SUPPLEMENTAL MATERIAL

Table S1. Risk of dementia and its subtypes according to quartiles of serum NT-proBNP, 2002 to 2012.

NT-proBNP (pg/mL)	Persons at risk	No. of events	Hazard ratio (95% CI)		
			Model 1	Model 2	Model 3
All-cause dementia					
Q1 (≤45)	407	35	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q2 (46–82)	405	81	1.88 (1.26–2.81)	1.78 (1.19–2.67)	1.79 (1.19–2.67)
Q3 (83–153)	414	105	2.12 (1.43–3.14)	1.87 (1.26–2.79)	1.88 (1.27–2.80)
Q4 (≥154)	409	156	3.40 (2.32–5.00)	2.75 (1.84–4.12)	2.84 (1.89–4.26)
P for trend			<0.001	<0.001	<0.001
Alzheimer's disease					
Q1 (≤45)	407	21	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q2 (46–82)	405	59	2.09 (1.27–3.46)	1.98 (1.20–3.29)	1.98 (1.20–3.29)
Q3 (83–153)	414	71	2.08 (1.26–3.43)	1.92 (1.16–3.17)	1.94 (1.17–3.20)
Q4 (≥154)	409	96	3.05 (1.86–4.99)	2.81 (1.68–4.70)	2.98 (1.78–4.97)
P for trend			<0.001	<0.001	<0.001
Vascular dementia					
Q1 (≤45)	407	9	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q2 (46–82)	405	19	1.95 (0.88–4.34)	1.84 (0.83–4.12)	1.85 (0.83–4.13)
Q3 (83–153)	414	22	2.12 (0.96–4.70)	1.74 (0.78–3.88)	1.75 (0.79–3.89)
Q4 (≥154)	409	52	5.58 (2.66–11.70)	3.71 (1.70–8.11)	3.76 (1.72–8.23)
P for trend			<0.001	<0.001	<0.001

CI, confidence interval; NT-proBNP, N-terminal pro-B-type natriuretic peptide.
Model 1: adjusted for age and sex.
Model 2: adjusted for age, sex, education level, systolic blood pressure, use of antihypertensive agents, use of heart disease agents, diabetes mellitus, hypercholesterolemia, body mass index, estimated glomerular filtration rate, atrial fibrillation, history of stroke, smoking habit, alcohol intake, and regular exercise.
Model 3: adjusted for the covariates included in model 2 plus serum high-sensitivity C-reactive protein.

Table S2. Risk of dementia with and without incident cardiovascular disease during follow-up period according to serum NT-proBNP levels among subjects without a history of cardiovascular disease and/or dementia at baseline, 2002 to 2012.

NT-proBNP (pg/mL)	Persons at risk	No. of events	Hazard ratio (95% CI)		
			Model 1	Model 2	Model 3
Incident dementia without cardiovascular disease*					
≤54	488	39	1.00 (reference)	1.00 (reference)	1.00 (reference)
55–124	563	120	1.98 (1.37–2.86)	1.87 (1.29–2.72)	1.87 (1.29–2.70)
125–299	305	90	2.22 (1.50–3.30)	1.85 (1.23–2.78)	1.90 (1.27–2.85)
≥300	156	49	3.03 (1.95–4.70)	2.68 (1.67–4.32)	2.82 (1.75–4.56)
P for trend			<0.001	<0.001	<0.001
1-SD increment in log (serum NT-proBNP levels)	1,512	298	1.41 (1.25–1.59)	1.40 (1.21–1.62)	1.43 (1.24–1.66)
Incident dementia with cardiovascular disease†					
≤54	488	7	1.00 (reference)	1.00 (reference)	1.00 (reference)
55–124	563	10	1.28 (0.48–3.45)	1.14 (0.42–3.08)	1.14 (0.42–3.09)
125–299	305	11	2.52 (0.93–6.88)	1.79 (0.63–5.09)	1.80 (0.63–5.12)
≥300	156	8	4.19 (1.42–12.37)	2.72 (0.77–9.62)	2.74 (0.77–9.77)
P for trend			0.004	0.10	0.10
1-SD increment in log (serum NT-proBNP levels)	1,512	36	1.59 (1.17–2.17)	1.34 (0.90–2.00)	1.34 (0.90–2.00)

