

Supplementary Table S1. Hazard ratios and 95% confidence intervals of all-cause dementia and its subtypes according to serum total homocysteine levels after excluding participants who developed dementia within the first two years of follow-up

Serum total homocysteine levels ($\mu\text{mol/L}$)	No. of events/ subjects	Hazard ratio (95% confidence interval)			
		Age- and sex-adjusted	P	Multivariable-adjusted*	P
All-cause dementia					
Quintile 1 (≤ 6.4)	51/326	1.00 (reference)		1.00 (reference)	
Quintile 2 (6.5–7.6)	53/296	1.14 (0.77–1.67)	0.52	1.19 (0.80–1.77)	0.38
Quintile 3 (7.7–9.0)	64/328	1.18 (0.81–1.72)	0.39	1.28 (0.87–1.90)	0.21
Quintile 4 (9.1–11.4)	68/300	1.27 (0.87–1.86)	0.22	1.36 (0.90–2.05)	0.15
Quintile 5 (≥ 11.5)	92/294	2.13 (1.46–3.12)	<0.001	2.31 (1.49–3.56)	<0.001
P for trend†		<0.001		<0.001	
Alzheimer's disease					
Quintile 1 (≤ 6.4)	37/326	1.00 (reference)		1.00 (reference)	
Quintile 2 (6.5–7.6)	38/296	1.15 (0.73–1.81)	0.55	1.21 (0.76–1.93)	0.42
Quintile 3 (7.7–9.0)	43/328	1.15 (0.73–1.80)	0.55	1.14 (0.72–1.83)	0.58
Quintile 4 (9.1–11.4)	45/300	1.19 (0.76–1.88)	0.44	1.23 (0.75–2.03)	0.41
Quintile 5 (≥ 11.5)	59/294	1.98 (1.26–3.13)	0.003	2.04 (1.20–3.48)	0.009
P for trend†		0.001		0.004	
Vascular dementia					
Quintile 1 (≤ 6.4)	14/326	1.00 (reference)		1.00 (reference)	
Quintile 2 (6.5–7.6)	9/296	0.68 (0.29–1.59)	0.38	0.71 (0.30–1.70)	0.45
Quintile 3 (7.7–9.0)	17/328	1.08 (0.52–2.24)	0.84	1.47 (0.68–3.21)	0.33
Quintile 4 (9.1–11.4)	17/300	1.14 (0.54–2.41)	0.73	1.34 (0.59–3.01)	0.48
Quintile 5 (≥ 11.5)	25/294	2.07 (0.99–4.34)	0.054	2.31 (0.98–5.45)	0.057
P for trend†		0.007		0.01	

*Adjusted for age, sex, education, hypertension, diabetes, serum total cholesterol, body mass index, estimated glomerular filtration rate, history of stroke, current smoking, current drinking, regular exercise, serum albumin, serum folate, and serum vitamin B12 levels (log-transformed).

†Trend tests were conducted by treating the quintiles as a continuous variable and assigning the midpoint concentration for each quintile.

Supplementary Table S2. Hazard ratios and 95% confidence intervals of all-cause dementia and its subtypes according to serum total homocysteine levels after excluding participants who did not fast overnight prior to blood sample collection

Serum total homocysteine levels ($\mu\text{mol/L}$)	No. of events/ subjects	Hazard ratio (95% confidence interval)			
		Age- and sex-adjusted	P	Multivariable-adjusted*	P
All-cause dementia					
Quintile 1 (≤ 6.4)	53/327	1.00 (reference)		1.00 (reference)	
Quintile 2 (6.5–7.6)	53/293	1.11 (0.76–1.63)	0.58	1.19 (0.81–1.76)	0.37
Quintile 3 (7.7–9.0)	67/330	1.16 (0.80–1.67)	0.44	1.29 (0.88–1.90)	0.19
Quintile 4 (9.1–11.4)	76/305	1.31 (0.91–1.89)	0.15	1.42 (0.96–2.11)	0.08
Quintile 5 (≥ 11.5)	105/298	2.18 (1.51–3.16)	<0.001	2.45 (1.61–3.75)	<0.001
P for trend†		<0.001		<0.001	
Alzheimer's disease					
Quintile 1 (≤ 6.4)	39/327	1.00 (reference)		1.00 (reference)	
Quintile 2 (6.5–7.6)	37/293	1.08 (0.69–1.70)	0.73	1.14 (0.72–1.81)	0.57
Quintile 3 (7.7–9.0)	45/330	1.10 (0.71–1.70)	0.67	1.14 (0.72–1.80)	0.58
Quintile 4 (9.1–11.4)	49/305	1.19 (0.76–1.84)	0.45	1.27 (0.79–2.06)	0.33
Quintile 5 (≥ 11.5)	64/298	1.93 (1.24–3.02)	0.004	2.11 (1.25–3.56)	0.005
P for trend†		0.001		0.001	
Vascular dementia					
Quintile 1 (≤ 6.4)	14/327	1.00 (reference)		1.00 (reference)	
Quintile 2 (6.5–7.6)	9/293	0.70 (0.30–1.63)	0.41	0.78 (0.33–1.86)	0.58
Quintile 3 (7.7–9.0)	17/330	1.08 (0.52–2.23)	0.84	1.50 (0.70–3.23)	0.30
Quintile 4 (9.1–11.4)	19/305	1.23 (0.59–2.53)	0.58	1.36 (0.62–2.98)	0.44
Quintile 5 (≥ 11.5)	35/298	2.64 (1.31–5.34)	0.007	2.86 (1.27–6.45)	0.01
P for trend†		<0.001		0.001	

