 (HR=15.7, p=0.012; Table 2, Figure 2). Individuals in Stage 2+ had higher progression rates than those in the SNAP group, although the difference was not statistically significant (HR=2.8 p=0.087).

3.2 Imaging biomarkers

Using neuroimaging 114 (54%) participants were in the normal group, 42 (20%) in Stage 1, 16 (8%) in Stage 2+, and 40 (19%) were in the SNAP group (Table 1, Figure e-1). The 5-year progression rate to CDR≥0.5 was 6% for the normal group, 17% for Stage 1, and 55% for Stage 2+, and 9% for the SNAP group. Survival analyses adjusted for covariates showed that individuals in Stage 2+ were more likely to progress to CDR≥0.5 compared to those in the normal group (Table 2, Figure 2; HR=4.7, p=0.037). Individuals in Stage 2+ had higher progression rates than those in the SNAP group, although the difference was not significant (HR=3.8, p=0.076). No difference in progression rate was found between Stage 2+ and Stage 1 (HR=2.0, p=0.303).

3.3 Combination of CSF and imaging biomarkers

Using a combination of CSF and imaging biomarkers, 79 (37%) participants were in the normal group, 30 (14%) in Stage 1, 24 (11%) in Stage 2+ with only tau abnormal, 10 (5%) in Stage 2+ with only HCV abnormal, 6 (3%) in Stage 2+ with both abnormal tau

and HCV, 23 (11%) in the SNAP group with only tau abnormal, 34 (16%) in the SNAP group with only HCV abnormal, and 6 (3%) in the SNAP group with both abnormal tau and HCV (Figure e-1). Baseline characteristics of these subgroups are presented in Table e-1 in the Supplement. The 5-year progression rate to CDR≥0.5 was 3% for the normal group, 0% for Stage 1, 29% for Stage 2+ with only tau abnormal, 40% for Stage 2+ with only HCV abnormal, 76% for Stage 2+ with both tau and HCV abnormal, 18% for the SNAP group with only tau abnormal, 4% for the SNAP group with only HCV abnormal, and 35% for the SNAP group with both tau and HCV abnormal. Survival analyses showed that individuals in all the subgroups of Stage 2+ and individuals with SNAP with both abnormal tau and HCV were more likely to progress to CDR≥0.5 compared to those in the normal group (Table e-2, Figure 1). However, for individuals in Stage 2+ with only abnormal HCV and Stage 2+ with both abnormal tau and HCV this difference was not significant anymore after correction for covariates (Stage 2+ tau HR=5.6, p=0.047; Stage 2+ HCV HR=9.6, p=0.074; Stage 2+ both HR=3.4, p=0.234; SNAP both HR=10.3, p=0.024). Individuals with SNAP with only abnormal HCV had a better prognosis than individuals with SNAP with both abnormal tau and HCV (HR=0.04, p=0.019), individuals in Stage 2+ with only abnormal tau (HR=0.07, p=0.030), and individuals in Stage 2+ with only abnormal HCV (HR=0.04, p=0.031).

3.4 Head-to-head comparison

Prevalence of preclinical AD (Stages 1 and 2+) was higher for imaging than CSF classifications (28 vs. 21%, p<0.001) while progression rates to CDR≥0.5 in individuals with preclinical AD were similar for CSF and imaging modalities (18 vs. 17%, p=0.943; Table 1). Table 3 presents the overlap for CSF and imaging NIA-AA classifications. Only 99 (47%) individuals had the same CSF and imaging classification. There was a moderate agreement in preclinical AD classification (*K*=0.528, 95% CI 0.397-0.659, p<0.001) between both modalities. Concordance was lowest for SNAP and Stage 2+.

When we compared biomarker values regardless of the NIA-AA classification, we found a moderate correlation between CSF $A\beta_{1-42}$ levels and β-amyloid-PET binding (rho= -0.425, p<0.001), with 83% concordance in classification as abnormal (Figure 3, Table e-3). The correlation between CSF t-tau and HCV was minimal (rho=0.027, p=0.694), with 59% concordance in the total group and 57% in the preclinical AD group.

5. Discussion

We found that CSF and imaging biomarkers could both be used to identify preclinical AD, and for each approach, advanced preclinical AD stages were associated with an increased risk of clinical decline. However, the NIA-AA classifications across modalities overlapped only partially. This resulted mainly from discordance between neuronal injury biomarkers.

