Supplemental Information

2-D DIGE LC-MS/MS Proteomic Analysis

Samples were processed and analyzed as described previously (1, 2). Briefly, discovery cohort CSF samples and a pooled reference sample were immunodepleted of six highly abundant proteins (albumin, IgG, α1-antitrypsin, IgA, haptoglobin, transferrin). Samples were randomly paired (CDR 0 and CDR 1), labeled with one of three cyanine dyes, and loaded with the labeled reference sample onto the same 2-D gel. Protein spot quantification and between-gel spot matching were performed on digitized images. To focus efforts on candidate biomarkers more likely to be measurable in the CSF of a majority of individuals, only gel features with significant intensity differences between CDR 0 and CDR 1 groups (Student's t-test, $\alpha = 0.05$) that were present in >50% of gels were excised, trypsinized, and subjected to LC-MS/MS. Proteins were identified from peptide fragmentation spectra using MASCOT (v2.8, Matrix Sciences) and the NCBI non-redundant protein database (downloaded 11/11/2008).

Table S1 A. Utility of CSF Biomarkers In Predicting Conversion from CDR 0 to CDR>0

	YKL-40/Aβ42			tau/Aβ42			ptau/Aβ42		
	HR	**95% CI**	***p* value**	**HR**	**95% CI**	**p value**	**HR**	**95% CI**	***p* value**
Biomarker-continuous	1.78	1.31-2.44	.0003	1.54	1.24-1.93	.0001	1.61	1.28-2.02	<.0001
Age, yr	1.05	0.99-1.10	.0844	1.07	1.01-1.12	.0177	1.06	1.01-1.12	.0181
Women	0.53	0.24-1.18	.1196	0.50	0.22-1.14	.1003	0.56	0.25-1.26	.1596

	YKL-40/Aβ42			tau/Aβ42			ptau/Aβ42		
	HR	**95% CI**	***p* value**	**HR**	**95% CI**	***p* value**	**HR**	**95% CI**	***p* value**
Biomarker-categorical	3.35	1.42-7.90	.0057	5.76	2.35-14.09	.0001	3.42	1.50-7.79	.0035
Age, yr	1.05	0.99-1.10	.0950	1.07	1.02-1.13	.0116	1.06	1.01-1.12	.0194
Women	0.71	0.31-1.63	.4181	0.66	0.29-1.49	.3123	0.65	0.28-1.50	.3110

Table S1 B. Utility of CSF Biomarkers In Predicting Progression from CDR 0.5 to CDR>0.5

	YKL-40/Aβ42			tau/Aβ42			ptau/Aβ42		
	HR	**95% CI**	***p* value**	**HR**	**95% CI**	***p* value**	**HR**	**95% CI**	***p* value**
Biomarker-continuous	1.37	0.92-2.04	.1171	1.45	1.07-1.97	.0167	1.29	0.97-1.73	.0803
Age, yr	1.01	0.95-1.08	.7218	1.01	0.95-1.07	.8311	1.01	0.95-1.08	.7509
Women	0.55	0.23-1.33	.1837	0.51	0.21-1.24	.1349	0.55	0.23-1.32	.1797

	YKL-40/Aβ42			tau/Aβ42			ptau/Aβ42		
	HR	**95% CI**	***p* value**	**HR**	**95% CI**	***p* value**	**HR**	**95% CI**	***p* value**
Biomarker-categorical	2.63	1.10-6.32	.0305	3.64	1.51-8.80	.0041	4.25	1.76-10.26	.0013
Age, yr	1.02	0.96-1.08	.5786	1.02	0.96-1.09	.4909	1.03	0.97-1.09	.4241
Women	0.59	0.25-1.37	.2157	0.50	0.21-1.21	.1242	0.47	0.19-1.16	.1000

Table S1. Cox proportional hazards models were used to assess the ability of CSF YKL-40/Aβ42, tau/Aβ42, and ptau/Aβ42 to predict **(A)** conversion from cognitive normalcy (CDR 0) to cognitive impairment (CDR>0) and **(B)** progression from very mild dementia (CDR 0.5) to mild or moderate dementia (CDR>0.5). Biomarker measures were analyzed as both continuous and

categorical variables, and were converted to standard Z-scores to allow comparison of hazard ratios between different biomarkers. In evaluating risk, “Biomarker” analyses (YKL-40/Aβ42, tau/Aβ42, ptau/Aβ42) were adjusted for age and gender. Likewise, analyses for “Age” were adjusted for biomarker and gender, and analyses for “Women” were adjusted for biomarker and age. HR, hazard ratio; CI, confidence interval.

