Supplementary Online Content

Pase MP, Beiser AS, Himali JJ, et al. Assessment of plasma total tau level as a predictive biomarker for dementia and related endophenotypes. *JAMA Neurol*. Published online March 4, 2019. doi:10.1001/jamaneurol.2018.4666

eFigure 4. Scatterplot of Plasma Total-Tau (x-axis) Against Each Cognitive and MRI Endophenotype (y-axis) in the Framingham Heart Study

eFigure 5. Scatterplot of log Plasma P-Pau (x-axis) Against Each Cognitive and MRI Endophenotype (y-axis) in the Framingham Heart Study

eFigure 6. Distribution of Untransformed Plasma Total-Tau and Standardized log of Plasma Total-Tau by Alzheimer's Disease Status, the Presence of Microinfarcts, and the Presence of Amyloid in the Framingham Heart Study Neuropathological Outcome Sample (N=42)

eFigure 7. Scatterplot of log Plasma Total-Tau (x-axis) Against the Density of Neurofibrillary Tangles in the Medial Temporal Lobe in the Framingham Heart Study Neuropathological Outcome Sample (N=42)

eFigure 8. Scatterplot of Plasma Total-Tau Against and CSF Total-Tau in the Memento Cohort

eReferences.

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

eMethods. Methods for plasma total-tau analysis

Frozen samples that had never been thawed were sent for analysis on dry ice and were stored at -80°C upon arrival at the analysis site. Samples for analysis were marked only with a participant code and analysis for total tau (t-tau) was completed blind to all clinical information. In preparation for analysis, samples were thawed at room temperature and then mixed thoroughly until visibly homogenous following gentle inverting. Samples were spun for 30 seconds to remove any liquid from the caps. 100 µL for singlet and 130 µL for duplicate runs were transferred to 1.7-mL microcentrifuge tubes pre-labeled with barcodes corresponding to the original sample tubes. Samples were then centrifuged at 20,000g for 3 minutes at 4C and then transferred to 96-well plates for testing. The HD-1 Analyzer automatically diluted the samples 4-fold in sample diluent. Of the samples, 11.6% were run in duplicate.

eMethods. Dementia surveillance and flagging of suspected cognitive impairment

Screening for possible cognitive impairment has been performed at each Framingham Heart Study (FHS) examination cycle using the Mini-Mental State Examination (MMSE)[1] augmented by a full neuropsychological test battery at selected examination cycles. The MMSE was used to flag suspected cognitive impairment if (i) performance fell below education-based cut-off scores,[2] (ii) a decline of 3 or more points was observed between consecutive exams, or (iii) a decrease of 5 or more points was observed from the participant's highest past MMSE score. Complimentary mechanisms to flag suspected cognitive impairment included annual health status updates, review of medical and nursing home records following medical events such as emergency room visits or hospitalization, referrals of concern from outside practitioners or study investigators, cognizance for possible cognitive problems by study physicians and technologists at study visits and call back exams, and concern expressed directly by the participant or their family. Once flagged with suspected cognitive impairment, participants completed annual neurological and neuropsychological assessments until they develop dementia or were adjudicated to be normal. If assessments were suggestive of possible mild cognitive impairment (MCI) or dementia, the case was referred to our dementia review committee, comprising a neurologist and neuropsychologist.

eMethods. Methods for evaluation of dementia endophenotypes

Cognitive outcomes included tests of verbal (episodic) memory (delayed recall on Logical Memory and Paired Associates from the Weschler Memory Scales), visual memory (Visual Reproductions delayed recall from the Weschler Memory Scale), verbal reasoning (Similarities from the Weschler Adult Intelligence Scale), processing

speed (Trail Making Test part A), executive functions (Trail Making Test Part B, with the B minus A score used as the outcome), visuospatial integration (Hooper Visual Organization Test), and estimated premorbid intellectual function (Wide Range Achievement Test Third Edition, reading subtest). Scores on the Trail Making Test, Hooper Visual Organization Test, and Wide Range Achievement Test were log-transformed to normalize their distributions. Trail Making Test scores were multiplied by negative one so that higher scores on all cognitive tests indicate superior performance.

Hippocampal volumes were measured using a Siemens 1T or 1.5T field strength machine. Before the year 2005, the MRI involved a T2-weighted double spin-echo coronal imaging sequence in contiguous slices of 4mm. After this date, we used 3-dimensional T1-weighted coronal spoiled gradient-recalled echo (SPGR) acquisition and fluid-attenuated inversion recovery (FLAIR) sequences. The methods for segmentation and quantification of brain volumes have been described previously.[3-6] Image analysis was completed by a neurologist (CD), who was blind to plasma total tau levels and subject demographics.

eMethods. Neuropathological methods for evaluating tau neurofibrillary tangles, senile plaques, and microinfarcts

The Framingham Heart Study commenced a brain donation program in 1997 with optional sign on. Brains of deceased participants are received fresh (median delay of ~6 hours) with neuropathological evaluations performed by a single neuropathologist who was blinded to plasma t-tau levels and all other clinical and demographic information. Full details of our methods have been published.[7] In brief, the frontal, temporal and occipital poles are removed from one hemisphere and snap frozen at -80 C. The remaining tissue is fixed in 4% periodate-lysine-paraformaldehyde (PLP) at 4°C for at least 2 weeks. Ten micron paraffin-embedded sections are evaluated from 30 brain regions. The density of tau neurofibrillary tangles was rated in a semi-quantitative fashion using Bielschowsky silver stained sections. The medial temporal lobe structures comprised the amygdala, entorhinal cortex, and hippocampus. Neurofibrillary tangles were rated as 1+: 1-10 neurofibrillary tangles/field; 2+: 11-20 neurofibrillary tangles/field; 3+: 21-30/field; 4+ ≥31/field. All measurements were made blind to plasma t-tau scores using areas of maximum involvement at a magnification of 200× using the average count from 3 microscopic fields.[7]

Diffuse and neuritic plaque density was rated across neocortical and medial temporal regions as previously described.[7] Diffuse and neuritic plaques were rated separately according to the following: a score of 1+ corresponds to a density of 1-9 plaques per 100 × microscopic field; 2+: 10-19 per field, 3+: 20-32 per field, and 4+: >32 plaques per field. Determinations were based on the average count in 3 microscopic fields in areas of maximum involvement at 100× magnification. With respect to CERAD ratings, 1+ corresponds to sparse, 2+ corresponds to moderate, and 3+ or 4+ corresponds to frequent plaques.

