

Supplementary Online Content

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eFigure 1. Participant flow chart

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

eMethods 1. Covariate details

Smoking was categorized as never smoked, former smoker and current smoker. Alcohol consumption was categorized into no/occasional drinking *vs.* light-to-heavy drinking. Physical activity was assessed using questions adapted from the 1985 National Health Interview Survey, which measured the sum of hours per week that the participant engaged in 5 categories of activities including walking for exercise, gardening or yard work, calisthenics or general exercise, bicycle riding (including stationary bikes) and swimming or water exercises. Height and weight were measured when participants with light clothes but without shoes. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Cognitive function (Mini-Mental State Examination, MMSE) were collected at each wave through structured interviews. Cardiovascular diseases (heart disease, and hypertension) and diabetes was collected based on self-report during the interview and clinical examination at baseline. Cerebrovascular disease was ascertained based on self-report and a neurological examination.

eMethods 2. SEM computation details

Structural equation modeling (SEM) was performed to derive a best-fitting measurement model to construct the lifespan CR based on stimulating mental and social activities during life course, using full information maximum likelihood. The model fit was assessed using chi-square (χ^2) goodness of fit, the comparative fit index (CFI), standardized root mean squared residual (SRMR) and the root mean square error of approximation (RMSEA). Cognitive activities at distinct stages across the life course, including years of education, cognitive activities in early-, mid- and late-life, social activity and social network in late life were initially incorporated in the SEM to generate the latent variable of lifespan CR score. Because the factor loading of social network was low making the model fit unsatisfactory, thus it was excluded from the final model. The predicted values (as scores) of the CR were obtained by summing the products of standardized observed factors and the corresponding SEM-factor score weights.

eTable 1. Pearson correlation coefficient matrix of observed contributors to cognitive reserve indicator included in the calculation of a latent variable

	Years of education	Early-life cognitive activity	Middle-age cognitive activity	Late-life cognitive activity
Years of education	1.00			
Early-life cognitive activity	0.41	1.00		
Mid-life cognitive activity	0.43	0.64	1.00	
Late-life cognitive activity	0.29	0.41	0.49	1.00
Social activity in late life	0.17	0.25	0.27	0.31

Pearson correlation coefficient, (R)

eTable 2. Baseline and neuropathological characteristics of the 611 autopsied participants by dementia

Characteristics	Dementia-free n=370	Incident dementia n=241	p
Age, mean (SD), y	82.38 (6.2)	83.97 (5.3)	<.001
Female	261 (70.5)	179 (74.3)	.31
Life-course cognitive reserve factors			
Years of education, mean (SD), y	14.65 (2.8)	14.48 (2.9)	.46
Early-life cognitive activity, mean (SD)	3.04 (0.6)	2.97 (0.6)	.13
Mid-life cognitive activity, mean (SD)	3.33 (0.6)	3.23 (0.7)	.06
Late-life cognitive activity, mean (SD)	3.28 (0.7)	3.12 (0.8)	.01
Social activity in late life, mean (SD)	2.57 (0.6)	2.49 (0.6)	.08
Social network, median (IQR)	5.00 (3.00–10.00)	5.00 (2.00–9.00)	.06
Smoking status			
Never	219 (59.2)	155 (64.3)	
Ever smoker	142 (38.4)	80 (33.2)	
Current smoker	9 (2.4)	6 (2.5)	
Alcohol consumption			
Never/occasional	243 (66.7)	167 (69.3)	.47
Light/moderate	82 (22.2)	52 (21.6)	
Heavy	45 (12.2)	22 (9.1)	
Physical activities, median (IQR)	1.88 (0.50–3.58)	2.33 (1.00–4.17)	.69
Body mass index, mean (SD), kg/m ²	26.76 (4.9)	26.36 (4.5)	.31
Type 2 diabetes	49 (13.2)	23 (9.5)	.17
Hypertension	270 (73.0)	152 (63.1)	.009
Heart disease	54 (14.6)	19 (7.9)	.01
Cerebrovascular disease	43 (12.1)	28 (12.2)	.98
MMSE, median (IQR)	28.00 (27.00–29.00)	28.00 (26.00–29.00)	<.001
Any APOE ε4 carriers	56 (15.3)	77 (32.1)	<.001
AD pathologies			
Global AD pathology burden, median (IQR)	0.45 (0.11–0.91)	0.89 (0.41–1.45)	<.001
Amyloid beta protein, median (IQR)	2.60 (0.27–6.29)	6.00 (2.67–8.59)	<.001
Neurofibrillary tangles, median (IQR)	3.19 (1.32–6.09)	7.56 (3.45–15.19)	<.001
Chronic infarcts			
Gross infarcts	119 (32.3)	103 (42.7)	.009
Microscopic infarcts	102 (27.6)	78 (32.4)	.21
Vascular disease pathology			
Cerebral atherosclerosis	276 (74.8)	205 (85.1)	.002
Cerebral amyloid angiopathy	271 (73.4)	204 (84.7)	.001
Arteriolosclerosis	245 (66.6)	179 (74.3)	.04
Lewy bodies	64 (17.7)	79 (34.2)	<.001
Hippocampal sclerosis	8 (2.2)	40 (16.6)	<.001

