Supplementary Online Content

Tarawneh R, D'Angelo G, Crimmins D, et al. Diagnostic and prognostic utility of the synaptic marker neurogranin in Alzheimer disease. *JAMA Neurol.* Published online March 28, 2015. doi:10.1001/jamaneurol.2016.0086.

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods

PARTICIPANTS AND CLINICAL ASSESSMENTS

All participants in this study were included in a previous study of CSF visinin-like protein (VILIP-1) in AD (*n*=309) to allow comparison of markers. CSF samples from 7 participants in the previous study (controls *n*=4, AD *n*=3) were not adequate for Ng measurements; and, therefore, were not included in this study. Clinical, psychometric, genotype, magnetic resonance imaging (MRI) and CSF biomarker measures of this cohort (*n*=302) were comparable to those in the previously reported cohort (*n*=309).

All clinical diagnoses were made in accordance with standard criteria[1-5]. Individuals with CDR ≥ 0.5 at baseline (*n*=95) included in this study were all given a clinical diagnosis of AD. The rate of post-mortem confirmation of a clinical diagnosis of AD who have been followed up longitudinally in our center is 92%, including the CDR 0.5 stage[6].

A psychometric test battery assessing a broad spectrum of cognitive functions[6] was administered to all participants within 1-2 weeks of the annual assessment. Standardized test scores were averaged to form four composite scores. The episodic memory composite included the sum of the three free recall trials from the Selective Reminding Test[7], Associate Learning subtest of the Wechsler Memory Scale (WMS)[8], immediate recall of the WMS Logical Memory, and Benton Visual Retention test. The semantic memory composite included the Information subtest from the Wechsler Adult Intelligence Scale (WAIS)[9], Boston Naming Test[10], and Animal Naming[10]. The working memory composite included WMS Mental Control, Digit Span Forward and Digit Span Backward, and Letter Fluency for S and P[11]. The visual-spatial composite included the WAIS Block Design, Digit Symbol subtests, and Trail-making Tests A and B[12]. The global psychometric composite score used was prorated based on other tests used to generate the original composite score because of changes in the psychometric test battery across the study period. The reference (normative) group used to standardize most of the tests prior to forming the composites consisted of 310 participants [mean (standard deviation); age, 74.5 years (8.6); education, 14.8 years (3.2)] who were enrolled as CDR 0, had at least one annual follow-up assessment, but never progressed to CDR > 0[13]. The means and standard deviations of three measures (Selective Reminding Test, Animal Naming, Trail Making B) not included in that report were based on the same robust sample but with slightly smaller sample sizes because these three tests were added to the battery after its initiation. Beginning September 1, 2005, the funding agency required changes in three tests in the battery: WMS Logical Memory was replaced by WMS-R Logical Memory Story[14]; WAIS Digit Symbol was replaced by WAIS-R Digit Symbol; WMS Digit Span Forward and Backward was replaced by the WMS-R version. All, but one of the changes, were trivial and therefore are ignored here. The Logical Memory change, however, was substantial (i.e., gist scoring, only one story compared with

verbatim scoring of two stories). Although smaller and with less follow-up than the group used for the other measures, the reference group used for z-score conversion for the WMS-R Story A was the first assessment of 78 people (mean age, 73.4 years) enrolled with CDR 0 since September, 2005, who remained CDR 0 throughout follow-up (mean 12.49; SD, 3.39).

CSF COLLECTION, PROCESSING AND ASSESSMENT

CSF Ng levels were measured using a two-site immunoassay that utilizes affinity-purified rabbit polyclonal antibodies directed against a construct of Ng fused to glutathione-S-transferase (GST). Purification and separation of the anti-Ng antibodies was performed by an affinity-efficient trapping and purification (ETRAP) technique developed in our laboratory[15]. Antibody P-4973 was reactive against a C-terminal 18 AA region of the molecule and was coupled to magnetic beads to extract Ng (capture step). The purified antibody P-4794 directed to a 21 AA epitope near the N-terminus was labeled with a fluorescent dye and used for the detection antibody. The assay utilizes an Erenna instrument (Singulex) and has a lower limit of quantification of < 2 pg/ml.

