

## Supplemental materials:

**Table S1: The leukocyte telomere length and dementia across sex subgroup.**

	Sex subgroup		<i>P</i> for interaction
	Male	Female	
<b>Dementia</b>			
LTL tertile			0.830
Highest	1 (Ref.)	1 (Ref.)	
Medial	1.07 (0.97-1.18)	1.04 (0.94-1.15)	
Lowest	1.17 (1.07-1.29)	1.10 (1.01-1.22)	
Per 1-SD reduction	1.08 (1.04-1.12)	1.04 (1.01-1.08)	
<b>Alzheimer's disease</b>			
LTL tertile			0.741
Highest	1 (Ref.)	1 (Ref.)	
Medial	1.32 (1.07-1.64)	1.17 (0.97-1.40)	
Lowest	1.35 (1.10-1.65)	1.24 (1.04-1.48)	
Per 1-SD reduction	1.10 (1.02-1.19)	1.08 (1.00-1.16)	
<b>Vascular's disease</b>			
LTL tertile			0.968
Highest	1 (Ref.)	1 (Ref.)	
Medial	1.01 (0.77-1.32)	1.01 (0.75-1.36)	
Lowest	1.20 (0.94-1.54)	1.14 (0.87-1.51)	
Per 1-SD reduction	1.08 (0.98-1.20)	1.06 (0.94-1.20)	

Flexible parametric survival models were used to calculate HRs, considered attained age as timescale, and adjusted for ethnicity, qualifications, Townsend deprivation index, smoking status, alcohol intake frequency, body mass index, Apolipoprotein E  $\epsilon$ 4, white blood cell count, family history of dementia, hypertension, hypercholesterolemia and hyperglycemia. LTL was categorized according to the tertiles of T/S ratio.

Abbreviations: LTL, leukocyte telomere length; SD, standard deviation.

**Table S2: The associations of leukocyte telomere length with risks of dementia and Alzheimer' disease after additional adjustment of potential confounders using Cox proportional hazards models.**

	Model 1 †	Model 1 + self-reported diabetes	Model 1 + self-reported CVD	Model 1 + depressive symptom	Model 1 + all of three
<b>Dementia</b>					
LTL tertile ‡					
Highest	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
Medial	1.05 (0.98-1.13)	1.05 (0.98-1.13)	1.05 (0.98-1.12)	1.05 (0.98-1.13)	1.05 (0.98-1.12)
Lowest	1.14 (1.06-1.21)	1.13 (1.06-1.21)	1.13 (1.05-1.21)	1.14 (1.06-1.21)	1.12 (1.05-1.20)
Self-reported diabetes	–	2.05 (1.90-2.22)	–	–	1.94 (1.79-2.10)
Self-reported CVD	–	–	1.70 (1.59-1.82)	–	1.61 (1.50-1.72)
Depressive symptom	–	–	–	1.87 (1.69-2.06)	1.77 (1.60-1.96)
<b>Alzheimer' disease</b>					
LTL tertile ‡					
Highest	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
Medial	1.23 (1.07-1.42)	1.24 (1.08-1.42)	1.23 (1.07-1.42)	1.23 (1.07-1.42)	1.23 (1.07-1.42)
Lowest	1.28 (1.12-1.46)	1.28 (1.12-1.46)	1.28 (1.12-1.46)	1.28 (1.12-1.46)	1.27 (1.12-1.45)
Self-reported diabetes	–	1.66 (1.41-1.96)	–	–	1.61 (1.36-1.90)
Self-reported CVD	–	–	1.35 (1.17-1.55)	–	1.30 (1.13-1.49)
Depressive symptom	–	–	–	1.56 (1.26-1.93)	1.51 (1.22-1.87)
<b>Vascular' disease</b>					
LTL tertile ‡					
Highest	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
Medial	1.01 (0.83-1.24)	1.02 (0.83-1.24)	1.00 (0.82-1.23)	1.01 (0.82-1.24)	1.00 (0.81-1.23)
Lowest	1.18 (0.98-1.42)	1.17 (0.97-1.41)	1.16 (0.96-1.39)	1.18 (0.97-1.43)	1.14 (0.94-1.39)
Self-reported diabetes	–	2.76 (2.29-3.32)	–	–	2.48 (2.04-3.03)
Self-reported CVD	–	–	2.57 (2.18-3.02)	–	2.36 (1.98-2.80)
Depressive symptom	–	–	–	2.26 (1.76-2.91)	2.03 (1.58-2.62)

† Flexible parametric survival models were used to calculate HRs, considered attained age as timescale, and adjusted for sex, ethnicity, qualifications, Townsend deprivation index, smoking status, alcohol intake frequency, body mass index, Apolipoprotein E ε4, white blood cell count,

family history of dementia, hypertension, hypercholesterolemia.