Individuals in preclinical AD stages demonstrated a higher rate of progression to CDR≥0.5 compared to individuals without preclinical AD, with similar results for CSF and imaging biomarkers. Only Stage 2+ showed an increased progression compared to the normal group. This suggests that individuals with both β-amyloid deposition and neuronal injury are most suitable for AD trial selection, although incongruences between markers of neuronal injury suggest disease heterogeneity.

Our combined model of CSF and imaging biomarkers, as well as the single modality analyses, demonstrated that Stage 2+ defined by either CSF tau or HCV led to similar clinical outcomes. The long-term clinical prognosis was the worst for Stage 2+ individuals who had both neuronal injury biomarkers abnormal. Also within the SNAP group, only individuals with abnormalities in both tau and HCV abnormal had higher

progression rates to CDR≥0.5 compared to those in the normal group. Although the number of individuals with preclinical AD or SNAP with both injury markers abnormal was small (n=6), this suggests a potential additive value of testing two neuronal injury measures to further refine the prognosis in this group.

In the current analyses, β-amyloid positivity using PET was slightly more common than β-amyloid positivity using CSF, which resulted in a higher prevalence of preclinical AD based on β-amyloid PET (28 vs. 21%). The slightly different cohorts used to define cutoffs, the timing when each biomarker demonstrates abnormality, and inherent signal-to-noise properties of the different techniques may drive this difference. However, the difference could also result from independent information provided by the amyloid markers (Mattsson et al., 2015). As with any study dichotomizing continuous variables, the choice of cutoff values is crucial. The current analyses established biomarker cutoffs using a Receiver Operating Characteristic (ROC) curve approach to differentiate cognitively normal individuals from mildly demented individuals with a clinical AD diagnosis. While other approaches have been implemented in the field to determine cutoffs for PET and MRI data (Cohen and Klunk, 2014; Jack et al., 2012; Mormino et al., 2014), this ROC approach is most common for analyses that include CSF data (De Meyer et al., 2010; Hulstaert et al., 1999; Jack et al., 2011; Kapaki et al., 2003; Mulder et al., 2010; Vos et al., 2013).

Our findings on the prevalence and outcome of preclinical AD are consistent with earlier reports based on only imaging biomarkers (Ivanoiu et al., 2015; Jack et al., 2012; Knopman et al., 2012; Mormino et al., 2014), only CSF biomarkers (Roe et al., 2013; Van Harten et al., 2013; Vos et al., 2013), or combined neuronal injury measures (Toledo et al., 2014) in that individuals at later preclinical stages are more likely to

show clinical decline in the future. Despite similar frequencies and longitudinal outcomes across the stages when using either CSF or imaging biomarkers (Table 1), the NIA-AA preclinical AD classification showed only 47% overlap between CSF and imaging based biomarkers. Our finding of high concordance between β-amyloid biomarkers (83%) and low concordance (59%) in neuronal injury is in line with previous studies that have examined the biomarkers separately.[2-6] By examining the scatterplot of continuous values (Figure 3) it is clear that the high congruency of β-amyloid data and low congruency of neuronal injury markers is not a byproduct of the selected cutoffs but an inherent property of the data.

The lower concordance between neuronal injury markers could be due to several reasons. First, both markers may reflect different aspects of AD. For example CSF levels of tau are likely sensitive to diffuse neuronal injury, while by its nature HCV measures focal changes. Further, the loss of grey matter assessed with MRI could be due both to the loss of dendritic branching as well as cell death. CSF values may instead be more sensitive to cell death and less so to changes in dendritic health. Second, each neuronal injury biomarker could become abnormal at a different stage of the AD process, although in our study individuals with an abnormal β-amyloid biomarker and abnormal tau did not differ in age or general cognitive performance from individuals with an abnormal β-amyloid biomarker and abnormal HCV. Third, unlike measures of β-amyloid that are relatively selective for AD, markers of neuronal injury are sensitive to multiple conditions. Smaller HCV is for instance also a feature of hippocampal sclerosis (Jack et al., 2002), TDP-43 proteinopathy (Whitwell et al., 2010), and argyrophilic grain disease, whereas elevated CSF tau is seen in cerebrovascular disease, Creutzfeldt-Jakob disease (Cohen et al., 2016), and traumatic brain injury (Tsitsopoulos and Marklund, 2013). Another reason for lower concordance between neuronal injury

markers could be the heterogeneity between p-tau$_{181}$ and p-tau$_{231}$, as a recent study suggests that the latter is superior in identifying AD (Spiegel et al., 2015). The heterogeneous nature of these neuronal injury biomarkers introduces the risk that even in the presence of abnormal β-amyloid they may not capture AD-specific pathology. The increased incidence of cognitive decline in later preclinical stages may be due both to more advanced AD trajectory, but also comorbid pathologies interacting with AD. This is a serious concern when selecting for clinical trials, and a fact that is overlooked when only one modality (e.g. imaging or CSF) is used to characterize pathology. In the future, tau-PET imaging may provide a localized measure of tauopathy that could help to better understand the neuronal injury pattern in AD versus non-AD (Villemagne et al., 2015).