Microinfarcts were defined as encephalomalacic lesions, 2 mm or smaller in greatest dimension, not identifiable on gross visual inspection. They included cavitated and non-cavitated chronic microinfarcts and microhemorrhages as defined previously.[7] The number of microinfarcts and microhemorrhages were tabulated across 5 neocortical regions and underlying white matter, hippocampus, entorhinal cortex, brainstem, and deep nuclei (i.e., caudate, putamen, globus pallidus, thalamus, and amygdala). The number of microinfarcts and microhemorrhages were scored for each region as follows: 0 = no microinfarcts; 1+ = 1-3 microinfarcts; 2+ = 4-8 microinfarcts; 3+ = 9-19 microinfarcts; 4+ = ≥20 microinfarcts.

eMethods. Overview of the Memento cohort

The Memento study is a longitudinal cohort study of dementia-free persons with subjective cognitive complaints or objective mild cognitive impairment, attending one of 29 memory clinics across France. Details regarding selection criteria and testing procedures have been described previously.[8] In brief, 2,323 participants were recruited between April 2011 and June 2014. Baseline measures include basic demography, medical history, a neurological and physical exam, medication use, cognitive and non-cognitive subjective complaints, neuropsychological testing, neuropsychiatric symptoms, lifestyle measures (i.e., physical activity), activities of daily living, brain MRI, and 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) on a subset.

Blood draw and plasma total tau analysis*:* At baseline, blood was drawn and stored in a centralized biobank (Genomic Analysis Laboratory-Biological Resource Centre [LAGCRB], Pasteur Institut Lille, BB-0033-00071). Half of the blood samples of each completed wave of the biobank are stored at Bordeaux hospital laboratory-Biological Resource Centre ("Plateforme Analytique de Recherche en Santé – Biologie Pathologie [PARS BP]"). Plasma samples used for this analysis came from PARS BP storage. Plasma t-tau was measured by

Quanterix (Lexington, MA) using a Simoa™ Tau 2.0 Kit and a Simoa HD-1 analyzer as per the protocol outlined for the Framingham Heart Study.

Lumbar puncture and cerebrospinal (CSF) analysis: Lumbar puncture was optional, with a 17% take up. We collected CSF in polypropylene tubes using an atraumatic needle under standardized conditions. CSF samples were transferred to the CSF bank within 4 hours of collection. Samples were centrifuged at 1000 × g at 4 °C for 10 minutes prior to aliquoting in polypropylene tubes (16 tubes of 250 µl) and storage at −80 °C. All tubes were stored in a centralized biobank (LAG-CRB, Pasteur Institut Lille, BB-0033-00071). Half of the CSF tubes of each completed wave of the biobank are stored at Bordeaux hospital laboratory-Biological Resource Centre ("Plateforme Analytique de Recherche en Santé – Biologie Pathologie [PARS BP]"). CSF tubes used for this analysis came from PARS BP storage. CSF total tau was measured by Quanterix (Lexington, MA) using a Simoa™ Tau 2.0 Kit and a Simoa HD-1 analyzer.

Case ascertainment for incident dementia: Follow-up for incident dementia occurred in person every 6 months with complete neuropsychological testing, clinical dementia rating, and assessment of activities of daily living. We also performed twice yearly physical and neurological exams as well as a review of medications, medical history and incident events. Such assessments alternated between examinations conducted in person and by phone (i.e., neurological exams occurred every 6 months and at least annually in person) During follow-up, suspected cases of dementia were reviewed by an independent committee. Dementia was diagnosed according to the *Diagnostic and Statistical Manual of Mental Disorders, 4th edition.*[9] A diagnosis of AD dementia was based on the criteria of the *National Institute of Neurological and Communicative Disorders and Stroke and the AD and Related Disorders Association for definite, probable, or possible AD.*[10]

eTable 1. Characteristics of the Framingham Heart Study Third Generation Participants, According to the Time of Attendance at the Exam Cycle When Blood was Drawn for Plasma Total-Tau.[a]

	Time of attendance at FHS clinic exam				
Characteristic	Late 2008 (Excluded Based on Assay)	Remainder of Sample		Late 2009	Remainder of Sample
No. of subjects	471	1778		427	1822
Demographics and clinical					
Age, yr	47±8	47±9		48±9 [c]	47±9
Male, No. (%)	211 (45)	847 (48)		214 (50)	844 (46)
College degree, No. (%)	244 (52) [b]	1028 (58)		243 (57)	1029 (56)
Total cholesterol, mg/dL	189±38	186±35		190±33 [c]	185±36
HDL cholesterol, mg/dL	61±17	59±18		60±18	60±18
BMI, kg/m^2	28±6	28±6		28±5	28±6
Smoking, No. (%)	39 (8)	170 (10)		42 (10)	167 (9)
Systolic BP, mmHg	115±13[b]	116±14		117±13	116±14
Treatment for BP, No. (%)	77 (16)	336 (19)		94 (22)	319 (18)
Prevalent DM, No. (%)	17 (4)	94 (5)		23 (5)	88 (5)
Prevalent CVD, No. (%)	13 (3)	46 (3)		9 (2)	50 (3)
APOE ε4[d], No. (%)	83 (18)†	391 (23)		89 (22)	385 (22)
Prevalent AF, No. (%)	5 (1)	22 (1)		9 (2)	18 (1)
Subclinical Outcomes					
Similarities, No. correct	17.3±3.1	17.3±3.1		17.3±3.1	17.3±3.1
Visual Reproductions, No. correct	9.0±2.5	8.8±2.6		8.8±2.7	8.9±2.6
Trial Making A, log units	0.93±0.31	0.93±0.31		0.92±0.30	0.93±0.31
Trail Making B-A, log units	-0.95±0.13	-0.96±0.14		-0.97±0.14	-0.95±0.14
LMD, No. correct	11.7±3.8 [b]	11.5±3.7		11.1±3.9 [c]	11.6±3.7
HVOT, log units	-1.38±0.50	-1.38±0.51		-1.38±0.52	-1.38±0.50
WRAT, log units	-1.91±0.59	-1.90±0.63		-1.92±0.63	-1.90±0.62
Paired Associates, No. correct	9.0±1.2	9.0±1.2		9.0±1.3	9.0±1.2
Hippocampal volume, %	0.54±0.05	0.54±0.04		0.55±0.05	0.54±0.04

[a]Plus-minus values are means ±SD.

[b]Significant difference between late 2008 and remainder of the sample groups at $p < 0.05$ after adjustments for age and sex (for demographic outcomes); age, sex, education, the time interval from blood draw to neuropsychological assessment for cognitive

outcomes; and age, sex, age squared, and the time interval from blood draw to MRI for hippocampal volume.
[c]Significant difference between late 2009 and remainder of the sample groups at p <0.05 after the same adjustments noted above.
[d]Positive for at least one APOE ε4 allele. AF = atrial fibrillation, BMI = body mass index, BP = blood pressure, CVD = cardiovascular disease, DM = diabetes mellitus, FHS = Framingham Heart Study, HDL = high density lipoprotein, HVOT = Hooper visual organization test, LMD = logical memory delayed recall, WRAT = wide range achievement test.