IN VIVO AMYLOID IMAGING

Imaging was conducted via a commercial scanner (961 HR ECAT PET scanner or 962 HR+ ECAT PET scanner; Siemens Corporation, New York, New York) as described[16]. The binding potential values from the prefrontal cortex, gyrus rectus, lateral temporal, and precuneus regions of interest (ROIs) were averaged to calculate a mean cortical binding potential (MCBP) value based on brain regions known to have high PIB uptake among participants with AD[16]. Two measures were used in the analyses, the quantitative MCBP and MCBP dichotomized at 0.18, so that group comparisons of CSF and MRI measures could be estimated for those with (positive) and without (negative) substantial brain amyloid plaque burden[17].

REGIONAL AND WHOLE BRAIN VOLUMETRY

A subset of the control (*n*=144) and AD (*n*=38) cohorts underwent MRI within 1.1 years of their LP (median interval, 1.7 months). The majority of individuals (79%, *n*=144) had their structural imaging within 6 months of their LP. MRI was performed using a Siemens Trio 3.0T scanner (*n*=136) or a Siemens Vision 1.5T scanner (*n*=46) (Siemens, Erlangen, Germany). One to four T1-weighted sagittal magnetization prepared rapid gradient-echo scans were acquired in one scanning session in each participant. Image processing steps were performed as previously described[18, 19]. Whole-brain volume was obtained using commercially available Freesurfer 5.0 software[20, 21], with segmentation classifying each voxel of the MR image as CSF, gray matter, or white matter. Normalized whole-brain volumes (nWBVs) were computed as the proportion of all voxels occupied by gray and white matter (equivalent to 100% minus the percentage of CSF) voxels, yielding a unit that represents the proportion of estimated total

intracranial volume (ICV). Regional volume estimates were obtained via the Freesurfer 5.0 image analysis suite, which implements an automated probabilistic labeling procedure[22, 23]. Regions of interest (ROIs) included the hippocampus, entorhinal cortex, and parahippocampal gyrus, precuneus, fusiform gyrus, and posterior cingulate cortex. The pericalcarine cortex was included as a control region since it is rarely affected in the early stages of AD[24]. Estimated ICV was used to adjust ROIs for head size variation based on a covariance approach as described[25]. To reduce the number of comparisons, the ROI volumes were averaged across hemispheres. There is evidence of reliability of Freesurfer-derived quantitative estimates across scanners from previous studies[26, 27]. However, to avoid any potential biases related to across-scanner and field strength aggregation, scanner type was entered as a covariate in all analyses.

STATISTICAL ANALYSES

Receiver operating characteristic (ROC) curve analyses assessed rates of agreement between CSF biomarkers and clinical diagnoses or PIB-positivity (SPSS v.15). In these analyses, the proposed cut-off value represents the value which provided the maximum rate of agreement with the clinical diagnoses for each biomarker or ratio.

Cox-proportional hazard models tested the effect of demographic variables (age, sex, education, and *APOE* ε4 genotype) and CSF biomarker measures, individually or in combination (using Principal Components Analyses), on the conversion rate from CDR 0 to CDR 0.5 or greater (SAS Inc, Cary, NC). Follow-up time was calculated as the interval from the baseline clinical assessment (CDR 0) to the time of the first annual assessment with CDR $\geq$ 0.5 or the time of the last annual assessment for individuals who remained at CDR 0. CSF biomarker measures were analyzed as continuous and categorical (dichotomized at the 85th percentile value) variables. Of the 164 participants included in this analysis, 26 participants (16%) progressed from CDR 0 to CDR $\geq$0.5 during follow-up.