Data are presented as mean (SD), median (IQR) or number (proportion %).

Abbreviations: SD, standard deviation; IQR, interquartile range; APOE ε4, apolipoprotein ε4 allele; MMSE, Mini-Mental State Examination.

Missing data: BMI=11, cerebrovascular disease=26, APOE ε4=6, MMSE=1, amyloid beta protein=14, neurofibrillary tangles=12, Lewy bodies=19.

eTable 3. Association of brain pathologies with middle and highest cognitive reserve at baseline using multinomial logistic regression

Brain pathologies	Middle cognitive reserve (n=203)	Highest cognitive reserve (n=195)
	OR (95% CI) ^a	OR (95% CI) ^a
AD pathologies		
Global AD pathology burden	0.89 (0.62–1.28)	0.78 (0.54–1.12)
Amyloid beta protein	0.99 (0.95–1.05)	0.99 (0.94–1.04)
Neurofibrillary tangles	0.99 (0.96–1.02)	0.97 (0.95–1.00)
Chronic infarcts		
Gross infarcts	0.87 (0.57–1.34)	0.49 (0.31–0.78)
Microscopic infarcts	1.00 (0.64–1.57)	1.00 (0.63–1.59)
Vascular disease pathology		
Cerebral atherosclerosis	0.71 (0.41–1.22)	1.04 (0.59–1.83)
Cerebral amyloid angiopathy	0.76 (0.45–1.26)	0.88 (0.52–1.47)
Arteriolosclerosis	1.24 (0.78–1.99)	1.63 (1.00–2.65)
Lewy bodies	1.30 (0.79–2.14)	1.04 (0.61–1.77)
Hippocampal sclerosis	0.76 (0.33–1.72)	1.30 (0.59–2.86)

MCI: mild cognitive impairment

^a Adjusted for age, sex, smoking, alcohol consumption, BMI, physical activity, heart disease, hypertension, cerebrovascular disease, diabetes, *APOE* ε4, and MMSE;

Missing data: BMI=11, cerebrovascular disease =26, *APOE* ε4=6, MMSE=1, amyloid beta protein=14, neurofibrillary tangles=12, Lewy bodies=19.

eTable 4. Hazard ratios (HRs) with 95% CIs of dementia and Alzheimer disease–related dementia in relation to cognitive reserve among participants with autopsies

Cognitive reserve	No. of subjects	Dementia				Alzheimer disease–related dementia			
		n	HR (95% CI) ^a	HR (95% CI) ^b	HR (95% CI) ^c	n	HR (95% CI) ^a	HR (95% CI) ^b	HR (95% CI) ^c
Continuous	550 ^d	217	0.94 (0.88–0.99)	0.95 (0.89–1.00)	0.93 (0.88–0.99)	201	0.93 (0.88–0.99)	0.95 (0.89–1.00)	0.94 (0.88–1.00)
Categorical									
Lowest	189	89	Reference	Reference	Reference	83	Reference	Reference	Reference
Middle	181	64	0.77 (0.55–1.07)	0.81 (0.58–1.12)	0.83 (0.60–1.16)	58	0.75 (0.53–1.06)	0.80 (0.57–1.13)	0.83 (0.58–1.18)
Highest	180	64	0.60 (0.42–0.85)	0.63 (0.45–0.90)	0.60 (0.42–0.86)	60	0.59 (0.41–0.85)	0.64 (0.44–0.91)	0.60 (0.41–0.87)
<i>P</i> value for trend			0.77 (0.65–0.92)	0.79 (0.67–0.95)	0.77 (0.65–0.92)		0.77 (0.64–0.92)	0.80 (0.67–0.96)	0.78 (0.65–0.93)
			.004	.01	.003		.004	.01	.006

^a Adjusted for age, sex, smoking, alcohol consumption, BMI, physical activity, heart disease, hypertension, cerebrovascular diseases, diabetes, *APOE* ε4, and MMSE.

