SUPPLEMENTAL MATERIAL

Data S1.

Supplemental Methods

Outcomes

Primary outcome*:* Starting at examination five, all participants were systematically screened for the development of dementia via the Mini-Mental State Examination (MMSE) and annual health status updates, and starting from examination seven, all participants were invited to complete an MRI brain and neuropsychological testing. If a participant, family member, or Framingham study physician was concerned about cognitive impairment, or the Mini-Mental State Examination (MMSE) score was below the education-based cutoff, three points lower than the preceding examination, or five points lower than the participant's previous highest recorded score, more in-depth cognitive testing was performed.[27] Participants with suspected cognitive impairment who did not meet diagnostic criteria for dementia underwent additional yearly neuropsychological assessments between the scheduled Offspring examinations.

Secondary outcomes: Removal of non-brain tissues: The skull is removed using an atlas-based method[28] followed by human quality control to provide generally minor cleanup if needed. Structural MRI brain images are then nonlinearly registered performed by a cubic B-spline deformation[29] to a minimal deformation template (MDT) synthetic brain image.[30] Image intensity inhomogeneity correction: B1 field inhomogeneity is a common problem that limits the precision of image segmentation. We utilize a template-based iterative method for correcting field inhomogeneity bias.[31] Gray matter, white matter and CSF measurement: our segmentation algorithm is based on an expectation-maximization (EM) algorithm that iteratively refines its segmentation estimates to produce outputs that are most consistent with the input intensities from the native-space T1 images along with a model of image smoothness.[32, 33] The segmentation yielded by these appearance models alone is refined using a Markov random field (MRF) model based on an adaptive priors model.[33] The MRF-based segmentation at the final iteration is used as the final output segmentation. Total brain volume (TBV) is defined as supratentorial brain volume as a percentage of the intracranial volume determined from coronal sections. White matter hyperintensity (WMH) is performed on a combination of FLAIR and 3D T1 images using a modified Bayesian probability structure based on a previously published method of histogram fitting.[34] Prior probability maps for WMH were created from more than 700 individuals with semi-automatic detection of WMH followed by manual editing. Likelihood estimates of the native image are calculated through histogram segmentation and thresholding. All segmentation is initially performed in standard space resulting in probability likelihood values of WMH at each voxel in the white matter. These probabilities are then thresholded at 3.5 SD above the mean to create a binary WMH mask. Further segmentation is based on a modified Bayesian approach that combines image likelihood estimates, spatial priors and tissue class constraints. The segmented WMH masks are then back-transformed on to native space for tissue volume calculation. Volumes are log-transformed to normalize population variance. The automatic hippocampal segmentation method employs a standard atlas based diffeomorphic approach,[35] with the minor modification of label refinement. We further modified this approach to include the European Alzheimer's Disease Consortium-Alzheimer's Disease Neuroimaging Initiative harmonized hippocampal masks using the following approach: 1) Subject image pre-processing with extraction of intracranial cavity, non-uniformity correction, tissue classification as discussed above; 2) Atlas Registration of all EADC-ADNI hippocampal masks[36-40] to each subject; 3) Atlas Fusion utilizing multi-atlas label fusion;[41, 42] and 4) Intensity-based label refinement. Covert brain infarcts (CBI): the presence of MRI infarction was determined from the size, location and imaging characteristics of the lesion. The image analysis system allowed for superimposition of the subtraction image, the proton density image and the T2 weighted image at three times magnified view to assist in interpretation of lesion characteristics. Signal void, best seen on the T2 weighted image, was interpreted to indicate a vessel. Only lesions 3mm or larger qualified for consideration as cerebral infarcts. Other necessary imaging characteristics included: 1) CSF density on the subtraction image, and 2) if the stroke was in the basal ganglia area, distinct separation from the circle of Willis vessels. Kappa values for agreement amongst the three raters are generally good and range from 0.73 to 0.90.[43, 44] Imaging data was centrally processed at the Imaging of Dementia and Aging (IDeA) laboratory located at UC Davis and analyzed by operators blinded to all participant characteristics including cognitive performance on neuropsychological testing.