Summary of eTable 1. For Framingham Heart Study (FHS) Third Generation Cohort participants, the plasma t-tau assays were run in order of attendance at the second core examination cycle. Persons excluded on the basis of their assay attended the core examination in late 2008. Reasons for poor correspondence between this set of samples and phantoms may be due to technical issues with sample storage or analysis. We examined whether persons excluded on the basis of their assays differed to the larger sample. As shown in Table S2, persons excluded on the basis of their assay differed to the remainder of the sample across education, systolic blood pressure, APOE ε4 allele status, and Logical Memory performance. To provide insight as to whether these differences were random or due to extraneous confounders, we compared participants attending the FHS clinic during the same months the following year (late 2009) to the remainder of the sample. Third Generation Cohort participants attending the core examination cycle in late 2009 also differed to the remainder of the sample on logical memory scores; they also had higher total cholesterol and tended to be older. Consequently, differences between persons included and excluded based on their total tau assay may reflect random variation or seasonal differences.

eTable 2. Characteristics of the Subclinical Outcome Measures.[a]

Characteristic	Sample Score
No. of subjects[b]	3832
Episodic Memory	
Logical Memory, No. correct	11.2±3.9
Paired Associate Learning, No. correct	8.6±1.5
Verbal Reasoning	
Similarities, No. correct	17.0±3.5
Visual Memory	
Visual Reproductions, No. correct	8.2±3.2
Visuospatial Integration	
Hooper Visual Organization Test, No. correct, median (Q1, Q3)	26.0 (24.5, 27.5)
Processing speed	
Trails A, minutes to completion median (Q1, Q3)	0.43 (0.35, 0.58)
Executive Function	
Trails B-A , time difference in min, median (Q1, Q3)	0.65 (0.45, 1.00)
Premorbid function	
Wide Ranging Achievement Test, No. correct, median (Q1, Q3)	50.0 (47.0, 53.0)
Neurodegeneration	
Hippocampal volume, % of intracranial volume	0.54±0.05

[a]Plus-minus values are means ±SD

[b]No. of subjects with brain imaging for hippocampal volume was 3238.

eTable 3. Characteristics of the Study Sample With Neuropathological Analysis of Tau Neurofibrillary Tangle Burden.[a]

Characteristic	Study Sample
No. of subjects	42
Age at blood draw, yr	82±9
Male, No. (%)	21 (50)
College degree, No. (%)	17 (40)
Total cholesterol, mg/dL	186±36
HDL cholesterol, mg/dL	58±17
Body mass index, kg/m^2, median (Q1,Q3)	25 (23, 28)
Current smoker, No. (%)	1 (2)
Systolic blood pressure, mmHg	133±18
Treatment for blood pressure, No. (%)	28 (67)
Prevalent diabetes mellitus, No. (%)	3 (8)
Prevalent cardiovascular disease, No. (%)	19 (45)
APOE ε4, No. (%)[b]	9 (21)
Prevalent atrial fibrillation, No. (%)	13 (31)
Plasma total tau, pg/mL, median (Q1, Q3)	4.32 (3.56, 5.75)
Time from blood draw to death, yr	4.7±1.6

[a]Plus-minus values are means ±SD.

[b]Positive for at least one APOE ε4 allele.

HDL = high density lipoprotein, Q = quartile.

eTable 4. Characteristics of the Memento Study Sample at Baseline.

Characteristic	All participants with both plasma tau and CSF-tau available	Persons with plasma and CSF drawn on the same day
No. of subjects	367	140
Age at blood draw, yr (SD)	69 (9)	68 (9)
Female, No. (%)	217 (53)	71 (51)
College degree, No. (%)	318 (78)	103 (74)
APOE ε4, No. (%)[a]	158 (40)	50 (38)
Mild Cognitive Impairment, No. (%)	261 (64)	115 (82)
Mini Mental State Examination, No. correct	28 (2)	27 (2)
Plasma total tau, pg/mL, median (Q1, Q3)	2.0 (1.6-2.6)	2.1 (1.6-2.7)
CSF total tau, pg/mL, median (Q1, Q3)	176.5 (110.0-289.5)	148.0 (100.0-255.0)

[a]Positive for at least one APOE ε4 allele.

eTable 5. Baseline Characteristics of the Memento Study Cohort by Incident AD Dementia Status at Follow-up

Baseline Characteristics	AD dementia status during follow-up (point date :31/12/2017)	
	No AD dementia (N=121)	AD dementia (N=19)
Age at blood draw, Median (Q1-Q3)	67 (63 to 75)	73 (65 to 78)
Sex, female (%)	52	42
At least one APOE ε4 allele (%)	38	39
CDR 0.5, (%)	79	100
MMSE, Score median (Q1-Q3)	28 (27 to 29)	25 (24 to 27)
Plasma total-tau, Median (log) (Q1-Q3)	0.72 (0.42-0.95)	0.92 (0.63-1.04)
CSF total-tau, Median (log) (Q1-Q3)	4.92 (4.56-5.40)	5.56 (5.18-6.20)

Results are displayed for participants with plasma and CSF drawn on the same day. AD = Alzheimer's disease, CDR = clinical dementia rating scale, CSF = cerebrospinal fluid.

eTable 6. Plasma Total-Tau Levels, by Age and Sex.[a]

	Whole Sample			Women			Men	
Age, yr	No. of Subjects	Plasma T-Tau Levels, pg/mL		No. of Subjects	Plasma T-Tau Levels, pg/mL		No. of Subjects	Plasma T-Tau Levels, pg/mL
20-29	101	4.10 (3.39, 4.71)		55	4.22 (3.50, 5.06)		46	3.95 (3.31, 4.44)
30-39	488	4.00 (3.34, 4.67)		267	4.16 (3.52, 5.00)		221	3.80 (3.21, 4.41)
40-49	1152	3.90 (3.27, 4.64)		600	4.07 (3.42, 4.71)		552	3.67 (3.06, 4.50)
50-59	1544	3.79 (3.16, 4.57)		812	4.04 (3.43, 4.89)		732	3.51 (2.88, 4.13)
60-69	1333	3.79 (3.15, 4.60)		723	4.04 (3.40, 4.81)		610	3.50 (2.91, 4.26)
70-79	785	4.05 (3.27, 5.03)		417	4.31 (3.52, 5.19)		368	3.71 (3.08, 4.72)
80-98	386	4.66 (3.81, 5.75)		224	4.85 (3.97, 5.93)		162	4.23 (3.61, 5.57)

[a]Plasma total tau (t-tau) levels are expressed as the Median (Q1, Q3). Across the sample, the overall median value for plasma t-tau in males and females was 3.63 and 4.14 pg/mL, respectively.

eTable 7. Correlates of Plasma Total-Tau.[a]

	Plasma Total Tau Threshold			Adjusted Association with Log Plasma Total Tau [b]	
Correlates	< 4 pg/mL	≥ 4 pg/mL		β±SE	P Value
No. of subjects	3085	2704		-	-
Age, yr	57±12	59±15		-	-
Male, No. (%)	1704 (55)	987 (37)		-	-
College degree, No. (%)	1502(49)	1168 (44)		-0.02±0.01	0.05
Current smoker, No. (%)	277 (9)	272 (10)		0.01±0.01	0.61
Total cholesterol, mg/dL	189±36	183±36		-0.001±0.0001	<.001
HDL cholesterol, mg/dL	58± 18	58±18		-0.002±0.0003	<.001
BMI, kg/m^2	28±5	29±6		0.01±0.001	<.001
Systolic BP, mmHg	123±17	123±18		0.0002±0.0003	0.50
Treatment for BP, no. (%)	1071 (35)	1118 (41)		0.07±0.01	<.001
Prevalent DM, No. (%)	246 (8)	368 (14)		0.11±0.01	<.001
Prevalent CVD, No. (%)	255 (8)	352 (13)		0.13±0.01	<.001
APOE ε4, No. (%)[c]	703 (24)	562 (22)		-0.01±0.01	0.46
Prevalent AF, No. (%)	112(4)	163 (6)		0.14±0.02	<.001

[a]Plus-minus values are means ±SD.