^b Additionally adjusted for global AD pathology burden.

^c Further adjusted for other brain pathologies including chronic gross infarcts, microscopic infarcts, cerebral atherosclerosis, cerebral amyloid angiopathy, arteriolosclerosis, Lewy bodies and hippocampal sclerosis.

^d Numbers of participants with missing values were 11 for BMI, 26 for cerebrovascular disease, 6 for *APOE* ε4, 1 for MMSE, and 19 for Lewy bodies.

eTable 5. Incidence rates (per 1000 person-years) of dementia and Alzheimer disease–related dementia by different levels of cognitive reserve and brain pathologies

Brain pathologies	Cognitive reserve	No. of total	Dementia		Alzheimer disease–related dementia	
			n	IR (95% CI) ^a	n	IR (95% CI) ^a
Global AD pathology burden						
Low				58.78 (45.39–72.18)		55.06 (41.69–68.44)
	Lowest	90	31	71.51 (45.80–97.22)	29	69.28 (43.73–94.84)
	Middle	91	21	48.91 (26.97–70.86)	17	42.22 (21.27–63.17)
	Highest	101	28	53.20 (32.49–73.90)	25	49.95 (29.30–70.59)
High				100.39 (83.40–117.38)		97.11 (80.19–114.03)
	Lowest	99	58	117.12 (87.22–147.02)	54	111.13 (81.70–140.55)
	Middle	90	43	105.37 (73.73–136.99)	41	104.12 (72.05–136.19)
	Highest	79	36	72.85 (48.80–96.90) *	35	71.12 (47.25–94.99) *
Gross infarcts						
None				70.97 (58.22–83.73)		68.92 (56.21–81.63)
	Lowest	107	43	90.76 (64.35–117.18)	41	87.84 (61.45–114.23)
	Middle	109	32	62.05 (40.27–83.84)	31	61.04 (39.23–82.85)
	Highest	134	46	61.43 (43.32–79.53)	44	59.32 (41.44–77.21)
Any				94.78 (75.16–114.40)		88.46 (69.01–107.90)
	Lowest	82	46	119.27 (83.26–155.28)	42	113.67 (77.74–149.60)
	Middle	72	32	93.07 (60.67–125.47)	27	85.61 (53.33–117.89)
	Highest	46	18	53.47(28.21–78.73) **	16	48.53 (24.11–72.96) **
Microscopic infarcts						
None				76.43 (63.79–89.08)		74.30 (61.70–86.90)
	Lowest	138	63	93.71 (70.13–117.30)	60	91.75 (68.06–115.43)
	Middle	131	44	74.16 (51.59–96.74)	42	72.43 (49.83–95.03)
	Highest	132	45	58.01 (40.25–75.77) *	43	55.52 (38.11–72.93) *
Any				94.27 (70.93–117.61)		86.99 (63.76–110.21)
	Lowest	60	32	120.49 (75.49–165.48)	28	113.86 (68.04–159.68)
	Middle	55	22	89.44 (50.39–128.48)	18	79.23 (41.15–117.31)
	Highest	53	22	67.42 (37.96–96.88) *	20	64.70 (34.93–94.47) *

^a Adjusted for age, sex, smoking, alcohol consumption, BMI, physical activity, heart disease, hypertension, cerebrovascular disease, diabetes and APOE ε4;

*vs. lowest CR: $P < .05$,

** vs. lowest CR: $P < .01$

Number of participants had missing data: BMI=11, cerebrovascular disease=26, APOE ε4=6.

eTable 6. Hazard ratios (HRs) with 95% CIs of the association of levels of cognitive reserve with dementia and Alzheimer disease–related dementia with multiple imputation for missing data