Our study has several limitations. Because participants agreed to take part in a longitudinal biomarker study they are unlikely to be representative of the general population. However, our cohort is similar to other research samples of cognitively normal older adults and people with preclinical AD. Furthermore, the number of participants who progressed to CDR≥0.5 was small so our study may have been underpowered for detecting between group differences in clinical outcomes. Results should therefore be interpreted carefully. Even though the majority only had a short time lag (mean=4 months), we allowed a time lag of up to 12 months at baseline between clinical, CSF, and imaging assessment, which could have influenced our findings. However, when we performed our analyses with a maximum time lag of 6 months between the baseline assessments, results were very similar (data not shown). Additionally, HCV was measured on 1.5T scans for a small subgroup (n=26). Nevertheless, when we performed analyses only in individuals with 3T scans, results remained essentially the same. The major strengths of this study are the availability of

large sample size of well-characterized cognitively normal participants with both CSF and imaging data and the long follow-up period of up to 9 years.

Our study implies that both CSF and imaging biomarkers may be used in research settings and AD trials for identification of preclinical AD and its associated clinical decline. However, the disparity between CSF and imaging neuronal injury biomarkers may lead to different NIA-AA staging classifications. As they reflect different pathophysiological processes this could imply that groups defined based on different neuronal injury markers could have different responses to therapeutic interventions as well. This highlights the need for further refinement of neuronal injury assessment as part of the NIA-AA preclinical AD criteria and the potential utility of integrating multiple modalities.

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Figure legends

Figure 1. Overview of NIA-AA preclinical AD classifications.

The "-/+" refers to whether a biomarker is normal or abnormal for that stage. As they were highly correlated and concordant, in the integrated classifications we allowed either CSF $A\beta_{1-42}$ or β-amyloid-PET to be abnormal for the β-amyloid measure while we differentiated between CSF and imaging abnormality for the neuronal injury biomarker. Abnormal values for biomarkers were: $A\beta_{1-42}$ <459 pg/mL, t-tau >339 pg/mL, p-tau >67 pg/mL, MCBP-PiB >0.2245, HCV <-0.3023. Aβ=amyloid beta; CSF=cerebrospinal fluid; HCV=hippocampal volume; PiB=Pittsburgh compound B; SNAP=suspected non-Alzheimer pathophysiology; t-tau=total tau; p-tau=phosphorylated tau.

Figure 2. Survival plots of preclinical AD for progression to CDR≥0.5 based on different biomarkers

Graphs show the survival probability for progression to CDR≥0.5 for each preclinical AD stage, uncorrected for covariates. The black line represents participants in the normal group; blue, Stage 1; red, Stage 2+; and grey, SNAP. Given the relatively small sample sizes for the subgroups in the combined analyses, we allowed either CSF $A\beta_{1-42}$ or β-amyloid-PET to be abnormal for the β-amyloid measure while we differentiated between CSF t-tau or p-tau and HCV for the neuronal injury biomarker. CDR=Clinical Dementia Rating scale, HCV=hippocampal volume, SNAP=Suspected Non-Alzheimer Pathophysiology.

Figure 3. Concordance between β-amyloid biomarkers and neuronal injury biomarkers by outcome

Results are concordance between β-amyloid biomarkers and neuronal injury biomarkers presented by outcome, i.e. CDR=0, CDR≥0.5, or CDR≥0.5 symptomatic AD. Lines are cut-offs used to define abnormality: $A\beta_{1-42}$ <459 pg/mL, t-tau >339 pg/mL, MCBP-PiB >0.2245, HCV <-0.3023. Concordant biomarkers are presented in the upper left and lower

right part of each figure. *K*=Cohen's kappa for agreement in biomarker classification. Aβ=amyloid beta; AD=Alzheimer's disease; CDR=clinical dementia rating scale; CSF=cerebrospinal fluid; MCBP=mean cortical binding potential; PiB=Pittsburgh compound B; t-tau=total tau.