For illustrative purposes, Kaplan-Meier estimates of conversion rates as a function of CSF biomarker measures (dichotomized at the 85th percentile value) were performed. Survival analyses were conducted using baseline CDR scores at the clinical assessment prior to the time of the LP (median interval, 3.5 months). The bootstrap method was used to compare CSF biomarkers (individually or in combination) as predictors of conversion in non-nested models[28, 29] (statistical software R). The strength of each biomarker (or combination of biomarkers) as a predictor of conversion is reported as the proportion of times the biomarker significantly predicted conversion in the bootstrap sample

Mixed linear models (PROC MIXED; SAS Institute Inc) that specified a random subject-specific intercept and a random subject-specific slope tested the ability of CSF biomarkers/ratios to predict annual change in CDR-SB, global, episodic memory, semantic memory, working memory, or visual spatial composite scores in individuals

with AD over the follow-up period (SASv9.2). These models allow for heterogeneity among subjects in baseline values and rates of change, and account for correlation among repeated measures on the same subject. Analyses were adjusted for age, sex, education, the *APOE* ε4 genotype, and baseline dementia severity (i.e. longitudinal CDR-SB models were adjusted for baseline global scores and global or individual composite models were adjusted for baseline CDR-SB to avoid the issue of circularity). First, we examined whether CSF Ng and Ng/Aβ42, as continuous measures, predicted rates of cognitive decline over the follow-up period. CSF Ng and Ng/Aβ42 measures were standardized to *z* scores prior to analyses. Estimated effects of CSF Ng and Ng/Aβ42 on annual change in cognitive measures are reported as β. Analyses were then repeated for CSF Ng and Ng/Aβ42 as categorical variables (dichotomized at the 33rd or 66th percentile value) to determine whether there were significant differences in rates of cognitive decline between individuals in the upper tercile *vs* those in the lower two terciles for CSF Ng or Ng/Aβ42. Baseline cognitive assessments were the closest assessments prior to the time of the LP.

eResults

PARTICIPANTS

The CSF neurogranin levels did not correlate with age in patients with AD (r = 0.04, P =.72) or controls (r = 0.10, P = .14). There were no significant differences in mean (SE) CSF neurogranin levels between men (1.6 ng/ml [0.07]) and women (1.7 ng/ml [0.08]) (P = .19).

CORRELATION OF CSF NEUROGRANIN WITH CSF AND IMAGING MARKERS OF AD

No correlations between the CSF neurogranin levels and nWBV (r = 0.03, P = .69), hippocampal (r = .13, P = 0.12), entorhinal (r = 0.02, P = .83), parahippocampal (r = -0.05, P = .58), fusiform (r = 0.12, P = .17), cingulate (r = 0.15, P = .08), precuneus (r = 0.07, P = .41), or pericalcarine (r = -0.10, P = .25) volumes were observed in controls (adjusting for age, sex, and scanner type).

The mean (SE) areas under the curve (AUC) were 0.85 (0.02; 95% CI, 0.80-0.90) for tau, 0.81 (0.03; 95% CI, 0.76-0.86) for p-tau181, 0.77 (0.03; 95% CI, 0.72-0.83) for Aβ42, 0.74 (0.03; 95% CI, 0.68-0.80) for VILIP-1, and 0.71 (0.03; 95% CI, 0.64-0.77) for neurogranin. The mean (SE) AUCs for the CSF marker ratios to amyloid-β 42 (Aβ42) were 0.88 (0.02; 95% CI, 0.84-0.92) for tau/Aβ42, 0.86 (0.02; 95% CI, 0.82-0.91) for p-tau181/Aβ42, 0.85 (0.02, 95% CI, 0.81-0.90) for VILIP-1/Aβ42, and 0.81(0.03, 95% CI, 0.76-0.86) for neurogranin/Aβ42.

The mean (SE) AUC was 0.86 (0.03; 95% CI, 0.79-0.92) for tau, 0.81 (0.04; 95% CI, 0.74-0.89) for p-tau181, 0.87 (0.03; 95% CI, 0.81-0.94) for Aβ42, 0.77 (0.04; 95% CI, 0.68-0.84) for VILIP-1, and 0.73 (0.04; 95% CI, 0.63-0.81) for neurogranin. The mean (SE) AUCs for the CSF marker ratios to Aβ42 were 0.95 (0.02; 95% CI, 0.91-0.99) for tau/Aβ42, 0.95 (0.02; 95% CI, 0.90-0.99) for p-tau181/Aβ42, 0.93 (0.02; 95% CI, 0.88-0.97) for VILIP-1/Aβ42, and 0.89 (0.03; 95% CI, 0.83-0.95) for neurogranin/Aβ42.