‡ LTL was categorized according to the tertile of T/S ratio. The SD of LTL was 0.131.

Abbreviations: LTL, leukocyte telomere length.

**Table S3: The associations of leukocyte telomere length with risks of dementia and Alzheimer' disease after excluding prevalent cancer at baseline using Cox proportional hazards models.**

	Events	Incidence rate per 1000 person-year	Hazard ratio	
			Model 1 *	Model 2 †
<b>Dementia</b>				
LTL tertile				
Highest	1206	0.77 (0.73-0.81)	1 (Ref.)	1 (Ref.)
Medial	1638	1.06 (1.01-1.11)	1.05 (0.98-1.14)	1.05 (0.97-1.13)
Lowest	2299	1.48 (1.42-1.55)	1.165 (1.08-1.25)	1.13 (1.05-1.22)
Per 1-SD reduction	5143	1.10 (1.07-1.13)	1.07 (1.04-1.10)	1.06 (1.03-1.09)
<b>Alzheimer' disease</b>				
LTL tertile				
Highest	292	0.18 (0.16-0.21)	1 (Ref.)	1 (Ref.)
Medial	459	0.29 (0.27-0.32)	1.21 (1.04-1.40)	1.22 (1.05-1.41)
Lowest	628	0.40 (0.37-0.44)	1.30 (1.13-1.49)	1.28 (1.11-1.47)
Per 1-SD reduction	1379	0.29 (0.28-0.31)	1.09 (1.03-1.15)	1.08 (1.02-1.15)
<b>Vascular's disease</b>				
LTL tertile				
Highest	146	0.09 (0.08-0.11)	1 (Ref.)	1 (Ref.)
Medial	208	0.13 (0.12-0.15)	1.06 (0.86-1.31)	1.04 (0.84-1.28)
Lowest	322	0.21 (0.18-0.23)	1.24 (1.02-1.51)	1.18 (0.97-1.44)
Per 1-SD reduction	676	0.14 (0.13-0.16)	1.09 (1.01-1.19)	1.07 (0.98-1.16)

\* Flexible parametric survival models were used to calculate HRs, considered attained age as timescale, and adjusted for sex.

† Flexible parametric survival models were used to calculate HRs, considered attained age as timescale, and adjusted for sex, ethnicity, qualifications, Townsend deprivation index, smoking status, alcohol intake frequency, body mass index, Apolipoprotein E ε4, white blood cell count, family history of dementia, hypertension, hypercholesterolemia and hyperglycemia.

Abbreviations: LTL, leukocyte telomere length; SD, standard deviation.

**Table S4: The associations of leukocyte telomere length with risks of dementia and Alzheimer's disease after excluding first two years of dementia cases during follow-up time.**

	Events	Incidence rate per 1000 person-year	Hazard ratio	
			Model 1 *	Model 2 †
<b>Dementia</b>				
LTL tertile				
Highest	1330	0.78 (0.74-0.82)	1 (Ref.)	1 (Ref.)
Medial	1810	1.07 (1.02-1.12)	1.06 (0.98-1.13)	1.05 (0.98-1.13)
Lowest	2522	1.49 (1.43-1.54)	1.15 (1.08-1.23)	1.12 (1.05-1.20)
Per 1-SD reduction	5662	1.11 (1.08-1.14)	1.07 (1.04-1.10)	1.06 (1.03-1.09)
<b>Alzheimer's disease</b>				
LTL tertile				
Highest	325	0.19 (0.17-0.21)	1 (Ref.)	1 (Ref.)
Medial	518	0.31 (0.28-0.33)	1.23 (1.07-1.42)	1.24 (1.08-1.42)
Lowest	698	0.41 (0.38-0.42)	1.30 (1.14-1.48)	1.29 (1.13-1.47)
Per 1-SD reduction	1541	0.30 (0.29-0.32)	1.09 (1.03-1.15)	1.09 (1.03-1.15)
<b>Vascular's disease</b>				
LTL tertile				
Highest	165	0.10 (0.08-0.11)	1 (Ref.)	1 (Ref.)
Medial	227	0.13 (0.12-0.15)	1.03 (0.84-1.26)	1.01 (0.82-1.23)
Lowest	359	0.21 (0.19-0.23)	1.23 (1.02-1.49)	1.17 (0.97-1.41)
Per 1-SD reduction	751	0.15 (0.14-0.16)	1.10 (1.01-1.19)	1.07 (0.99-1.16)

\* Flexible parametric survival models were used to calculate HRs, considered attained age as timescale, and adjusted for sex.