[b]Association between each correlate and the log of plasma total tau in regression adjusted for age and sex.

[c] Positive for at least one APOE ε4 allele.

AF = atrial fibrillation, BMI = body mass index, BP = blood pressure, CVD = cardiovascular disease, DM = diabetes mellitus, HDL = high density lipoprotein

eTable 8. Cumulative Hazards and Reclassification Based on Total-Tau for the Outcome of Probable AD-Dementia

Sample	Events/ N	Cumulative Hazard (95% CI)		HR[a] (95% CI), p	Relative IDI (95% CI)	Overall NRI (95% CI)	NRI, events NRI, non-events
		Tau < median	Tau > median				
Whole Sample	93/ 1453	0.069 (0.042 to 0.113)	0.119 (0.076 to 0.186)	1.74 (1.08 to 2.78) 0.022	8.5% (4.2 to 12.5%)	0.383 (0.002 to 0.729)	0.333 0.049
APOE ε4 carriers	55/ 1148	0.036 (0.018 to 0.072)	0.067 (0.036 to 0.125)	1.87 (0.98 to 3.55) 0.057	8.8% (3.9 to 13.7)	0.537 (0.050 to 0.888)	0.505 0.032
APOE ε4 non-carriers	38/ 305	0.317 (0.102 to 0.462)	0.407 (0.186 to 0.891)	1.87 (0.91-3.85) 0.087	15.7% (5.0 to 27.4)	0.200 (-0.343 to 0.992)	0.068 0.132

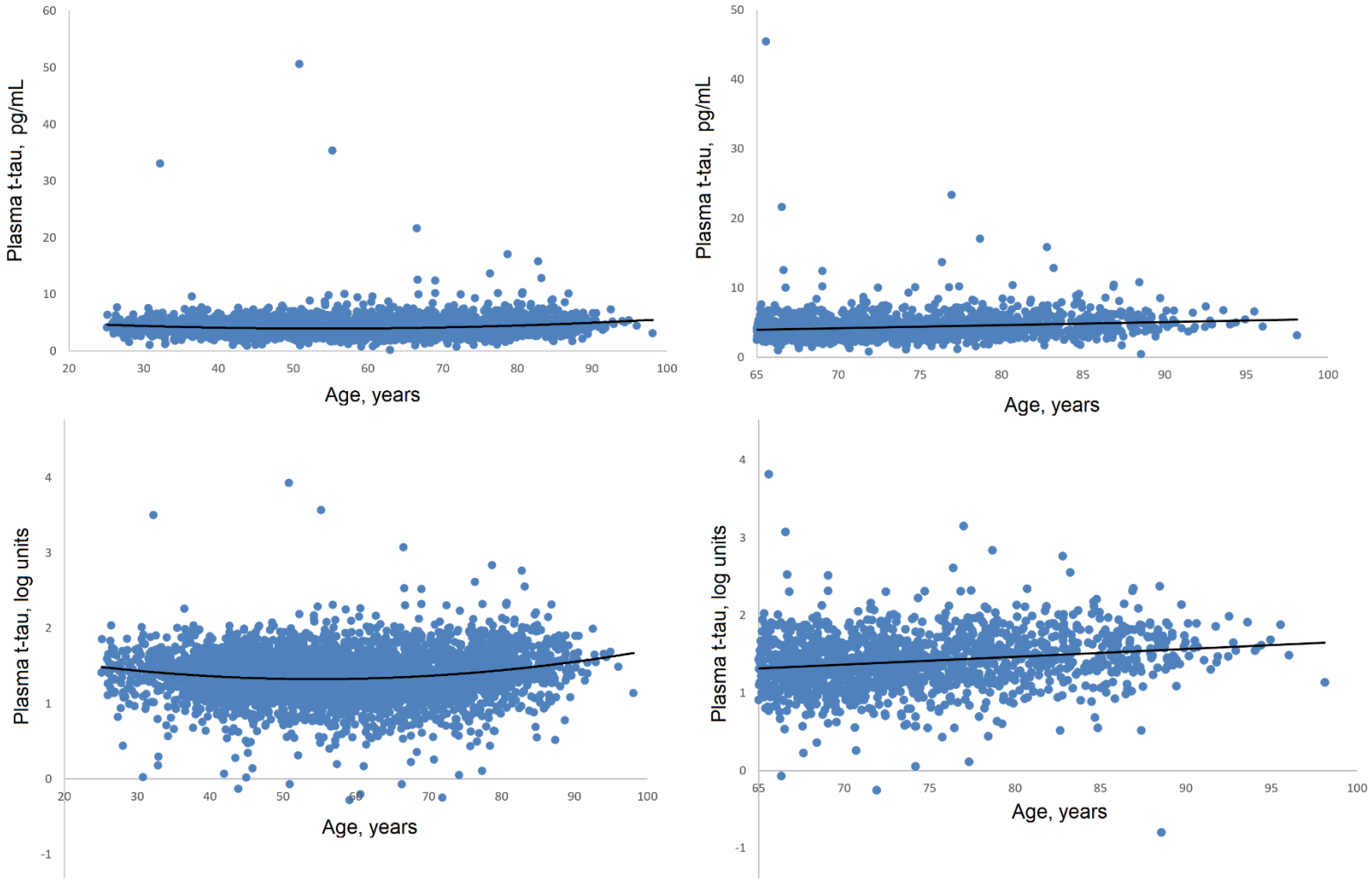
The median value for plasma t-tau was 4.09pg/mL. All models are adjusted for age and sex. For the whole sample, there were 26 events of probable AD-dementia (of n=726) below the median and 67 events of probable AD-dementia (of n=727) above the median. Among APOE ε4 non-carriers, there were 13 events of probable AD-dementia (of n=561) below the median and 42 events of probable AD-dementia (of n=587) above the median. Among APOE ε4 carriers, there were 13 events of probable AD-dementia (of n=165) below the median and 25 events of probable AD-dementia (of n=140) above the median.

[a]The HR is for persons with plasma t-tau values above the median versus below the median.