CI, confidence interval; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SD, standard deviation.
The SD of log-transformed NT-proBNP levels (pg/mL) was 1.035.
The exclusion criteria of this analysis were subjects with dementia at baseline, subjects with cardiovascular disease at baseline, and subjects without available serum for measuring the serum NT-proBNP level.
* Incident dementia without cardiovascular disease was defined as the development of dementia without incident cardiovascular disease before the onset of dementia during follow-up.
† Incident dementia with cardiovascular disease was defined as the development of cardiovascular disease and subsequent dementia during the follow-up period.
Model 1: adjusted for age and sex.
Model 2: adjusted for age, sex, education level, systolic blood pressure, use of antihypertensive agents, use of heart disease agents, diabetes mellitus, hypercholesterolemia, body mass index, estimated glomerular filtration rate, atrial fibrillation, smoking habit, alcohol intake, and regular exercise.
Model 3: adjusted for the covariates included in model 2 plus high-sensitivity C-reactive protein.

Table S3. Risk of dementia with and without incident diabetes mellitus during the follow-up period according to serum NT-proBNP levels among subjects without a history of diabetes and/or dementia at baseline, 2002 to 2012.

NT-proBNP (pg/mL)	Persons at risk	No. of events	Hazard ratio (95% CI)		
			Model 1	Model 2	Model 3
Incident dementia without diabetes mellitus*					
≤54	400	40	1.00 (reference)	1.00 (reference)	1.00 (reference)
55–124	455	100	1.57 (1.08–2.29)	1.45 (1.00–2.12)	1.45 (0.99–2.11)
125–299	257	81	1.81 (1.21–2.70)	1.42 (0.94–2.15)	1.45 (0.96–2.19)
≥300	143	48	2.65 (1.70–4.13)	1.97 (1.21–3.22)	2.03 (1.24–3.32)
P for trend			<0.001	0.02	0.01
1-SD increment in log (serum NT-proBNP levels)	1,255	269	1.41 (1.24–1.60)	1.33 (1.14–1.56)	1.35 (1.15–1.59)
Incident dementia with diabetes mellitus†					
≤54	400	3	1.00 (reference)	1.00 (reference)	1.00 (reference)
55–124	455	9	2.64 (0.70–9.99)	2.53 (0.66–9.65)	2.52 (0.66–9.60)
125–299	257	7	3.95 (0.96–16.18)	3.76 (0.90–15.69)	3.79 (0.91–15.81)
≥300	143	6	9.18 (2.18–38.62)	9.89 (2.17–45.11)	10.07 (2.19–46.23)
P for trend			0.002	0.003	0.003
1-SD increment in log (serum NT-proBNP levels)	1,255	25	1.65 (1.14–2.41)	1.86 (1.17–2.97)	1.89 (1.17–3.04)

CI, confidence interval; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SD, standard deviation.

The SD of log-transformed NT-proBNP levels (pg/mL) was 1.062.

The exclusion criteria of this analysis were subjects with dementia at baseline, subjects with diabetes mellitus at baseline, and subjects without available serum for measuring the serum NT-proBNP level.

* Incident dementia without diabetes mellitus was defined as the development of dementia without incident diabetes mellitus before the onset of dementia during follow-up.

† Incident dementia with diabetes mellitus was defined as the development of diabetes mellitus and subsequent dementia during the follow-up period.

Model 1: adjusted for age and sex.

Model 2: adjusted for age, sex, education level, systolic blood pressure, use of antihypertensive agents, use of heart disease agents, hypercholesterolemia, body mass index, estimated glomerular filtration rate, atrial fibrillation, history of stroke, smoking habit, alcohol intake, and regular exercise.

Model 3: adjusted for the covariates included in model 2 plus high-sensitivity C-reactive protein.

Table S4. Reclassification of the 10-year predicted absolute risk of development of dementia, 2002 to 2012.

	Basic model*+ log (NT-proBNP)			
	Participants, n			
Basic model*	<25% risk	25–50% risk	>50% risk	Total
Participants who developed dementia				
<25% risk	85	13	0	98
25–50% risk	6	108	20	134
>50% risk	0	5	140	145
Total	91	126	160	377
Participants who did not develop dementia				
<25% risk	786	35	0	819
25–50% risk	38	232	17	287
>50% risk	0	17	135	152
Total	824	282	152	1,258

Net reclassification improvement was estimated as 0.062 (Z_{NRI}=3.21, *P*=0.001).
NT-proBNP, N-terminal pro-B-type natriuretic peptide.
* The basic model included age, sex, education level, systolic blood pressure, use of antihypertensive agents, diabetes mellitus, hypercholesterolemia, body mass index, estimated glomerular filtration rate, atrial fibrillation, history of stroke, smoking habit, alcohol intake, regular exercise, and serum high-sensitivity C-reactive protein.