Cognitive reserve	No. of subjects	Dementia			Alzheimer disease–related dementia		
		n	HR (95% CI) ^a	HR (95% CI) ^b	n	HR (95% CI) ^a	HR (95% CI) ^b
Continuous	1530 ^c	378	0.89 (0.85–0.93)	0.92 (0.88–0.97)	348	0.89 (0.85–0.93)	0.92 (0.88–0.97)
Categorical (tertiles)							
Lowest	509	148	Reference	Reference	136	Reference	Reference
Middle	504	117	0.74 (0.58–0.94)	0.81 (0.63–1.03)	108	0.74 (0.57–0.95)	0.80 (0.62–1.04)
Highest	517	113	0.59 (0.46–0.76)	0.66 (0.51–0.86)	104	0.59 (0.46–0.77)	0.65 (0.50–0.86)
<i>P for trend</i>			0.77 (0.68–0.87)	0.81 (0.71–0.93)		0.77 (0.67–0.87)	0.81 (0.70–0.93)
			<.001	.002		<.001	.003

^a Adjusted for age and sex.

^b Adjusted for age, sex, smoking, alcohol consumption, BMI, physical activity, heart disease, hypertension, cerebrovascular diseases, diabetes, APOE ε4, death and MMSE.

^c Missing data (BMI=30, alcohol consumption=1, cerebrovascular disease=139, heart disease=1, APOE ε4=72, MMSE=1)

eTable 7. Hazard ratios (HRs) and 95% CIs of the association of cognitive reserve with dementia and Alzheimer disease–related dementia after excluding MCI

Cognitive reserve	No. of subjects	Dementia			Alzheimer disease–related dementia		
		n	HR (95% CI) ^a	HR (95% CI) ^b	n	HR (95% CI) ^a	HR (95% CI) ^b
Continuous	1018 ^c	197	0.90 (0.85–0.96)	0.90 (0.84–0.96)	176	0.89 (0.84–0.95)	0.89 (0.83–0.95)
Categorical (tertiles)							
Lowest	307	73	Reference	Reference	66	Reference	Reference
Middle	341	62	0.74 (0.53–1.04)	0.75 (0.53–1.06)	55	0.73 (0.51–1.05)	0.74 (0.51–1.08)
Highest	370	62	0.56 (0.40–0.79)	0.54 (0.38–0.77)	55	0.54 (0.38–0.78)	0.52 (0.35–0.76)
<i>P for trend</i>			0.75 (0.63–0.89)	0.74 (0.61–0.88)		0.74 (0.61–0.88)	0.72 (0.59–0.87)
			<.001	.001		<.001	<.001

MCI: mild cognitive impairment

^a Adjusted for age and sex

^b Adjusted for age, sex, smoking, alcohol consumption, BMI, physical activity, heart disease, hypertension, cerebrovascular diseases, diabetes, APOE ε4, death and MMSE.

^c Missing data (BMI=23, cerebrovascular disease=99, heart disease=1, APOE ε4=44)

eTable 8. Hazard ratios (HRs) and 95% CIs of the association of cognitive reserve with dementia and Alzheimer disease–related dementia among all participants: results from competing risk models

Cognitive reserve	No. of subjects	Dementia			Alzheimer disease–related dementia		
		n	HR (95% CI) ^a	HR (95% CI) ^b	n	HR (95% CI) ^a	HR (95% CI) ^b
Continuous	1364 ^c	349	0.92 (0.88–0.96)	0.94 (0.89–0.99)	320	0.92 (0.88–0.97)	0.94 (0.89–0.99)
Categorical (tertiles)							
Lowest	442	138	Reference	Reference	126	Reference	Reference
Middle	453	108	0.70 (0.54–0.91)	0.74 (0.56–0.97)	99	0.70 (0.54–0.92)	0.74 (0.56–0.98)
Highest	469	103	0.66 (0.51–0.85)	0.68 (0.51–0.89)	95	0.66 (0.51–0.86)	0.68 (0.51–0.91)
<i>P for trend</i>			0.81 (0.71–0.92)	0.82 (0.71–0.94)		0.81 (0.71–0.93)	0.82 (0.71–0.95)
			.001	.005		.002	.009

^a Adjusted for age and sex.

^b Adjusted for age, sex, smoking, alcohol consumption, BMI, physical activity, heart disease, hypertension, cerebrovascular disease, diabetes, APOE ε4, and MMSE.