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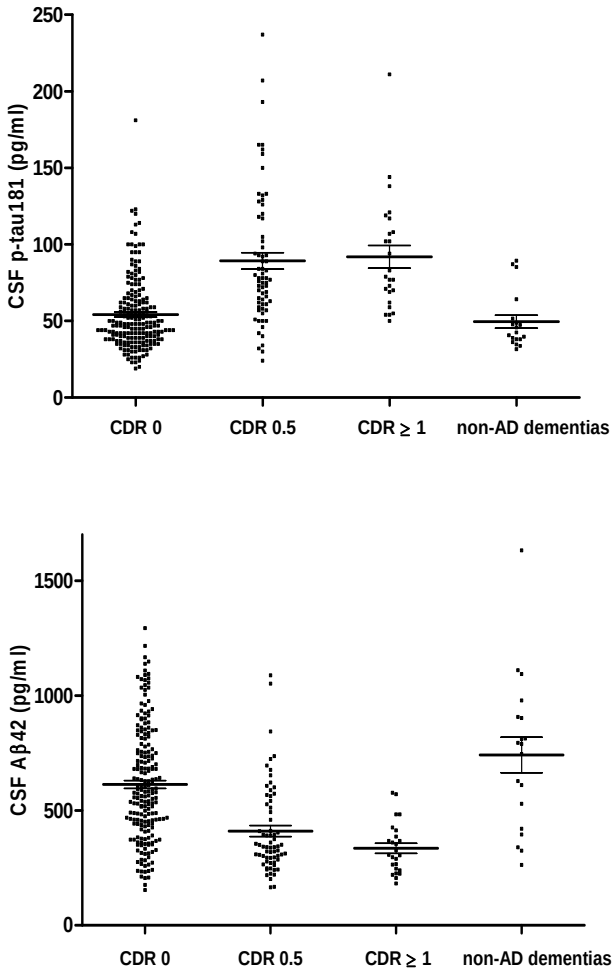
eFigure 1. CSF p-tau181 and Aβ42 Levels by CDR Category

A **B**



(A) CSF p-tau181 levels were higher in the CDR 0.5 (mean ± SE, 89pg/ml ± 5) and CDR≥ 1 (92pg/ml ± 7) cohorts compared to controls [CDR 0] (54pg/ml ± 2, $p<0.001$) and non-AD dementias (50pg/ml ± 4, $p<0.001$). **(B)** CSF Aβ42 levels were lower in CDR 0.5 (410pg/ml ± 24) and CDR ≥ 1 (335pg/ml ± 22) cohorts compared to controls (613 pg/ml ±18, $p<0.001$) and non-AD dementias (741pg/ml ± 77, $p<0.001$).

eTable 1. Rates of Agreement Between CSF Biomarkers and Clinical Diagnoses or PIB Status

Rates of Agreement Between CSF Biomarkers and Clinical Diagnoses[a]				
	AD versus Controls		AD vs non-AD Dementias	
CSF biomarker	Sensitivity	Specificity	Sensitivity	Specificity
Ng	77% (68-85%)	52% (49-58%)	77% (68-85%)	74% (54-93%)
VILIP-1	80% (72-88%)	52% (44-58%)	80% (72-88%)	74% (54-93%)
tau	84% (77-92%)	75% (67-81%)	84% (77-92%)	68% (48-90%)
p-tau181	82% (74-90%)	64% (58-71%)	82% (74-90%)	74% (54-91%)
Aβ42	78% (70-86%)	63% (56-70%)	78% (70-86%)	74% (54-93%)
Ng/Aβ42	82% (74-90%)	71% (65-77%)	82% (74-90%)	95% (85-100%)
VILIP-1/Aβ42	85% (75-90%)	74% (67-80%)	85% (78-92%)	95% (85-100%)
tau/Aβ42	84% (77-92%)	87% (82-91%)	84% (77-92%)	89% (76-100%)
p-tau181/Aβ42	91% (85-96%)	76% (70-82%)	91% (85-96%)	79% (61-97%)
Rates of Agreement Between CSF Biomarkers and PIB status				
	PIB positive vs PIB negative[b]			
CSF biomarker	Sensitivity		Specificity	
Ng	79% (68-90%)		60% (50-70%)	
VILIP-1	80% (69-90%)		78% (70-86%)	
tau	78% (67-89%)		81% (74-89%)	
p-tau181	78% (67-90%)		75% (67-84%)	
Aβ42	96% (91-100%)		75% (67-84%)	
Ng/Aβ42	85% (75-95%)		87% (80-94%)	
VILIP-1/Aβ42	85% (76-95%)		87% (81-94%)	
tau/Aβ42	85% (75-95%)		92% (87-98%)	
p-tau181/Aβ42	90% (82-98%)		85% (78-92%)	