Table S5. Predictive ability, reclassification, and discrimination of dementia by serum NT-proBNP, 2002 to 2012.

	Harrell's c-statistics	*P* value for Harrell's c-statistics difference	Continuous NRI (95% CI)	*P* value for NRI	IDI (95% CI)	*P* value for IDI
Framingham risk score*	0.749	<0.001	0.190 (0.076–0.305)	0.001	0.017 (0.007–0.026)	<0.001
Framingham risk score*+log (serum NT-proBNP levels)	0.767					
CAIDE risk score†	0.568	<0.001	0.427 (0.314–0.540)	<0.001	0.058 (0.042–0.073)	<0.001
CAIDE risk score†+log (serum NT-proBNP levels)	0.686					

CI, confidence interval; IDI, integrated discrimination improvement; NRI, net reclassification improvement; NT-proBNP, N-terminal pro-B-type natriuretic peptide.
***** The Framingham risk score included age, marital status, body mass index, stroke, diabetes, and cancer (ischemic attack omitted).
† The CAIDE risk score included age, education status, sex, systolic blood pressure, body mass index, total cholesterol, and physical activity.

Table S6. Risk of dementia and its subtypes according to serum NT-proBNP levels, after the exclusion of subjects whose events occurred within 3 years after baseline, 2002 to 2012.

NT-proBNP (pg/mL)	Persons at risk	No. of events	Hazard ratio (95% CI)		
			Model 1	Model 2	Model 3
All-cause dementia					
≤54	514	51	1.00 (reference)	1.00 (reference)	1.00 (reference)
55–124	595	121	1.70 (1.21–2.37)	1.57 (1.12–2.19)	1.56 (1.12–2.19)
125–299	336	88	1.83 (1.27–2.64)	1.49 (1.03–2.17)	1.53 (1.05–2.22)
≥300	190	42	2.34 (1.53–3.57)	1.79 (1.11–2.89)	1.83 (1.13–2.97)
P for trend			<0.001	0.03	0.01
Alzheimer's disease					
≤54	514	28	1.00 (reference)	1.00 (reference)	1.00 (reference)
55–124	595	89	2.05 (1.33–3.17)	2.00 (1.30–3.09)	1.99 (1.29–3.08)
125–299	336	59	1.89 (1.18–3.04)	1.72 (1.06–2.78)	1.77 (1.09–2.87)
≥300	190	25	2.27 (1.30–3.96)	2.04 (1.10–3.77)	2.12 (1.14–3.94)
P for trend			0.01	0.045	0.03
Vascular dementia					
≤54	514	13	1.00 (reference)	1.00 (reference)	1.00 (reference)
55–124	595	26	1.70 (0.86–3.35)	1.48 (0.75–2.92)	1.48 (0.75–2.91)
125–299	336	29	3.27 (1.64–6.50)	2.28 (1.12–4.65)	2.34 (1.15–4.76)
≥300	190	11	3.13 (1.36–7.16)	1.84 (0.70–4.84)	1.88 (0.71–4.95)
P for trend			<0.001	0.048	0.04

CI, confidence interval; NT-proBNP, N-terminal pro-B-type natriuretic peptide.
Model 1: adjusted for age and sex.
Model 2: adjusted for age, sex, education level, systolic blood pressure, use of antihypertensive agents, use of heart disease agents, diabetes mellitus, hypercholesterolemia, body mass index, estimated glomerular filtration rate, atrial fibrillation, history of stroke, smoking habit, alcohol intake, and regular exercise.
Model 3: adjusted for the covariates included in model 2 plus serum high-sensitivity C-reactive protein.

Table S7. Risk of dementia and its subtypes according to serum NT-proBNP levels, after the exclusion of subjects with cancer or chronic renal failure, 2002 to 2012.