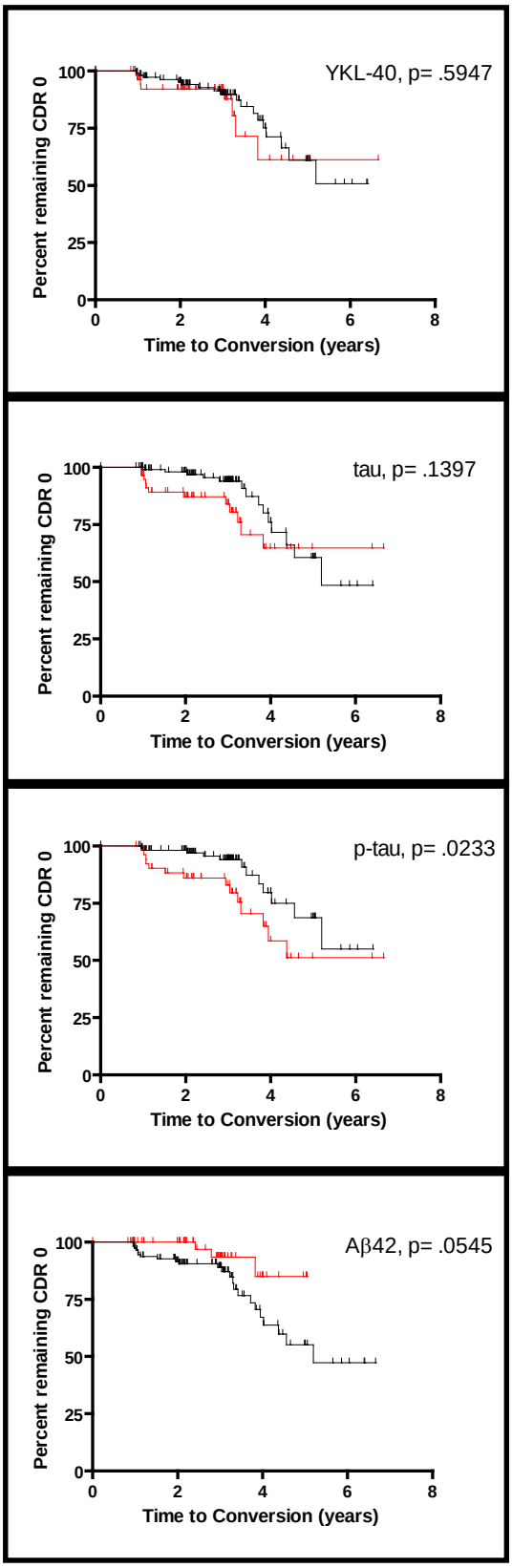

Figure S1. CSF YKL-40, tau, p-tau, and Aβ42 as predictors of conversion from CDR 0 to CDR>0. Kaplan-Meier estimates of rates of conversion are shown with red curves representing the upper tertile and black curves representing the lower two tertiles.

Table S2. Utility of CSF Biomarkers In Predicting Conversion from CDR 0 to CDR>0

	YKL-40			tau			ptau			Aβ42		
	HR	**95% CI**	***p* value**	**HR**	**95% CI**	***p* value**	**HR**	**95% CI**	***p* value**	**HR**	**95% CI**	***p* value**
Biomarker-continuous	0.95	0.61-1.47	.8081	1.45	1.11-1.90	.0072	1.47	1.14-1.91	.0036	0.41	0.23-0.73	.0021
Age, yr	1.06	1.01-1.12	.0211	1.07	1.01-1.12	.0170	1.07	1.01-1.12	.0148	1.05	1.00-1.10	.0672
Women	0.50	0.22-1.12	.0919	0.50	0.22-1.12	.0914	0.51	0.23-1.13	.0981	0.50	0.23-1.12	.0923

	YKL-40			tau			ptau			Aβ42		
	HR	**95% CI**	***p* value**	**HR**	**95% CI**	***p* value**	**HR**	**95% CI**	***p* value**	**HR**	**95% CI**	***p* value**
Biomarker-categorical	1.00	0.42-2.33	.9901	1.88	0.86-4.09	.1114	2.69	1.22-5.93	.0139	0.34	0.10-1.16	.0841
Age, yr	1.06	1.01-1.11	.0225	1.06	1.01-1.12	.0211	1.07	1.01-1.13	.0105	1.05	1.00-1.11	.0429
Women	0.51	0.23-1.13	.0968	0.52	0.24-1.16	.1097	0.55	0.25-1.23	.1449	0.49	0.22-1.08	.0754

Table S2. Cox proportional hazards models were used to assess the ability of CSF YKL-40, tau, ptau, and Aβ42 to predict conversion from cognitive normalcy (CDR 0) to cognitive impairment (CDR>0). Biomarker measures were analyzed as both continuous and categorical variables. In evaluating risk, “Biomarker” analyses (YKL-40, tau, ptau, Aβ42) were adjusted for age and gender. Likewise, analyses for “Age” were adjusted for biomarker and gender, and analyses for “Women” were adjusted for biomarker and age. HR, hazard ratio; CI, confidence interval.