The global cognitive performance outcome was created using principal component analysis and forcing a single score solution, combining weighted loadings for the individual cognitive tests described above.

Table S1. Baseline characteristics according to clinical cut-offs for NT-proBNP.

Variable No. (%)	**NT-proBNP** **0 to <125 pg/mL** **(n=377)**	**NT-proBNP** **125 to <300 pg/mL** **(n=468)**	**NT-proBNP** **≥300 pg/mL** **(n=745)**
Age, y, mean (SD)	66.4 (4.8)	67.5 (5.3)	70.6 (5.8)
Women	137 (36.3)	253 (54.1)	447 (60.0)
Systolic blood pressure, mmHg, mean (SD)	129.7 (15.7)	130.3 (17.3)	134.9 (21.3)
BMI, kg/m^2, median (Q1, Q3)	28.4 (25.8-31.8)	27.4 (24.8-30.8)	26.9 (24.1-30.4)
GDF15, pg/mL, median (Q1, Q3)	687.0 (878.0, 2640.0)	696.5 (579.0, 906.5)	858.0 (671.0, 1150.0)
Education			
No high school degree	21 (5.8)	20 (4.4)	60 (8.3)
High school degree	124 (34.0)	152 (33.5)	247 (34.0)
Some years of college	102 (28.0)	142 (31.3)	205 (28.2)
College degree	118 (32.3)	140 (30.9)	214 (29.5)
Anti-hypertensive medication	128 (34.0)	177 (37.9)	393 (52.8)
Current smoker	35 (9.3)	46 (9.9)	53 (7.1)
ApoE4 allele	75 (20.2)	97 (21.2)	181 (24.5)
Prevalent CVD	34 (9.0)	48 (10.3)	217 (29.1)
Atrial fibrillation	6 (1.6)	14 (3.0)	75 (10.1)
Stroke	7 (1.9)	7 (1.5)	27 (3.6)
CHF	2 (0.5)	1 (0.2)	23 (3.1)
eGFR, ml/min, median (Q1, Q3)	81.5 (70.4-90.0)	79.9 (69.6, 88.5)	72.8 (62.6, 84.5)
Diabetes mellitus	60 (16.2)	67 (14.5)	133 (18.0)

GDF15, growth differentiation factor 15; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; SD, standard deviation; CVD, cardiovascular disease; APOE E4, apolipoprotein E4 allele; CHF, congestive heart failure; eGFR, estimated glomerular filtration rate.

Table S2. GDF15 and NT-proBNP and risk of incident dementia and AD, excluding those with prior stroke.

	Dementia						Alzheimer's disease					
	Model 1		Model 2		Model 3		Model 1		Model 2		Model 3	
Biomarker	**HR (95% CI)**	**P-value**	**HR (95% CI)**	**P-value**	**HR (95% CI)**	**P-value**	**HR (95% CI)**	**P-value**	**HR (95% CI)**	**P-value**	**HR (95% CI)**	**P-value**
GDF15												
Per SDU increase	1.57 (1.30-1.91)	<0.001	1.57 (1.23-1.99)	<0.001	1.46 (1.14-1.88)	0.003	1.47 (1.16-1.85)	0.001	1.39 (1.05-1.85)	0.02	1.30 (0.97-1.74)	0.08
T2 versus T1	1.25 (0.77-2.02)	0.36	1.34 (0.82-2.19)	0.25	1.25 (0.76-2.05)	0.38	0.93 (0.53-1.61)	0.79	0.99 (0.57-1.75)	0.98	0.94 (0.53-1.66)	0.83
T3 versus T1	2.46 (1.57-3.86)	<0.001	2.38 (1.46-3.89)	<0.001	2.11 (1.27-3.51)	0.004	2.26 (1.38-3.71))	0.001	2.08 (1.21-3.59)	0.008	1.91 (1.09-3.35)	0.02
NT-proBNP												
Per SDU increase	1.47 (1.19-1.80)	<0.001	1.39 (1.10-1.75)	0.005	1.31 (1.04-1.65)	0.02	1.41 (1.10-1.80)	0.006	1.30 (0.99-1.70)	0.06	1.24 (0.95-1.63)	0.11
T2 versus T1	1.04 (0.65-1.67)	0.87	0.99 (0.61-1.62)	0.97	0.94 (0.57-1.53)	0.79	1.09 (0.64-1.87)	0.74	1.00 (0.57-1.74)	0.99	0.96 (0.55-1.67)	0.89
T3 versus T1	1.97 (1.27-3.05)	0.002	1.79 (1.12-2.86)	0.02	1.57 (0.96-2.54)	0.07	1.74 (1.04-2.89)	0.03	1.51 (0.87-2.61)	0.14	1.35 (0.77-2.39)	0.30