*Adjusted for age, sex, education, hypertension, diabetes, serum total cholesterol, body mass index, estimated glomerular filtration rate, history of stroke, current smoking, current drinking, regular exercise, serum albumin, serum folate, and serum vitamin B12 levels (log-transformed).

†Trend tests were conducted by treating the quintiles as a continuous variable and assigning the midpoint concentration for each quintile.

Supplementary Table S3. Hazard ratios and 95% confidence intervals of all-cause dementia according to serum total homocysteine levels in subgroups

Subgroups	No. of events	No. of subjects	HR (95% CI)*	P	P for heterogeneity
Overall	372	1588	1.79 (1.38–2.33)	<0.001	
Age					
<75 years	152	1095	2.33 (1.45–3.71)	<0.001	0.34
≥75 years	220	493	1.78 (1.29–2.47)	<0.001	
Sex					
Female	237	912	1.84 (1.29–2.63)	<0.001	0.73
Male	135	676	1.58 (1.05–2.40)	0.03	
Education					
>9 years	125	750	2.11 (1.34–3.33)	0.001	0.03
≤9 years	247	838	1.58 (1.13–2.20)	0.007	
Hypertension					
No	125	648	1.53 (0.91–2.56)	0.11	0.72
Yes	247	940	1.85 (1.36–2.53)	<0.001	
Diabetes					
No	292	1239	2.00 (1.49–2.69)	<0.001	0.33
Yes	80	349	1.22 (0.66–2.26)	0.53	
Serum total cholesterol					
<5.69 mmol/L	275	1119	1.68 (1.24–2.27)	<0.001	0.38
≥5.69 mmol/L	97	469	2.53 (1.45–4.41)	0.001	
Body mass index					
<25 kg/m ²	293	1163	1.82 (1.36–2.44)	<0.001	0.15
≥25 kg/m ²	79	425	1.48 (0.74–2.93)	0.27	
eGFR					
≥60 mL/min/1.73 m ²	284	1361	1.67 (1.20–2.31)	0.002	0.59
<60 mL/min/1.73 m ²	88	227	1.61 (1.00–2.61)	0.05	
History of stroke					
No	340	1507	1.82 (1.34–2.47)	<0.001	0.65
Yes	32	81	0.88 (0.33–2.34)	0.79	
Current smoking					
No	320	1356	1.84 (1.38–2.45)	<0.001	0.73
Yes	52	232	1.08 (0.52–2.25)	0.83	
Current drinking					
No	264	1021	1.64 (1.19–2.26)	0.002	0.63
Yes	108	567	2.02 (1.22–3.34)	0.006	
Regular exercise					
<3 times/week	329	1385	1.77 (1.34–2.35)	<0.001	0.69
≥3 times/week	43	203	2.03 (0.85–4.83)	0.11	
Serum albumin					

≤4.3 g/dL†	235	909	1.89 (1.34–2.65)	<0.001	0.75
>4.3 g/dL†	137	679	1.69 (1.07–2.67)	0.02	
Serum folate					
≤4.8 ng/mL†	186	783	1.42 (1.00–2.04)	0.05	0.10
>4.8 ng/mL†	186	805	2.89 (1.91–4.37)	<0.001	
Serum vitamin B12					
≤458 pg/mL†	193	793	1.82 (1.30–2.54)	<0.001	0.94
>458 pg/mL†	179	795	1.46 (0.93–2.29)	0.10	

Abbreviations: HR, Hazard ratios; CI, confidence interval; eGFR, estimated glomerular filtration rate

*HRs (95% CIs) of all-cause dementia were estimated for participants in the highest quintile of serum total homocysteine (≥ 11.5 $\mu\text{mol/L}$) versus those in the lower quintiles (< 11.5 $\mu\text{mol/L}$). The risk estimates were adjusted for age, sex, education, hypertension, diabetes, serum total cholesterol, body mass index, estimated glomerular filtration rate, history of stroke, current smoking, current drinking, regular exercise, serum albumin, serum folate, and serum vitamin B12 levels (log-transformed). The subgroup variable was excluded from the corresponding model.