Table 1. Characteristics of the total cohort and the NIA-AA classification groups based on CSF versus imaging biomarkers

	Total cohort	Modality	Normal	Stage 1	Stage 2+	SNAP
N (%)	212 (100%)	CSF Imaging	127 (60%) 114 (54%)	26 (12%) 42 (20%)	19 (9%) 16 (8%)	40 (19%) 40 (19%)
Age	66.1 (9.3)	CSF Imaging	63.4 (9.0) 64.0 (9.4)	68.1 (9.6) 70.6 (5.9)	73.5 (5.6) 74.0 (6.9)	69.8 (7.8) * 64.3 (9.6)
Female, *n*	132 (62%)	CSF Imaging	80 (63%) 78 (68%)	15 (58%) 19 (45%)	9 (47%) 11 (69%)	28 (70%) 24 (60%)
Education, *y*	15.8 (2.6)	CSF Imaging	15.9 (2.5) 16.0 (2.4)	14.8 (3.0)* 16.4 (2.6)	16.5 (2.5) * 14.1 (3.4)	16.0 (2.4) 15.5 (2.5)
MMSE	29.2 (1.2)	CSF Imaging	29.3 (0.9) 29.3 (1.2)	29.0 (1.3) 29.0 (1.4)	28.6 (1.7) 28.9 (1.4)	29.0 (1.4) 29.2 (0.9)
Cognitive composite‡	0.08 (0.6)	CSF Imaging	0.2 (0.6) 0.2 (0.6)	0.1 (0.6) -0.1 (0.6)	-0.4 (0.6) -0.2 (0.5)	-0.1 (0.6) 0.1 (0.6)
APOE-ε4, n	70 (33%)	CSF Imaging	33 (26%) 26 (23%)	15 (58%) 24 (57%)	9 (47%) 8 (50%)	13 (33%) 12 (30%)
CSF $A\beta_{1-42}$	676.2 (272.8)	CSF Imaging	720.6 (203.2) 736.8 (258.9)	341.4 (75.8)* 485.0 (240.4)	363.6 (70.4) 446.8 (175.7)	901.1 (287.4) 795.7 (222.6)
CSF t-tau	278.3 (149.0)	CSF Imaging	205.9 (57.0)* 246.0 (115.0)	210.5 (67.6)* 379.8 (187.1)	503.0 (162.6)* 359.4 (203.6)	445.5 (145.2)* 231.5 (99.8)
CSF p-tau	53.1 (23.7)	CSF Imaging	42.4 (11.0) * 47.5 (17.8)	43.2 (9.2) * 70.5 (31.8)	87.4 (30.0) * 62.0 (26.2)	77.6 (23.4)* 47.4 (17.4)
MCBP for PiB	0.31 (0.4)	CSF Imaging	0.16 (0.17) * 0.12 (0.05)	0.49 (0.47) * 0.74 (0.46)	0.89 (0.46) 0.91 (0.55)	0.35 (0.51)* 0.11 (0.04)
HCV, *z*	0.06 (0.7)	CSF Imaging	0.0 (0.7)* 0.4 (0.5)	0.1 (0.7) 0.4 (0.5)	0.1 (0.6)* -0.9 (0.3)	0.2 (0.7)* -0.7 (0.3)
Progression to CDR≥0.5, *n*	18 (9%)	CSF Imaging	4 (3%) 5 (4%)	1 (4%) 5 (12%)	7 (37%) 5 (31%)	6 (15%) 3 (8%)
Progression to CDR≥0.5 symptomatic AD, *n*	8 (4%)	CSF Imaging	1 (1%) 0 (0%)	1 (4%) 2 (5%)	4 (21%) 5 (31%)	2 (5%) 1 (3%)

Results are mean (SD) or number (%) for participant classification based on CSF or imaging biomarkers. ‡The cognitive composite is a z-score derived from the selective reminding task, animal fluency test, and Trail Making Test part A. Scores from each test were converted to *Z* scores relative to overall cohort performance and averaged to create a cognitive composite score. Aβ=amyloid beta; AD=Alzheimer disease; *APOE*=apolipoprotein E; CSF=cerebrospinal fluid; HCV=hippocampal volume; MCBP=mean cortical binding potential; MMSE=Mini-Mental State Examination; PiB=Pittsburgh compound B; SNAP=suspected non-Alzheimer pathophysiology. *P<0.05 compared to imaging classification.