GDF15, growth differentiation factor 15; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; HR, hazard ratio; CI, confidence interval; ; T1, tertile 1; T2, tertile 2; T3, tertile 3

Model 1: adjusted for age and sex.

Model 2: adjusted for age, sex, education, systolic blood pressure, use of antihypertensive medication, body mass index, current smoking, estimated glomerular filtration rate, prevalent diabetes mellitus, prevalent cardiovascular disease and ApoE4 carrier status

Model 3: Model 2 + adjustment for GDF15 (NT-proBNP analysis) and NT-ProBNP (GDF15 analysis)GDF15 and NT-proBNP were natural logarithmically transformed and standardized

Table S3. GDF15 and NT-proBNP and risk of incident dementia and AD, excluding those with CHF.

	Dementia						Alzheimer's disease					
	Model 1		Model 2		Model 3		Model 1		Model 2		Model 3	
Biomarker	**HR (95% CI)**	**P-value**	**HR (95% CI)**	**P-value**	**HR (95% CI)**	**P-value**	**HR (95% CI)**	**P-value**	**HR (95% CI)**	**P-value**	**HR (95% CI)**	**P-value**
GDF15												
Per SDU increase	1.59 (1.31-1.92)	<0.001	1.54 (1.21-1.95)	<0.001	1.44 (1.13-1.84)	0.004	1.49 (1.19-1.88)	<0.001	1.37 (1.03-1.81)	0.03	1.28 (0.96-1.70)	0.10
T2 versus T1	1.20 (0.75-1.94)	0.45	1.28 (0.78-2.08)	0.33	1.22 (0.75-2.01)	0.43	0.94 (0.54-1.64)	0.83	0.99 (0.56-1.74)	0.97	0.95 (0.54-1.69)	0.87
T3 versus T1	2.51 (1.62-3.91)	<0.001	2.38 (1.46-3.88)	<0.001	2.18 (1.32-3.60)	0.002	2.41 (1.48-3.93)	<0.001	2.14 (1.24-3.68)	0.006	2.00 (1.14-3.50)	0.02
NT-proBNP												
Per SDU increase	1.41 (1.15-1.74)	0.001	1.35 (1.07-1.71)	0.01	1.28 (1.02-1.62)	0.04	1.36 (1.07-1.74)	0.01	1.28 (0.98-1.68)	0.07	1.24 (0.94-1.62)	0.13
T2 versus T1	0.91 (0.57-1.44)	0.68	0.81 (0.50-1.32)	0.39	0.77 (0.47-1.24)	0.28	0.97 (0.57-1.63)	0.90	0.82 (0.47-1.42)	0.48	0.79 (0.46-1.36)	0.39
T3 versus T1	1.84 (1.20-2.81)	0.005	1.70 (1.07-2.69)	0.03	1.50 (0.94-2.41)	0.09	1.68 (1.02-2.75)	0.04	1.48 (0.87-2.54)	0.15	1.35 (0.77-2.34)	0.29

GDF15, growth differentiation factor 15; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; HR, hazard ratio; CI, confidence interval; T1, tertile 1; T2, tertile 2; T3, tertile 3

Model 1: adjusted for age and sex.

Model 2: adjusted for age, sex, education, systolic blood pressure, use of antihypertensive medication, body mass index, current smoking, estimated glomerular filtration rate, prevalent diabetes mellitus, prevalent cardiovascular disease and ApoE4 carrier status.