†Cut-off values are the median.

Supplementary Table S4. Baseline characteristics of participants by the MTHFR C677T genotype

	CC genotype (n=614)	CT/TT genotype (n=944)	P
Age, years	71 (8)	71 (8)	0.17
Male, %	45.4	41.4	0.12
Education \leq 9 years, %	54.4	51.5	0.26
Systolic blood pressure, mmHg	138 (20)	137 (21)	0.45
Diastolic blood pressure, mmHg	79 (11)	79 (11)	0.64
Use of antihypertensive agents, %	36.6	35.9	0.77
Hypertension, %	60.0	58.9	0.73
Diabetes, %	22.6	21.5	0.60
Serum total cholesterol, mmol/L	5.3 (0.9)	5.2 (0.9)	0.46
Body mass index, kg/m ²	23.1 (3.2)	23.0 (3.3)	0.70
eGFR $<$ 60 mL/min/1.73 m ² , %	14.8	14.0	0.64
History of stroke, %	4.4	5.5	0.33
Current smoking, %	14.3	14.7	0.83
Current drinking, %	36.6	35.7	0.70
Regular exercise (\geq 3 times/week), %	12.4	13.2	0.62
Serum albumin, g/dL	4.3 (0.3)	4.3 (0.3)	0.60
Serum folate, ng/mL	5.7 (2.7)	5.3 (5.0)	0.06
Serum vitamin B12, pg/mL*	476 (343–643)	445 (332–621)	0.11
Serum tHcy, μ mol/L*	8.1 (6.5–10.2)	8.5 (6.9–10.9)	$<$ 0.001

Abbreviations: MTHFR, methylenetetrahydrofolate reductase; eGFR, estimated glomerular filtration rate

Data are shown as mean (standard deviation) or frequency.

*Values are median (interquartile range).

Supplementary Table S5. Hazard ratios and 95% confidence intervals of all-cause dementia and its subtypes according to MTHFR C677T genotype

MTHFR C677T genotype	Hazard ratio (95% confidence interval)			
	Age- and sex-adjusted	P	Multivariable-adjusted*	P
All-cause dementia				
CC genotype	1.00 (reference)		1.00 (reference)	
CT genotype	1.14 (0.91–1.42)	0.26	1.13 (0.90–1.42)	0.28
TT genotype	1.42 (1.04–1.94)	0.03	1.50 (1.09–2.06)	0.01
Alzheimer's disease				
CC genotype	1.00 (reference)		1.00 (reference)	
CT genotype	1.23 (0.94–1.63)	0.13	1.24 (0.94–1.64)	0.13
TT genotype	1.32 (0.88–1.98)	0.18	1.36 (0.91–2.05)	0.14
Vascular dementia				
CC genotype	1.00 (reference)		1.00 (reference)	
CT genotype	1.13 (0.73–1.75)	0.58	1.07 (0.68–1.66)	0.77
TT genotype	1.28 (0.69–2.37)	0.43	1.38 (0.74–2.57)	0.31

Abbreviation: MTHFR, methylenetetrahydrofolate reductase

*Adjusted for age, sex, education, hypertension, diabetes, serum total cholesterol, body mass index, estimated glomerular filtration rate, history of stroke, current smoking, current drinking, regular exercise, serum albumin, serum folate, and serum vitamin B12 levels (log-transformed).

Supplementary Table S6. Crude and age- and sex-adjusted incidence rate of all-cause dementia according to education and serum total homocysteine levels*

	Crude incidence rate /10 ³ person year		Age- and sex-adjusted incidence rate (95% CI) /10 ³ person years	
	tHcy <11.5 μmol/L	tHcy ≥11.5 μmol/L	tHcy <11.5 μmol/L	tHcy ≥11.5 μmol/L
Education >9 years	13.7	47.4	18.7 (14.3–23.1)	47.9 (28.0–67.8)
Education ≤9 years	31.5	60.1	33.4 (28.3–38.3)	52.6 (38.0–67.1)

Abbreviations: tHcy, total homocysteine; CI, confidence interval

*Serum tHcy was categorized into two groups: quintiles 1 through 4 (<11.5 μmol/) and quintile 5 (≥11.5 μmol/L).