Ng, neurogranin; VILIP-1, visinin-like protein-1; p-tau181, tau phosphorylated at threonine 181; Aβ42, amyloid-beta peptide 1-42. The upper analyses included cognitively normal controls (*n*=207) and individuals with a clinical diagnosis of Alzheimer's disease (AD) (*n*=95). Individuals in the AD and control cohorts who underwent PET-PIB (*n*=152) were categorized by PIB status as PIB-positive (*n*=53) or PIB-negative (*n*=99) irrespective of clinical diagnoses. For each biomarker or ratio, the proposed cut-off value represents the value which provided the maximum rate of agreement with the clinical diagnoses or PIB status.

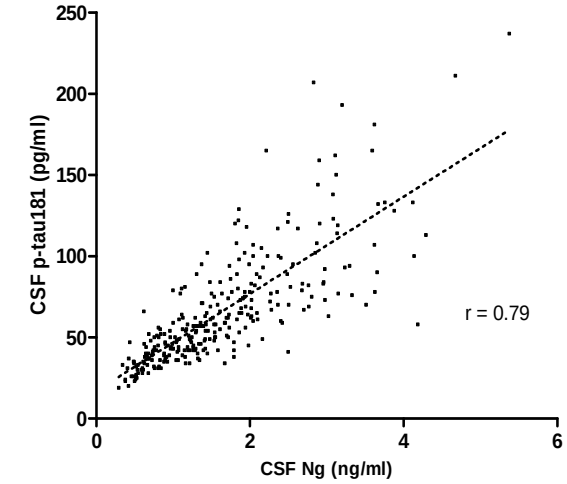
a Proposed cut-off values for CSF Ng, VILIP-1, tau, p-tau181, and Aβ42 were 1.3ng/ml, 375pg/ml, 350pg/ml, 55pg/ml, and 500pg/ml, respectively. Proposed cutoff values for the Ng/Aβ42, VILIP-1/Aβ42, tau/Aβ42, and p-tau181/Aβ42 ratios were 0.003, 0.8, 0.7, and 0.1, respectively. The 95% confidence intervals are in parentheses.

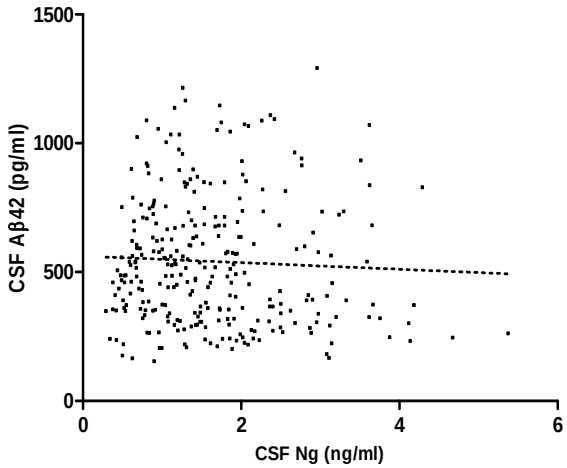
b Individuals in the AD and control cohorts who underwent PET-PIB (*n*=152) were categorized by PIB status as PIB-positive (*n*=53) or PIB-negative (*n*=99) irrespective of clinical diagnoses.