Model 3: Model 2 + adjustment for GDF15 (NT-proBNP analysis) and NT-ProBNP (GDF15 analysis)

GDF15 and NT-proBNP were natural logarithmically transformed and standardized

Table S4. Risk of incident dementia and AD dementia by NT-proBNP clinical cut-offs.

	Dementia				Alzheimer's disease dementia			
	Model 1		Model 2		Model 1		Model 2	
NT-proBNP	**HR (95% CI)**	**P-value**	**HR (95% CI)**	**P-value**	**HR (95% CI)**	**P-value**	**HR (95% CI)**	**P-value**
0-124.9 pg/mL	ref		ref		ref		ref	
125-299.9 pg/mL	1.14 (0.61-2.12)	0.68	1.32 (0.69-2.52)	0.41	1.27 (0.62-2.63)	0.51	1.42 (0.67-3.00)	0.36
≥300 pg/mL	1.66 (0.95-2.92)	0.08	1.63 (0.89-2.99)	0.11	1.57 (0.80-3.07)	0.20	1.48 (0.73-3.03)	0.28

Model 1: adjusted for age and sex.
Model 2: adjusted for age, sex, education, systolic blood pressure, use of antihypertensive medication, body mass index, current smoking, estimated glomerular filtration rate, prevalent diabetes mellitus, prevalent cardiovascular disease and ApoE4 carrier status.
NT-proBNP was natural logarithmically transformed and standardized.

Table S5. Summary meta-analysis.

	FHS		Hisayama		Combined meta-analysis		
	N	HR (95% CI)	N	HR (95% CI)	N	HR (95% CI)	p
Dementia	1590	1.40 (1.14, 1.71)	1635	1.43 (1.29, 1.59)	3225	1.42 (1.30, 1.56)	<0.001
AD Dementia	1590	1.34 (1.06, 1.70)	1635	1.30 (1.13, 1.49)	3225	1.31 (1.16, 1.48)	<0.001

Model adjusted for age and sex.
NT-proBNP was natural logarithmically transformed and standardized.

Table S6. Model discrimination and risk reclassification following addition of GDF15 and NT-proBNP.

	Dementia				Alzheimer's disease dementia			
	C-statistic (95% CI)	Relative IDI (95% CI)	Overall NRI (95% CI)	*NRI, events NRI, nonevents	C-statistic (95% CI)	Relative IDI Statistic (95% CI)	Overall NRI Statistic (95% CI)	*NRI, events NRI, nonevents
Model 2	0.81 (0.77-0.84)	-	-	-	0.85 (0.81-0.88)	-	-	-
Model 2 + GDF15	0.82 (0.78-0.85)	0.11 (0.04-0.18)	0.27 (0.06-0.48)	0.18 0.09	0.85 (0.81-0.88)	0.06 (0.02-0.11)	0.29 (0.06-0.52)	0.22 0.07
Model 2 + NT-proBNP	0.81 (0.77-0.85)	0.05 (0.01-0.09)	0.21 (0.02-0.40)	0.19 0.02	0.85 (0.81-0.88)	0.02 (-0.004-0.05)	0.18 (-0.03-0.40)	0.19 -0.01
Model 2 + GDF15 and NT-proBNP	0.82 (0.78-0.85)	0.15 (0.07-0.24)	0.25 (0.05-0.45)	0.18 0.07	0.85 (0.81-0.88)	0.08 (0.03-0.14)	0.18 (-0.06-0.41)	0.16 0.02

IDI, integrated discrimination improvement; NRI, net reclassification improvement; GDF15, growth differentiation factor 15; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; CI, confidence interval.
Model 2: adjusted for age, sex, education, systolic blood pressure, use of antihypertensive medication, body mass index, current smoking, estimated glomerular filtration rate, prevalent diabetes mellitus, prevalent cardiovascular disease and ApoE4 carrier status.
GDF15 and NT-proBNP were natural logarithmically transformed and standardized
* Proportion of events correctly reclassified
Proportion of non-events correctly reclassified
† Versus model 2

Table S7. GDF15, NT-proBNP and neuropsychological test performance.