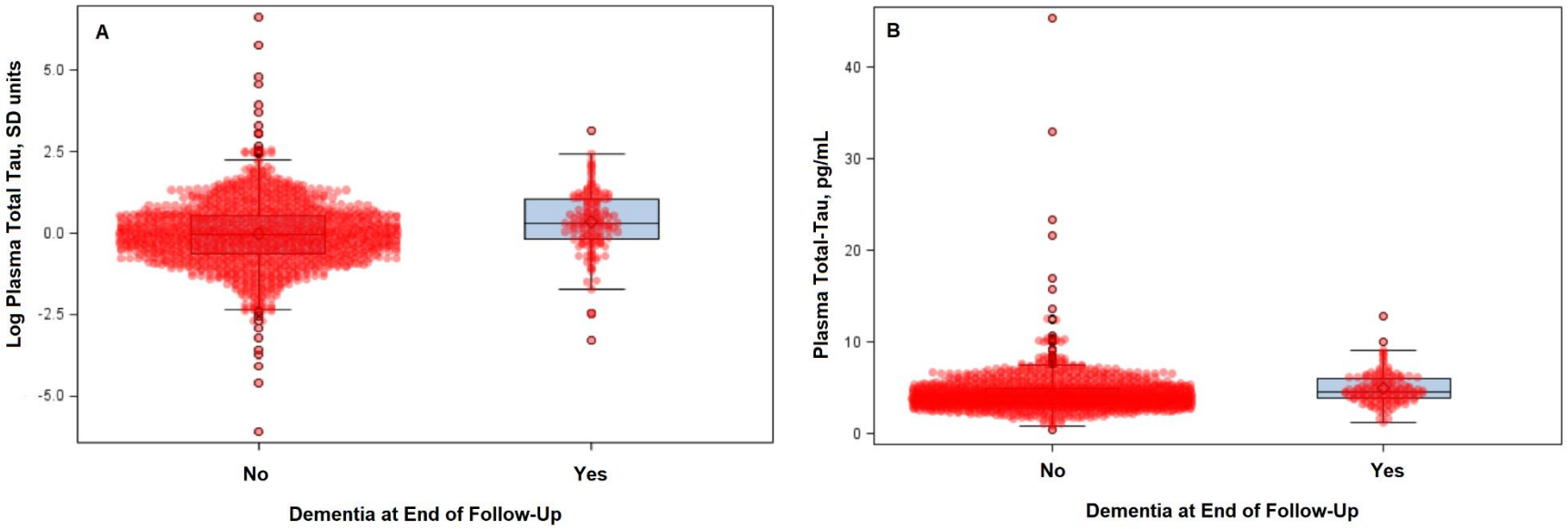
eTable 9. Sample Size Estimates for a Dementia Prevention Trial Using Biomarker Enrichment Based on Plasma Total-Tau and APOE Status

Trial Duration	5 years			10 Years	
Outcome	All-dementia	AD dementia		All-dementia	AD dementia
	N (% of whole sample)	N (% of whole sample)		N (% of whole sample)	N (% of whole sample)
Selection criteria					
Whole sample	8756 (100)	14618 (100)		3348 (100)	4362 (100)
APOE ε4+	4360 (50)	5460 (37)		1656 (49)	1798 (41)
Plasma t-tau>median & APOE ε4+	2712 (31)	2896 (20)		1220 (36)	1480 (34)
Plasma t-tau>median	5460 (62)	7292 (50)		2280 (68)	2714 (62)

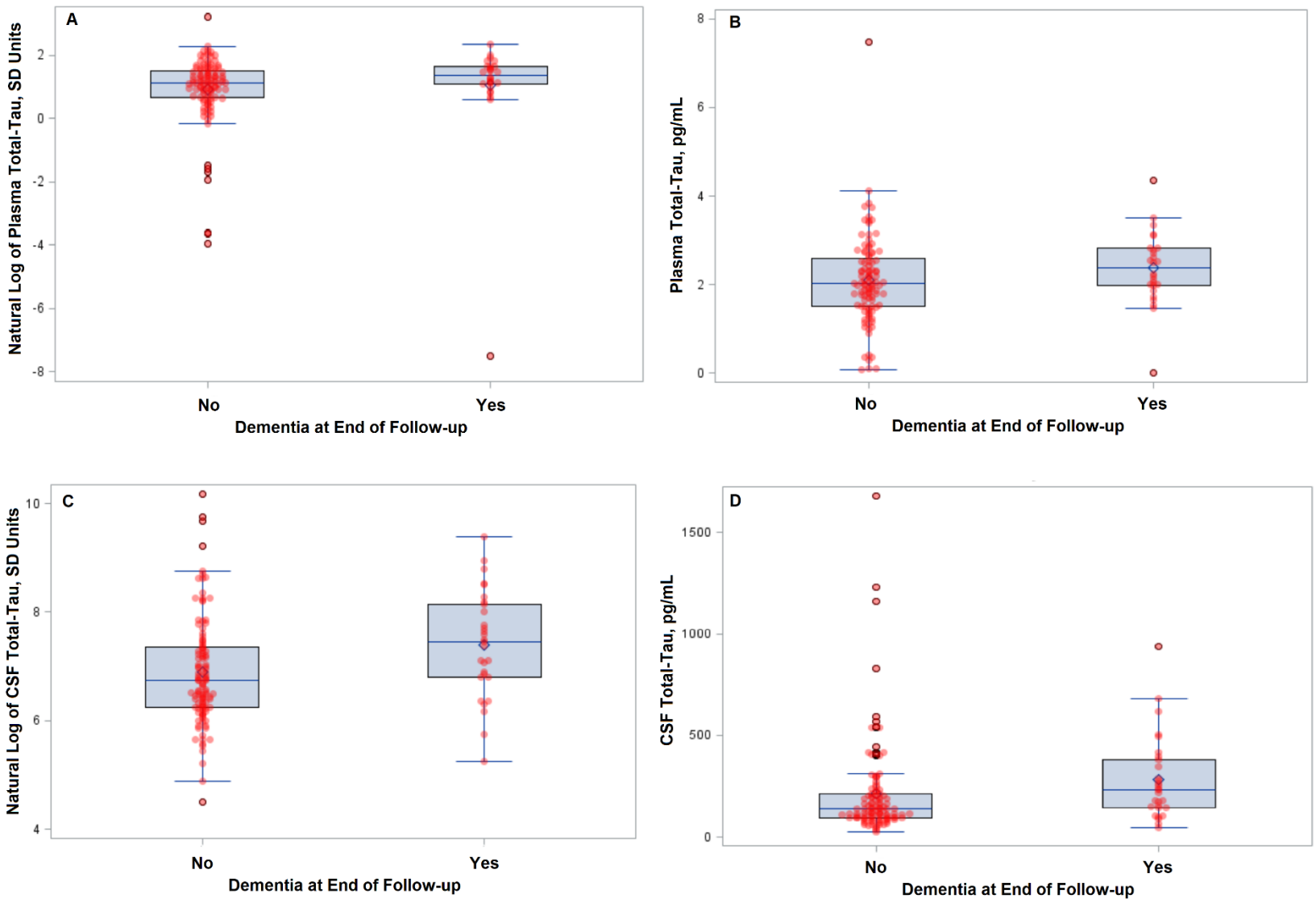
Note: Table displays the sample size needed to generate 80% power for a dementia prevention trial with a treatment effect of at least 0.25 (i.e. a 25% reduction in event rate: Hazard Ratio ≤ 0.75) and with alpha set at 0.05 (two-tailed). Estimates are displayed for trials of 5-years and 10-years duration with both all-dementia and AD-dementia as outcomes. Estimates rely on the event rates observed in our Framingham Heart Study dementia analysis sample. The median value for plasma t-tau was 4.09pg/mL.
APOE ε4 allele = the presence of at least one APOE ε4 allele.