With the exception of the CSF Ng data, the other data are reprinted with permission from "Tarawneh et al, CSF VILIP-1: Diagnostic and Prognostic Marker of Alzheimer disease, Annals of Neurology, 2011; 70:274-285.

eFigure 2. Correlations of CSF Ng With CSF p-tau181 and Aβ42 Levels

A **B**





(A) CSF Ng levels demonstrated significant correlations with CSF p-tau181 levels in the combined AD and control cohorts (r=0.79, p<0.001, n=289) **(B)** No significant correlations between CSF Ng and CSFAβ42 levels were observed in the combined cohort (AD and controls) (r=-0.05, p=0.43, n=288).

eTable 2. Baseline Demographic, Clinical, Genotype, CSF, and MRI Characteristics of Individuals With MRI and CSF Measures

Clinical Characteristics	**Controls (*n*=144)**	**AD (*n*=38)**	***p* value**
Age at LP, mean ±SE, years	71.9 ± 0.6	74.4 ± 1.4	0.06
Gender F/M (%F)[a]	89/55 (62%)	20/18 (53%)	0.35
APOE genotype, ε4+/ε4- (ε4+ %)[a]	44/100 (31%)	22/16 (59%)	0.002[b]
LP to MRI interval, mean ±SE, years	0.32 ± 0.03	0.33 ± 0.03	0.89
Interval from baseline clinical assessment to MRI, mean ±SE, years	0.55 ± 0.03	0.59 ± 0.03	0.64
Baseline CSF Biomarker Measures			
CSF Ng, mean ±SE, ng/ml	1.4 ± 0.06	2.0 ± 0.16	<0.001[b]
CSF VILIP-1, mean ±SE, pg/ml	385 ± 12	519 ± 32	<0.001[b]
CSF tau, mean ±SE, pg/ml	292 ± 13	584 ± 43	<0.001[b]
CSF p-tau181, mean ±SE, pg/ml	53 ± 2	90 ± 7	<0.001[b]
CSF Aβ42, mean ±SE, pg/ml	611 ± 21	406 ± 31	<0.001[b]
CSF Ng/Aβ42, mean ±SE	0.003 ± 0.0002	0.006 ± 0.001	<0.001[b]
CSF tau/Aβ42, mean ±SE	0.59 ± 0.04	1.71 ± 0.18	<0.001[b]
CSF p-tau181/Aβ42, mean ±SE	0.11 ± 0.01	0.26 ± 0.03	<0.001[b]
CSF VILIP-1/Aβ42, mean ±SE	0.74 ± 0.04	1.52 ± 0.12	<0.001[b]
Baseline MRI Volume Measures			
nWBV, mean ±SE	0.77 ± 0.003	0.73 ± 0.004	<0.001[b]
Hippocampus, mean ±SE, mm^3	7339 ± 70	6103 ± 163	<0.001[b]
Entorhinal cortex, mean ±SE, mm^3	3531 ± 56	2866 ± 115	<0.001[b]
Parahippocampal gyrus, mean ±SE, mm^3	3342 ± 41	3074 ± 86	0.004[b]
Fusiform gyrus, mean ±SE, mm^3	16352 ± 199	14208 ± 331	<0.001[b]
Precuneus, mean ±SE, mm^3	16745 ± 192	14993 ± 360	<0.001[b]
Posterior cingulate, mean ±SE, mm^3	5902 ± 77	5574 ± 128	0.05[b]
Pericalcarine cortex, mean ±SE, mm^3	4033 ± 65	3882 ± 121	0.29

a Chi square (χ^2) tests were used for group comparisons

b $p<0.05$

eTable 3. Baseline Demographic, Clinical, Genotypic, and CSF Biomarker Characteristics of Controls With Longitudinal Psychometric Assessments