	Global cognition (weighted score units)		Similarities (n correct)		Visual Reproductions (n correct after delay)		Logical Memory (n correct after delay)		Trail Making B-A (min)†		Hooper Visual Organization Test**	
Biomarker	β±SE	p-value	β±SE	p-value	β±SE	p-value	β±SE	p-value	β±SE	p-value	β±SE	p-value
GDF15												
Per SDU increase*	-0.08±0.02	0.002	-0.20±0.10	0.04	-0.24±0.09	0.009	0.04±0.10	0.72	-0.01±0.01	0.12	-0.03±0.01	0.02
T2 versus T1	0.03±0.04	041	0.01±0.16	0.95	0.12±0.16	0.45	0.33±0.17	0.05	0.01±0.01	0.50	0.02±0.03	0.50
T3 versus T1	-0.11±0.04	0.01	-0.26±0.17	0.13	-0.35±0.17	0.04	0.13±0.19	0.49	-0.02±0.01	0.17	-0.04±0.03	0.12
NT-proBNP												
Per SDU increase*	-0.04±0.02	0.03	-0.14±0.08	0.07	-0.16±0.08	0.04	-0.04±0.08	0.65	-0.01±0.01	0.31	-0.01±0.01	0.39
T2 versus T1	0.01±0.04	0.76	0.11±0.16	0.50	0.03±0.16	0.85	0.10±0.17	0.57	-0.002±0.01	0.86	0.03±0.03	0.31
T3 versus T1	-0.07±0.04	0.09	-0.17±0.17	0.30	-0.38±0.16	0.02	0.03±0.18	0.87	-0.01±0.01	0.33	-0.02±0.03	0.36

GDF15, growth differentiation factor 15; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; SDU, Standard deviation units; SE, Standard error. Model: adjusted for age, age squared, sex, education, time from blood draw to neuropsychological testing, systolic blood pressure, use of antihypertensive medication, body mass index, current smoking, estimated glomerular filtration rate, prevalent diabetes mellitus and prevalent cardiovascular disease.
*Natural log transformed and standardized
†Natural log transformed to restore normality (higher scores indicate better performance)

Table S8. GDF15, NT-proBNP and annualized change in neuropsychological test performance.

	Global cognition		Similarities		Visual Reproductions		Logical Memory		Trail Making B-A		Hooper Visual Organization Test	
Biomarker	β±SE	p-value	β±SE	p-value	β±SE	p-value	β±SE	p-value	β±SE	p-value	β±SE	p-value
GDF15												
Per SDU increase*	-0.06±0.02	0.008	-0.03±0.02	0.14	-0.03±0.02	0.17	-0.05±0.02	0.046	0.02±0.01	0.002	-0.06±0.02	0.0002
T2 versus T1	-0.03±0.04	0.51	-0.02±0.03	0.54	-0.02±0.03	0.43	-0.02±0.04	0.67	-0.004±0.01	0.75	-0.03±0.02	0.23
T3 versus T1	-0.11±0.04	0.009	-0.04±0.03	0.23	-0.03±0.03	0.31	-0.05±0.04	0.24	0.02±0.01	0.11	-0.09±0.03	0.001
NT-proBNP												
Per SDU increase*	-0.02±0.02	0.26	-0.02±0.02	0.35	0.02±0.01	0.29	-0.02±0.02	0.25	-0.003±0.01	0.60	-0.03±0.01	0.02
T2 versus T1	-0.02±0.04	0.67	0.003±0.03	0.92	0.003±0.03	0.93	-0.01±0.04	0.75	-0.005±0.01	0.69	-0.03±0.02	0.28
T3 versus T1	-0.04±0.04	0.30	-0.02±0.03	0.46	0.04±0.03	0.21	-0.04±0.04	0.28	-0.004±0.01	0.76	-0.06±0.03	0.02

GDF15, growth differentiation factor 15; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; SDU, Standard deviation units; SE, Standard error.
Model: adjusted for age, age squared, sex, education, time from blood draw to neuropsychological testing, systolic blood pressure, use of antihypertensive medication, body mass index, current smoking, estimated glomerular filtration rate, prevalent diabetes mellitus and prevalent cardiovascular disease.
*Natural log transformed and standardized
†Natural log transformed