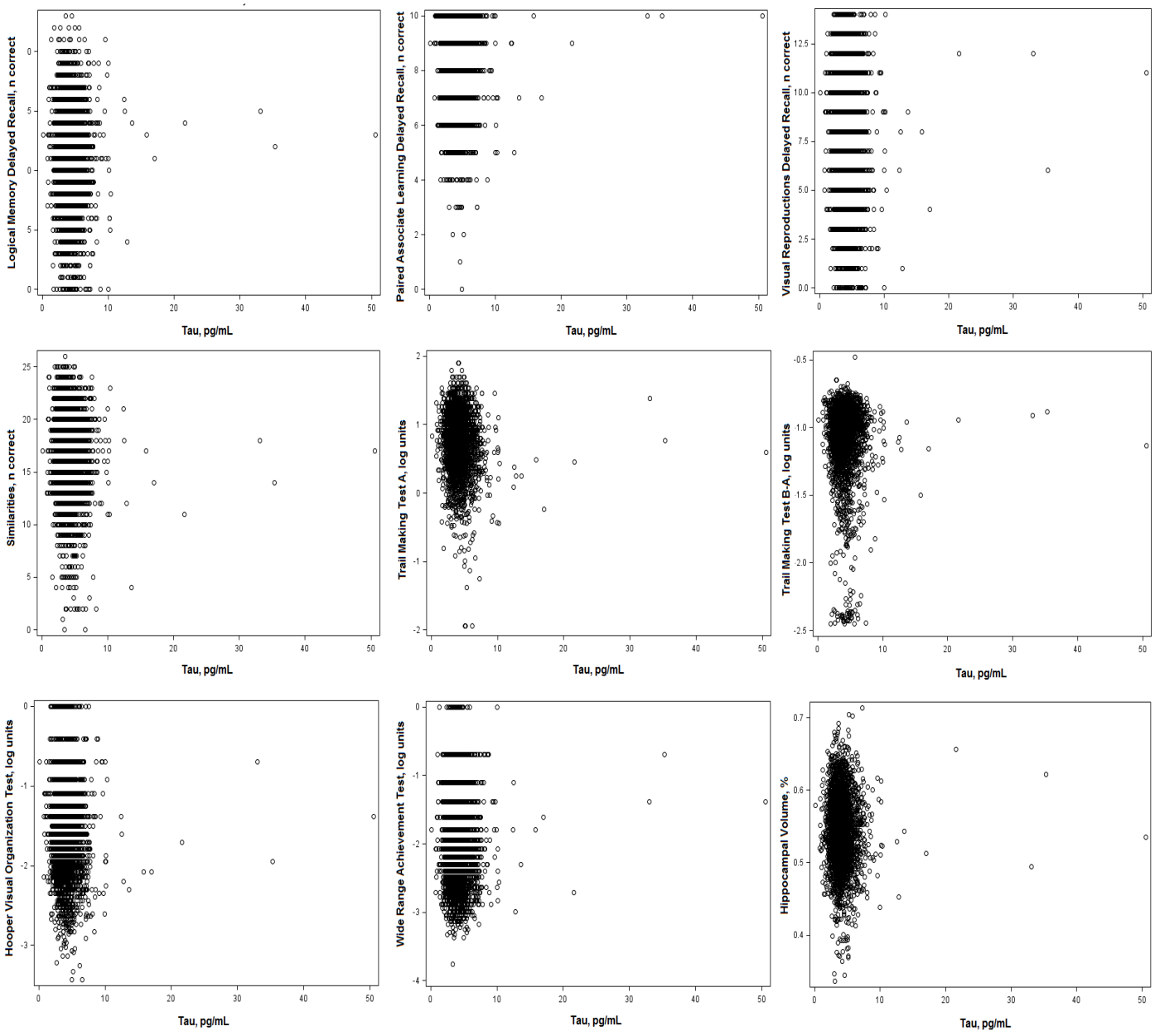
eFigure 1. Scatterplot of Age Against Plasma Total-Tau in the Framingham Heart Study Larger Sample Studied for Cognition and Hippocampal Volume (left) and the Subset Older Than Age 65 Studied for Risk of Dementia (right). In the larger sample, plasma t-tau was associated with both age (β±SE=0.005±0.001, p<0.0001) and age squared (β±SE=0.0006±0.0005, p<0.0001). In the dementia study sample, plasma t-tau was associated with age (β±SE=0.03±0.004, p<0.0001) but not age squared (β±SE =0.0004±0.0005, p=0.38).



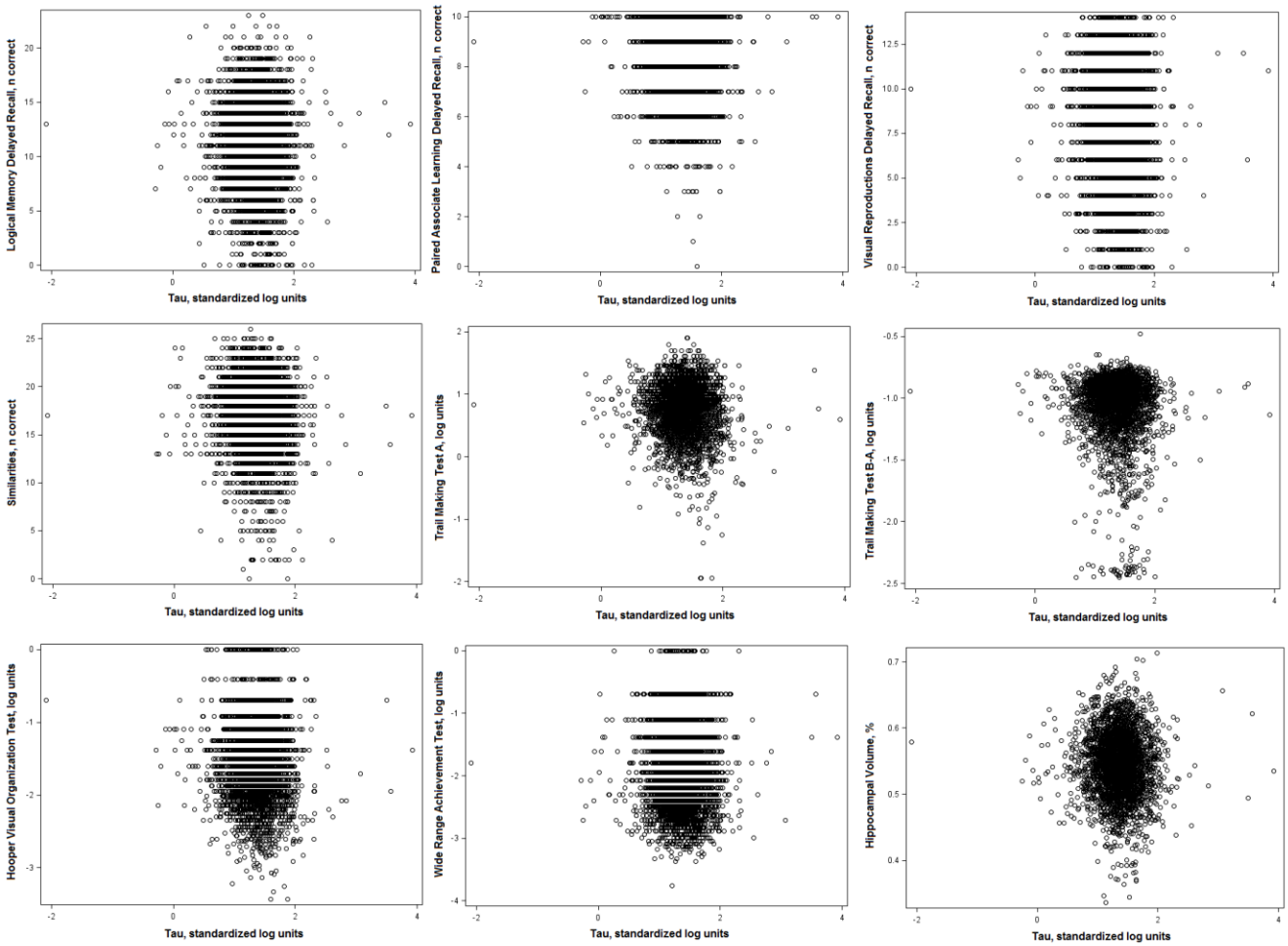
eFigure 2. Distribution of (A) log Plasma Total-Tau and (B) Untransformed Plasma Total-Tau by Incident Dementia Status in the Framingham Heart Study.