Characteristics	**Non-converters (*n*=138)**	**Converters (*n*=26)**	***p* value**
Age at LP, mean ±SE, years	71.7 ± 0.6	77.4 ± 1.3	<0.001[a]
Gender *n* F/M (%F)	88/50 (64%)	16/10 (62%)	0.83[b]
Education, mean ±SE, years	15.5 ± 0.2	15.5 ± 0.9	0.98
APOE genotype, ε4+/ε4- (%ε4+)[c]	45/93 (33%)	6/20 (23%)	0.34[b]
Baseline MMSE, mean ±SE	29.1 (1.1)	29.0 (1.2)	0.71
MMSE at follow-up, mean ±SE	29.0 (1.2)	27.3 (2.2)	<0.001 [a]
Baseline CDR-SB, mean (SE, range)	0.05 (0.21, 0-2)	0.12 (0.33, 0-1.5)	0.17
CDR-SB at follow-up, mean (SE, range)	0.02 (0.13, 0-1)	1.27 (1.02, 0.5-4)	<0.001[a]
Follow-up time, mean ±SE, years	2.8 ± 0.1	2.9 ± 0.3	0.91
PIB+ / PIB– (%PIB+)[d]	17/69 (20%)	6/5 (55%)	0.01[a,b]
CSF Ng (ng/ml), mean ±SE	1.34 ± 0.06	1.99 ± 0.18	<0.001[a]
CSF VILIP-1 (pg/ml), mean ±SE	376 ± 11	503 ± 35	<0.001[a]
CSF tau (pg/ml), mean ±SE	280 ± 12	412 ± 40	<0.001[a]
CSF p-tau181 (pg/ml), mean ±SE	52 ± 2	66 ± 5	0.004[a]
CSF Aβ42 (pg/ml), mean ±SE	640 ± 21	527 ± 48	0.033[a]
CSF Ng/Aβ42, mean ±SE	0.002 ± 0.0002	0.005 ± 0.0006	<0.001[a]
CSF VILIP-1/Aβ42, mean ±SE	0.67 ± 0.04	1.12 ± 0.12	<0.001[a]
CSF tau/Aβ42, mean ±SE	0.52 ± 0.04	0.99 ± 0.15	<0.001[a]
CSF p-tau181/Aβ42, mean ±SE	0.10 ± 0.01	0.16 ± 0.03	0.002[a]

APOE, Apolipoprotein E; CDR, Clinical Dementia Rating; CDR-SB, Clinical Dementia Rating-sum of boxes; MMSE, Mini-Mental State Examination, PIB, Pittsburgh Compound B; LP, lumbar puncture; Ng, neurogranin; VILIP-1, visinin-like protein-1. With the exception of the CSF Ng data, the other data in this table were previously published in "Tarawneh et al, CSF VILIP-1: Diagnostic and Prognostic Marker of Alzheimer disease, Annals of Neurology, 2011; 70:274-285[30], and are reprinted with permission.

a p <0.05

b Chi-square (χ^2) tests were used for group comparisons.

c *APOE* ε4+ genotype was defined by the presence of at least one *APOE* ε4 allele.

d These values represent the percentage of (PIB+) individuals among all individuals who were evaluated by PET-PIB in each of the "non-converters" (*n*=86) and "converters" (*n*=11) cohorts.

eTable 4. Baseline Demographic and CSF Biomarker Variables as Predictors of Time to Conversion From CDR 0 to CDR ≥ 0.5

Characteristic or Biomarker	Hazard ratio (95% CI)	Wald χ^2_1	*p* value
Age[a]	1.08 (1.03-1.13)	10.6	0.001[b]
Education	0.99 (0.88-1.12)	0.02	0.90
Female gender	0.69 (0.31-1.51)	0.87	0.35
APOE ε4+ genotype	0.79 (0.32-1.96)	0.26	0.61
CSF Ng	1.89 (1.29 – 2.78)	10.5	0.001[b]
CSF VILIP-1	1.004 (1.002-1.006)	11.55	0.001[b]
CSF tau	1.003 (1.001-1.005)	9.96	0.002[b]
CSF p-tau181	1.013 (1.000-1.026)	4.11	0.04[b]
CSF Aβ42	0.998 (0.996-1.000)	2.53	0.11
CSF Ng/Aβ42[c]	27.86 (6.93- 112.1)	21.90	<0.001[b]
CSF VILIP-1/Aβ42	4.67 (2.45-8.87)	22.05	<0.001[b]
CSF tau/Aβ42	2.61 (1.60-4.27)	14.67	<0.001[b]
CSF p-tau181/Aβ42[c]	1.69 (1.22-2.34)	9.83	0.002[b]