^c Missing data (BMI=30, alcohol consumption=1, cerebrovascular disease=139, heart disease=1, APOE ε4=72, MMSE=1)

eTable 9. Hazard ratios (HRs) and 95% CIs of the association of cognitive reserve^a with dementia and Alzheimer disease–related dementia among all participants

Cognitive reserve	No. of subjects	Dementia			Alzheimer disease–related dementia		
		n	HR (95% CI) ^b	HR (95% CI) ^c	n	HR (95% CI) ^b	HR (95% CI) ^c
Continuous	1364 ^d	349	0.39 (0.27–0.56)	0.54 (0.37–0.79)	320	0.39 (0.27–0.57)	0.52 (0.35–0.76)
Categorical (tertiles)							
Lowest	441	140	Reference	Reference	128	Reference	Reference
Middle	451	105	0.69 (0.53–0.89)	0.76 (0.58–0.98)	96	0.69 (0.53–0.90)	0.75 (0.57–0.98)
Highest	472	104	0.54 (0.42–0.70)	0.60 (0.45–0.78)	96	0.54 (0.42–0.71)	0.59 (0.44–0.78)
<i>P for trend</i>			0.73 (0.64–0.83)	0.78 (0.68–0.89)		0.74 (0.64–0.84)	0.77 (0.67–0.88)
			<.001	<.001		<.001	<.001

^a Included early-, mid- and late-life cognitive activities and social activity in late life.

^b Adjusted for age and sex.

^c Adjusted for age, sex, smoking, alcohol consumption, BMI, physical activity, heart disease, hypertension, cerebrovascular disease, diabetes, *APOE* ε4, and MMSE.

^d Missing data (BMI=30, alcohol consumption=1, cerebrovascular disease=139, heart disease=1, *APOE* ε4=72, MMSE=1)

eTable 10. Hazard ratios (HRs) and 95% CIs of the association of cognitive reserve^a with dementia and Alzheimer disease–related dementia among all participants

Cognitive reserve	No. of subjects	Dementia			Alzheimer disease–related dementia		
		n	HR (95% CI) ^b	HR (95% CI) ^c	n	HR (95% CI) ^b	HR (95% CI) ^c
Continuous	1364 ^d	349	0.89 (0.84–0.94)	0.93 (0.87–0.98)	320	0.89 (0.83–0.94)	0.92 (0.87–0.98)
Categorical (tertiles)							
Lowest	442	135	Reference	Reference	122	Reference	Reference
Middle	459	109	0.66 (0.51–0.85)	0.74 (0.57–0.96)	102	0.67 (0.52–0.88)	0.75 (0.57–0.98)
Highest	463	105	0.61 (0.48–0.79)	0.70 (0.54–0.92)	96	0.62 (0.47–0.81)	0.69 (0.52–0.92)
<i>P for trend</i>			0.78 (0.68–0.89)	0.84 (0.74–0.97)		0.78 (0.68–0.90)	0.83 (0.72–0.96)
			<.001	.02		<.001	.01

^a Included education, early- and mid-life cognitive activities.

^b Adjusted for age and sex.

^c Adjusted for age, sex, smoking, alcohol consumption, BMI, physical activity, heart disease, hypertension, cerebrovascular disease, diabetes, *APOE* ε4, and MMSE.

^d Missing data (BMI=30, alcohol consumption=1, cerebrovascular disease=139, heart disease=1, *APOE* ε4=72, MMSE=1)

eTable 11. Hazard ratios (HRs) and 95% CIs of the associations of individual cognitive reserve indicators with dementia and Alzheimer disease–related dementia among all participants