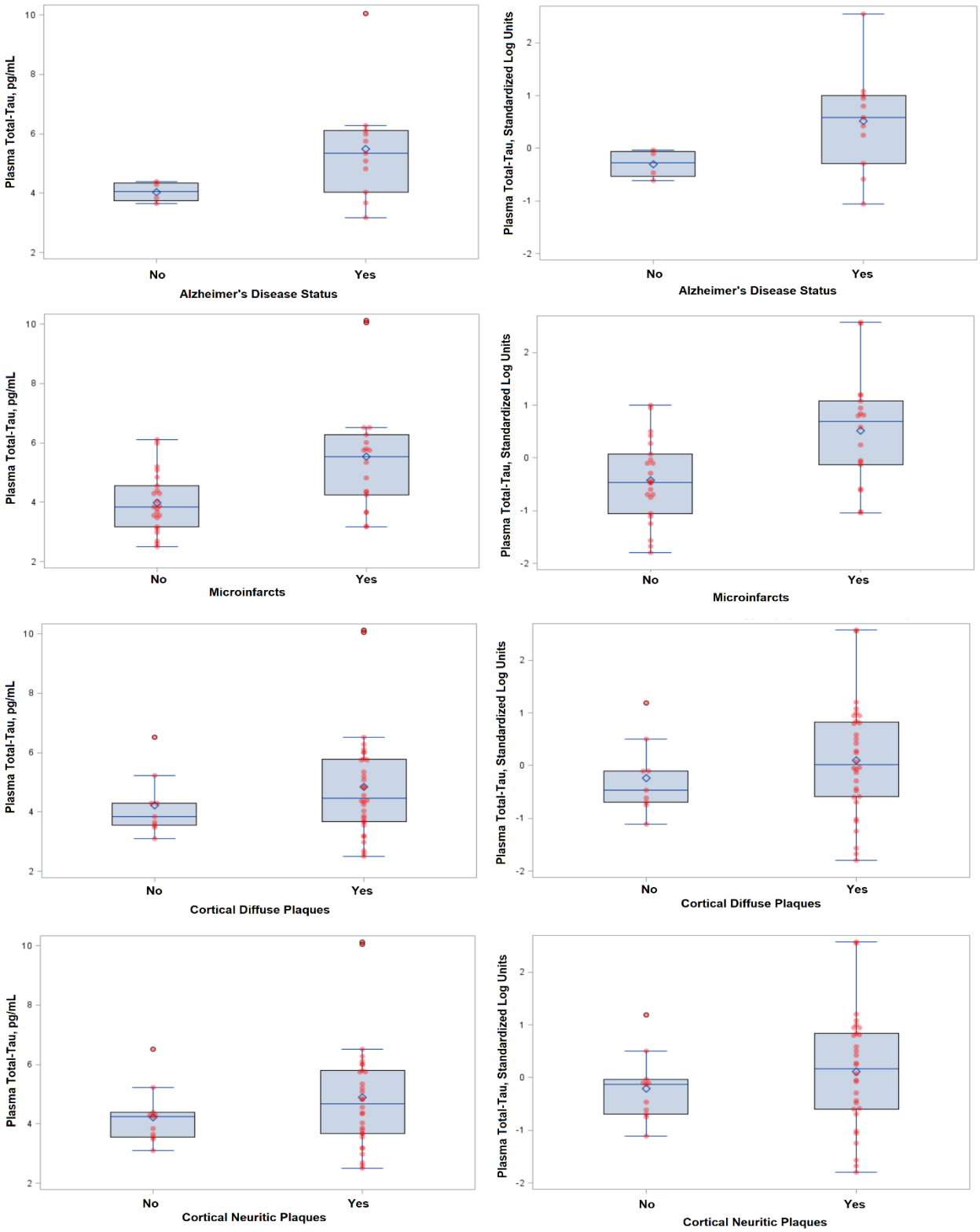
eFigure 3. Distribution of (A) log Plasma Total-Tau, (B) Untransformed Plasma Total-Tau, (C), Standardized log of CSF Total-Tau, and (D) Untransformed CSF Total-Tau by Incident Dementia Status in the Memento Cohort.



eFigure 4. Scatterplot of Plasma Total-Tau (x-axis) Against Each Cognitive and MRI Endophenotype (y-axis) in the Framingham Heart Study. Values of plasma t-tau were left raw (untransformed). Trail Making scores are inverse transformed such that higher scores indicate superior task performance

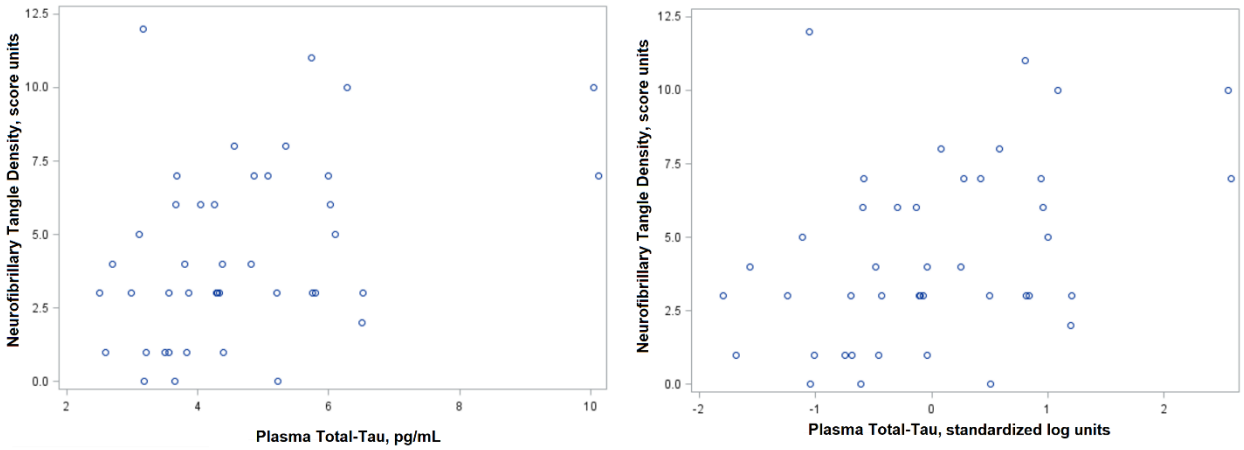


eFigure 5. Scatterplot of log Plasma Total-Tau (x-axis) Against Each Cognitive and MRI Endophenotype (y-axis) in the Framingham Heart Study. Values of plasma t-tau were log transformed and standardized. Trail Making scores are inverse transformed such that higher scores indicate superior task performance.