NT-proBNP (pg/mL)	Persons at risk	No. of events	Hazard ratio (95% CI)		
			Model 1	Model 2	Model 3
All-cause dementia					
≤54	476	51	1.00 (reference)	1.00 (reference)	1.00 (reference)
55–124	547	127	1.70 (1.22–2.37)	1.59 (1.14–2.22)	1.58 (1.13–2.20)
125–299	299	102	2.03 (1.43–2.90)	1.65 (1.14–2.38)	1.69 (1.17–2.43)
≥300	160	61	3.10 (2.10–4.57)	2.62 (1.72–4.00)	2.72 (1.78–4.17)
P for trend			<0.001	<0.001	<0.001
Alzheimer's disease					
≤54	476	29	1.00 (reference)	1.00 (reference)	1.00 (reference)
55–124	547	93	2.01 (1.31–3.06)	1.95 (1.27–2.98)	1.93 (1.26–2.96)
125–299	299	67	2.01 (1.27–3.17)	1.82 (1.14–2.91)	1.90 (1.19–3.04)
≥300	160	31	2.51 (1.48–4.24)	2.53 (1.44–4.44)	2.81 (1.59–4.95)
P for trend			0.002	0.005	0.001
Vascular dementia					
≤54	476	13	1.00 (reference)	1.00 (reference)	1.00 (reference)
55–124	547	26	1.58 (0.80–3.10)	1.43 (0.72–2.81)	1.42 (0.72–2.81)
125–299	299	34	3.45 (1.76–6.74)	2.40 (1.19–4.81)	2.40 (1.20–4.84)
≥300	160	24	5.85 (2.89–11.84)	3.63 (1.67–7.92)	3.64 (1.67–7.94)
P for trend			<0.001	<0.001	<0.001

CI, confidence interval; NT-proBNP, N-terminal pro-B-type natriuretic peptide.
Model 1: adjusted for age and sex.
Model 2: adjusted for age, sex, education level, systolic blood pressure, use of antihypertensive agents, use of heart disease agents, diabetes mellitus, hypercholesterolemia, body mass index, estimated glomerular filtration rate, atrial fibrillation, history of stroke, smoking habit, alcohol intake, and regular exercise.
Model 3: adjusted for the covariates included in model 2 plus serum high-sensitivity C-reactive protein.

Table S8. Risk of dementia and its subtypes according to serum NT-proBNP levels, after the exclusion of subjects with hormone replacement therapy, 2002 to 2012.

NT-proBNP (pg/mL)	Persons at risk	No. of events	Hazard ratio (95% CI)		
			Model 1	Model 2	Model 3
All-cause dementia					
≤54	514	55	1.00 (reference)	1.00 (reference)	1.00 (reference)
55–124	592	141	1.76 (1.28–2.42)	1.67 (1.21–2.30)	1.67 (1.21–2.29)
125–299	336	111	2.03 (1.44–2.85)	1.65 (1.16–2.34)	1.69 (1.19–2.40)
≥300	190	70	3.02 (2.08–4.38)	2.38 (1.58–3.58)	2.46 (1.63–3.72)
P for trend			<0.001	<0.001	<0.001
Alzheimer's disease					
≤54	514	32	1.00 (reference)	1.00 (reference)	1.00 (reference)
55–124	592	104	2.04 (1.36–3.05)	2.01 (1.34–3.01)	2.00 (1.33–3.00)
125–299	336	75	2.03 (1.32–3.14)	1.82 (1.17–2.84)	1.90 (1.22–2.96)
≥300	190	36	2.42 (1.47–3.97)	2.23 (1.31–3.82)	2.43 (1.41–4.16)
P for trend			0.001	0.01	0.003
Vascular dementia					
≤54	514	13	1.00 (reference)	1.00 (reference)	1.00 (reference)
55–124	592	28	1.73 (0.89–3.37)	1.58 (0.81–3.08)	1.58 (0.81–3.08)
125–299	336	35	3.53 (1.82–6.88)	2.51 (1.26–5.00)	2.52 (1.26–5.04)
≥300	190	26	5.92 (2.95–11.91)	3.54 (1.63–7.69)	3.56 (1.64–7.73)
P for trend			<0.001	<0.001	<0.001

CI, confidence interval; NT-proBNP, N-terminal pro-B-type natriuretic peptide.
Model 1: adjusted for age and sex.
Model 2: adjusted for age, sex, education level, systolic blood pressure, use of antihypertensive agents, use of heart disease agents, diabetes mellitus, hypercholesterolemia, body mass index, estimated glomerular filtration rate, atrial fibrillation, history of stroke, smoking habit, alcohol intake, and regular exercise.
Model 3: adjusted for the covariates included in model 2 plus serum high-sensitivity C-reactive protein.