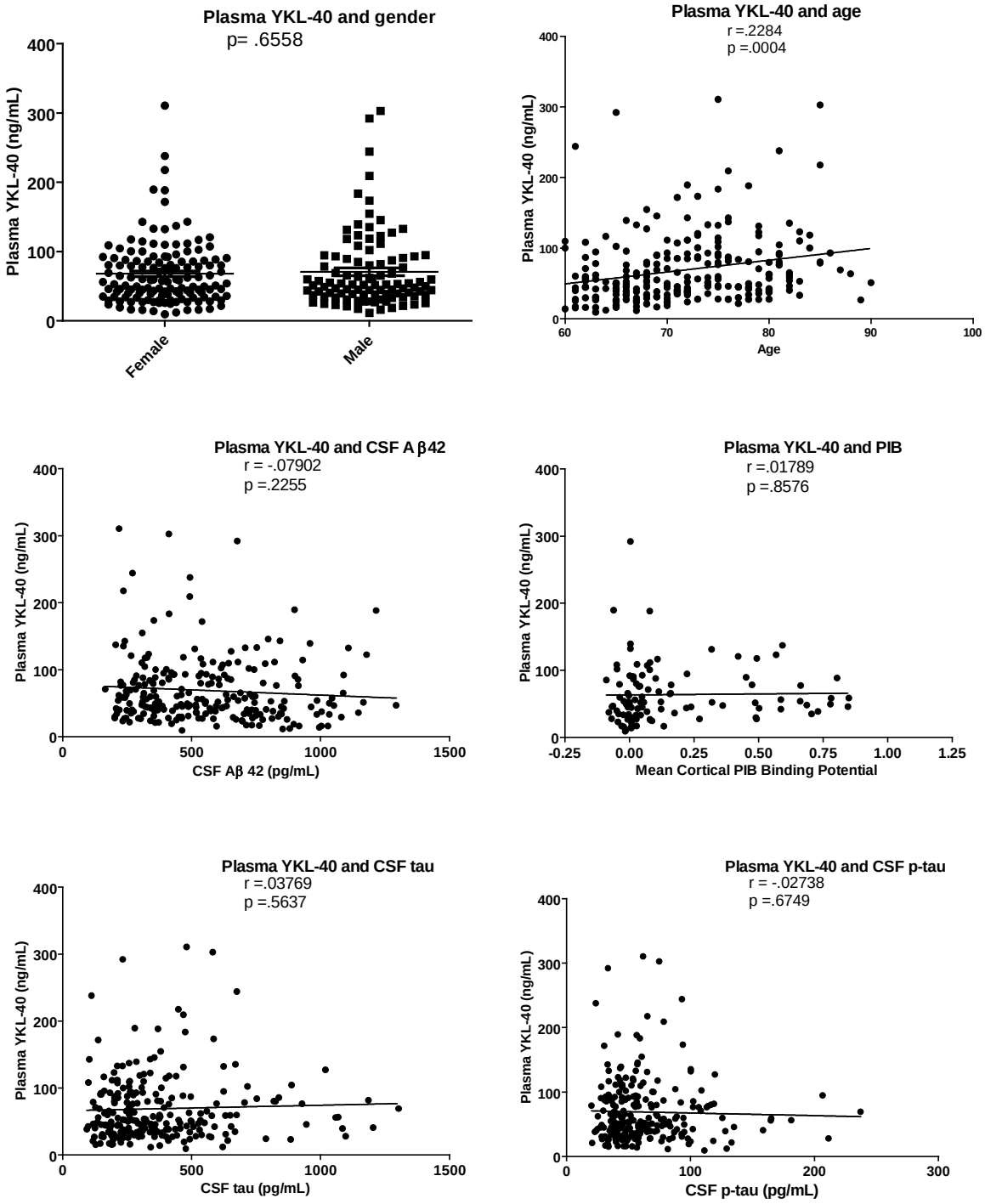

Figure S2. Plasma YKL-40 levels do not vary based on gender, but are correlated with age. Plasma YKL-40 levels are not correlated with other CSF biomarkers such as Aβ42, tau, p-tau181, or with mean cortical PIB binding potential.

1. Hu Y, Malone J, Fagan A, Townsend R, Holtzman D (2005): Comparative proteomic analysis of intra- and interindividual variation in human cerebrospinal fluid. *Mol & Cell Proteom*. 4:2000-2009.
2. Hu Y, Hosseini A, Kauwe J, Gross J, Cairns N, Goate A, *et al.* (2007): Identification and validation of novel CSF biomarkers for early stages of Alzheimer's disease. *Proteomics - Clin Appl*. 1:1373-1384.