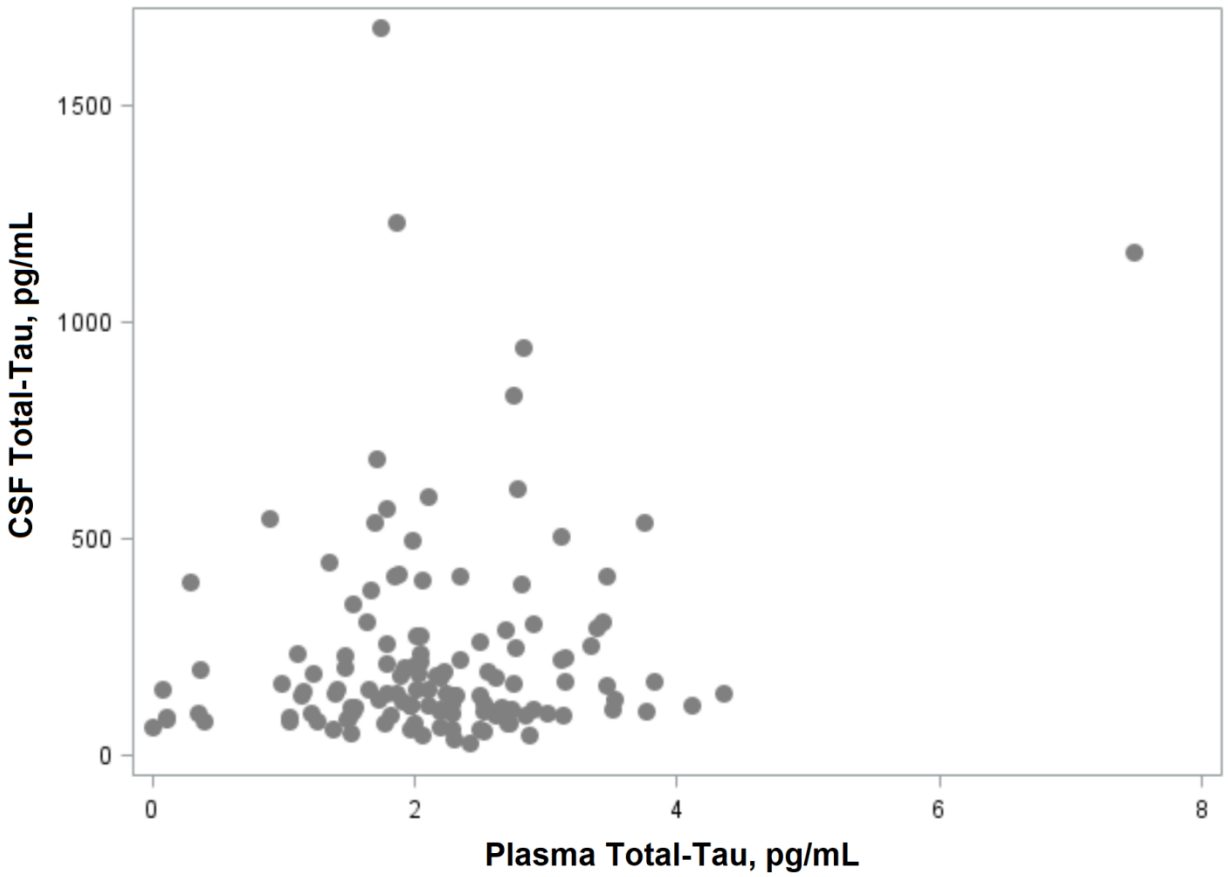


eFigure 6. Distribution of Untransformed Plasma Total-Tau and Standardized log of Plasma Total-Tau by Alzheimer's Disease Status, the Presence of

Microinfarcts, and the Presence of Amyloid in the Framingham Heart Study Neuropathological Outcome Sample.



eFigure 7. Scatterplot of Plasma Total-Tau Against the Density of Neurofibrillary Tangles in the Medial Temporal Lobe in the Framingham Heart Study Neuropathological Outcome Sample (N=42).



eFigure 8. Scatterplot of Plasma Against CSF Total-Tau in the Memento Cohort.

eReferences

1. Folstein MF, Folstein SE, McHugh PR. 'Mini mental state'. A practical method for grading the cognitive state of patients for the clinician. Journal of Psychiatric Research 1975;12:189-98.

2. Bachman DL, Wolf PA, Linn R, et al. Prevalence of dementia and probable senile dementia of the Alzheimer type in the Framingham Study. Neurology 1992;42:115-9.

3. DeCarli C, Fletcher E, Ramey V, Harvey D, Jagust WJ. Anatomical mapping of white matter hyperintensities (WMH): exploring the relationships between periventricular WMH, deep WMH, and total WMH burden. Stroke 2005;36:50-5.

4. Fletcher E, Carmichael O, Decarli C. MRI non-uniformity correction through interleaved bias estimation and B-spline deformation with a template. Conference proceedings : Annual International Conference of the IEEE Engineering in Medicine and Biology Society IEEE Engineering in Medicine and Biology Society Conference 2012;2012:106-9.

5. Fletcher E, Singh B, Harvey D, Carmichael O, Decarli C. Adaptive image segmentation for robust measurement of longitudinal brain tissue change. Conference proceedings : Annual International Conference of the IEEE Engineering in Medicine and Biology Society IEEE Engineering in Medicine and Biology Society Conference 2012;2012:5319-22.

6. Aljabar P, Heckemann RA, Hammers A, Hajnal JV, Rueckert D. Multi-atlas based segmentation of brain images: Atlas selection and its effect on accuracy. NeuroImage 2009;46:726-38.

7. Au R, Seshadri S, Knox K, et al. The Framingham Brain Donation Program: Neuropathology Along the Cognitive Continuum. Current Alzheimer research 2012;9:673-86.

8. Dufouil C, Dubois B, Vellas B, et al. Cognitive and imaging markers in non-demented subjects attending a memory clinic: study design and baseline findings of the MEMENTO cohort. Alzheimers Research & Therapy 2017;9:67.

9. American Psychatric Association. Diagnostic and Statistical Manual of Mental Disorders 4th ed. Text Revision. 4th ed. Arlington, VA2000.

10. McKhann G, Drachman D, Folstein M. Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA work group under the auspices of Department of Health and Human Services Task Force on Alzheimer's disease. Neurology 1984;34:939-44.