Cox proportional hazard models were used to assess the ability of demographic variables (age, sex, education, and *APOE* ε4 genotype) and baseline levels of CSF biomarkers Ng, VILIP-1, tau, p-tau181, Aβ42, Ng/Aβ42, VILIP-1/Aβ42, tau/Aβ42, and p-tau181/Aβ42 (as continuous variables) to predict conversion from normal cognition (CDR 0) to cognitive impairment (CDR ≥0.5) over the 2-3 year follow-up period. CI, confidence intervals; Aβ42, amyloid-β peptide 1-42; p-tau181, tau phosphorylated at threonine 181; Ng, neurogranin, VILIP-1, visinin-like protein-1; *APOE*, Apolipoprotein E. Analyses for all CSF biomarker measures were adjusted for age, sex, education, and *APOE* ε4 genotype. With the exception of the CSF Ng data, the other data were previously published in "Tarawneh et al, CSF VILIP-1: Diagnostic and Prognostic Marker of Alzheimer disease, Annals of Neurology, 2011; 70:274-285[30] are reprinted with permission.

a Hazard ratio for age after adjusting for the CSF biomarker measures (Ng,VILIP-1,tau, p-tau181, and Aβ42) and demographic variables (education, gender, and *APOE* ε4+ genotype): 1.07 (CI: 1.01-1.145, *p*= 0.048)

b *p* value <0.05

c Because of the small values of the p-tau181/Aβ42 and Ng/Aβ42 ratios, these values were transformed by multiplying each value by a constant of 10 and 100, respectively, prior to analysis.

eTable 5. Rates of Cognitive Decline as a Function of CSF Ng and Ng/Aβ42 Levels in AD

Rates of Decline in Clinical Dementia Rating- Sum of Boxes (per year)			
CSF biomarker [a]	Lower two terciles	Upper tercile	*p* value [b]
Ng	0.82 ± 0.12	1.40 ± 0.21	0.03[c]
Ng/Aβ42	0.86 ± 0.12	1.39 ± 0.20	0.02[c]
Rates of Decline in Global Psychometric Composite Scores (per year)			
CSF biomarker [a]	Lower two terciles	Upper tercile	*p* value [b]
Ng	-0.17 ± 0.04	-0.37 ± 0.07	0.02[c]
Ng/Aβ42	-0.14 ± 0.04	-0.44 ± 0.07	<0.001[c]
Rates of Decline in Episodic Memory Composite Scores (per year)			
CSF biomarker [a]	Lower two terciles	Upper tercile	*p* value [b]
Ng	-0.11 ± 0.04	-0.49 ± 0.07	<0.001[c]
Ng/Aβ42	-0.14 ± 0.05	-0.47 ± 0.08	0.001[c]

Mixed linear models were used to estimate rates of decline in CDR-SB, global psychometric composite scores, and episodic memory composite scores in the AD cohort over time as a function of CSF Ng levels (adjusting for age, education, sex, the *APOE* ε4 genotype, and baseline dementia severity). In these analyses, CSF Ng and Ng/Aβ42 were examined as categorical variables (dichotomized at 66th percentile values; 2.0 ng/ml for Ng and 0.007 for Ng/Aβ42) to compare rates of decline between individuals in the upper tercile *vs* those in the lower two terciles for CSF biomarker measures.

a The 66th percentile cut-off value in the AD cohort was 2.0 ng/ml for Ng and 0.007 for Ng/Aβ42.

b *p* values reflect whether CSF Ng and Ng/Aβ42 levels (dichotomized at the 66th percentile value) significantly predict rates of cognitive decline in the AD cohort (adjusting for age, education, gender, the *APOE* ε4 genotype, and baseline dementia severity). Longitudinal CDR-SB models were adjusted for baseline global composite scores, and global or individual composite models were adjusted for baseline CDR-SB.

c *p* value <0.05.