Table 2. Predictive accuracy of preclinical AD for progression to CDR≥0.5 based on CSF versus imaging biomarkers

Unadjusted		CSF		Imaging	
	Comparison	Hazard Ratio	P Value	Hazard Ratio	P Value
Stage 1	Normal	1.2 (0.1-10.9)	0.857	3.2 (0.9-11.1)	0.066
	Stage 2+		0.022		0.023
	SNAP		0.169		0.366
Stage 2+	Normal	14.2 (4.2-48.7)	<0.001	13.6 (3.9-47.7)	<0.001
	SNAP		0.083		0.004
SNAP	Normal	5.4 (1.5-19.3)	0.009	1.7 (0.4-6.9)	0.492
Adjusted		CSF		Imaging	
	Comparison	Hazard Ratio	P Value	Hazard Ratio	P Value
Stage 1	Normal	0.6 (0.1-5.8)	0.676	2.3 (0.6-8.8)	0.224
	Stage 2+		0.012		0.303
	SNAP		0.124		0.418
Stage 2+	Normal	9.7 (2.6-37.2)	0.001	4.7 (1.1-19.7)	0.037
	SNAP		0.087		0.076
SNAP	Normal	3.4 (0.9-12.6)	0.061	1.2 (0.3-5.8)	0.785

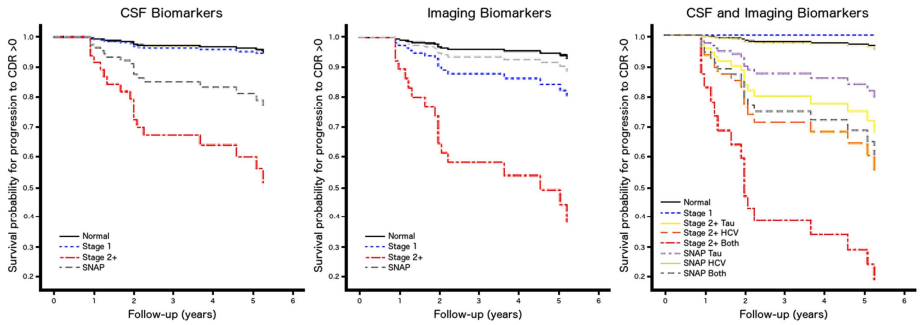
Results are hazard ratios (95% CI) for progression to CDR≥0.5 relative to cognitively normal individuals without any AD pathology. Analyses were performed both unadjusted and adjusted for age, sex, education, and *APOE* genotype, based on CSF biomarkers versus imaging biomarkers. P values are presented for comparisons with other groups. SNAP=suspected non-Alzheimer pathophysiology.

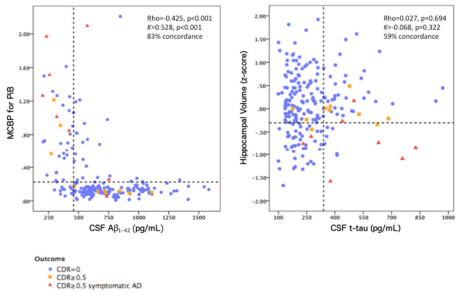
Table 3. Overlap in preclinical AD classification based on CSF and imaging biomarkers

		CSF biomarkers			
		Normal N=127	Stage 1 N=26	Stage 2+ N=19	SNAP N=40
Imaging biomarkers	Normal	**79 (62%)**	10 (39%)	2 (11%)	23 (58%)
	Stage 1	9 (7%)	**11 (42%)**	14 (74%)	8 (20%)
	Stage 2+	5 (4%)	5 (19%)	**3 (16%)**	3 (8%)
	SNAP	34 (27%)	-	-	**6 (15%)**

Results are number (%) of subjects in the classification groups based on CSF classification.
CSF=cerebrospinal fluid; SNAP=suspected non-Alzheimer pathophysiology.

	CSF Biomarkers		Imaging Biomarkers		CSF and Imaging Biomarkers		
	β-amyloid	Neuronal Injury	β-amyloid	Neuronal Injury	β-amyloid	Neuronal Injury	
	$A\beta_{1-42}$	T-tau or p-tau	PiB-PET	HCV	$A\beta_{1-42}$ or PiB-PET	T-tau or p-tau	HCV
Normal	-	-	-	-	-	-	-
Stage 1	+	-	+	-	+	-	-
Stage 2+	+	+	+	+	+	+	-
					+	-	+
					+	+	+
SNAP	-	+	-	+	-	+	-
					-	-	+
					-	+	+





Highlights

- CSF and neuroimaging AD biomarkers are often used interchangeably
- Advanced preclinical AD predicts greater risk of future clinical decline
- Neuronal injury markers from different modalities have low concordance
- Using different neuronal injury measures impacts the preclinical AD staging
- Preclinical AD staging may reflect both AD pathology and comorbidities