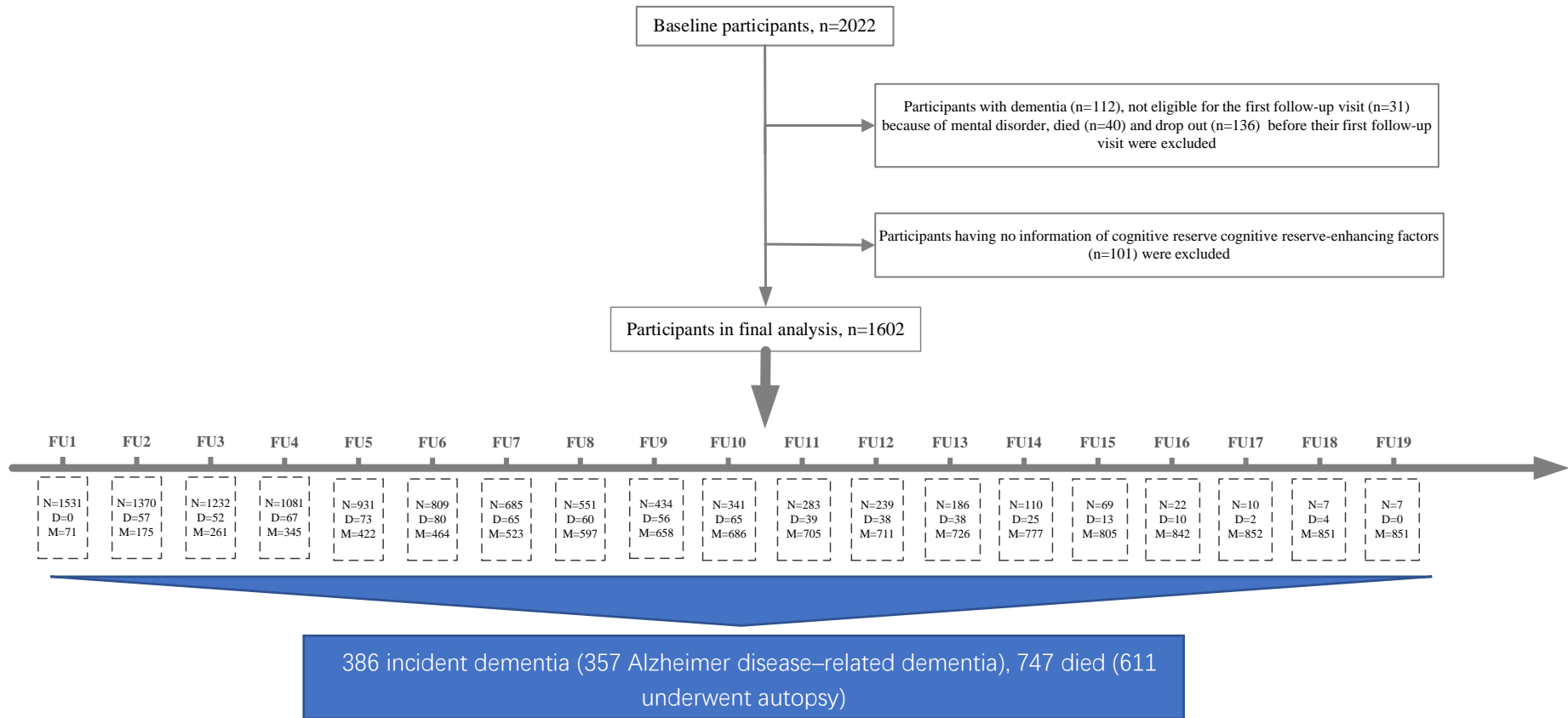
Cognitive reserve indicator	Dementia		Alzheimer disease–related dementia	
	HR (95% CI) ^a	HR (95% CI) ^b	HR (95% CI) ^a	HR (95% CI) ^b
Years of education	0.97 (0.93–1.00)	1.01 (0.98–1.06)	0.97 (0.94–1.00)	1.02 (0.98–1.06)
Early-life cognitive activity	0.77 (0.65–0.92)	0.86 (0.72–1.03)	0.78 (0.65–0.93)	0.87 (0.72–1.05)
Mid-life cognitive activity	0.70 (0.60–0.82)	0.80 (0.68–0.94)	0.70 (0.59–0.82)	0.80 (0.67–0.95)
Late-life cognitive activity	0.70 (0.61–0.79)	0.78 (0.67–0.90)	0.71 (0.62–0.82)	0.80 (0.69–0.93)
Social activity in late life	0.61 (0.50–0.74)	0.69 (0.56–0.85)	0.58 (0.47–0.71)	0.65 (0.53–0.81)
Social network	0.98 (0.96–1.00)	0.98 (0.96–0.99)	0.98 (0.96–1.00)	0.98 (0.96–1.00)

^a Adjusted for age and sex.

^b Adjusted for age, sex, smoking, alcohol consumption, BMI, physical activity, heart disease, hypertension, cerebrovascular disease, diabetes, *APOE* ε4, death and MMSE.

Missing data (BMI=30, alcohol consumption=1, cerebrovascular disease=139, heart disease=1, *APOE* ε4=72, MMSE=

eFigure 1. Participant flow chart



eFigure 2. Kaplan-Meier survival curves of dementia by cognitive reserve