† Flexible parametric survival models were used to calculate HRs, considered attained age as timescale, and adjusted for sex, ethnicity, qualifications, Townsend deprivation index, smoking status, alcohol intake frequency, body mass index, Apolipoprotein E ε4, white blood cell count, family history of dementia, hypertension, hypercholesterolemia and hyperglycemia.

Abbreviations: LTL, leukocyte telomere length; SD, standard deviation.

**Table S5: The effect modification of familial factors on the associations between leukocyte telomere length and dementia.**

	APOE $\epsilon$ 4 gene		Family history of dementia	
	Carrier	Non-carrier	With	Without
<b>Dementia</b>				
LTL tertile				
Highest	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
Medial	1.08 (0.98-1.20)	1.03 (0.93-1.14)	1.21 (1.04-1.42)	1.02 (0.94-1.10)
Lowest	1.14 (1.04-1.25)	1.14 (1.04-1.25)	1.14 (0.98-1.32)	1.14 (1.06-1.23)
P for interaction	0.624		0.036	
<b>Alzheimer's disease</b>				
LTL tertile				
Highest	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
Medial	1.25 (1.05-1.49)	1.21 (0.97-1.52)	1.27 (0.97-1.65)	1.22 (1.04-1.44)
Lowest	1.32 (1.12-1.56)	1.22 (0.98-1.51)	1.26 (0.97-1.63)	1.29 (1.11-1.51)
P for interaction	0.865		0.870	
<b>Vascular's disease</b>				
LTL tertile				
Highest	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
Medial	0.96 (0.73-1.27)	1.07 (0.80-1.42)	0.79 (0.49-1.26)	1.07 (0.86-1.33)
Lowest	1.11 (0.86-1.44)	1.26 (0.97-1.64)	1.15 (0.76-1.73)	1.19 (0.97-1.46)
P for interaction	0.773		0.420	

All models considered attained age as timescale, and adjusted for sex, ethnicity, qualifications, Townsend deprivation index, smoking status, alcohol intake frequency, body mass index, Apolipoprotein E  $\epsilon$ 4, family history of dementia, white blood cell count, hypertension, hypercholesterolemia and hyperglycemia. LTL was categorized according to the tertiles of T/S ratio.

Abbreviations: APOE  $\epsilon$ 4, Apolipoprotein E  $\epsilon$ 4; LTL, leukocyte telomere length

**Table S6: Interaction between leukocyte telomere length and sex on brain volume.**

	White matter volume		Gray matter volume		Total brain volume		White matter hyperintensity volumes	
	$\beta$ (95% CI)	P	$\beta$ (95% CI)	P	$\beta$ (95% CI)	P	$\beta$ (95% CI)	P
LTL tertile								
Highest	0 (Ref.)		0 (Ref.)		0 (Ref.)		0 (Ref.)	
Medial	-2318.6 (-3634.3, -1002.8)	0.001	372.8 (-840.2, 1585.9)	0.547	60.7 (-152.0, 273.6)	0.576	-1945.7 (-3981.9, 90.5)	0.061
Lowest	-903.8 (-2171.7, 364.1)	0.162	631.5 (-537.4, 1800.4)	0.290	-73.1 (-278.1, 131.9)	0.485	-272.4 (-2234.5, 1689.7)	0.786
Sex	9725.7 (8344.9, 11106.5)		-22145.5 (-23418.5, -20872.4)		68.3 (-154.9, 291.5)	0.549	-12429.8 (-14556.6, -10283.0)	
Interaction								
Medial LTL tertile * male	811.7 (-1099.3, 2722.7)	0.405	-1639.6 (-3401.7, 121.9)	0.068	182.5 (-126.4, 491.5)	0.247	-828.1 (-3785.5, 2129.2)	0.583
Lowest LTL tertile * male	26.3 (-1879.5, 1932.1)	0.978	-1442.69 (-3199.6, 314.4)	0.108	322.3 (14.1, 630.4)	0.040	-1416.1 (-4365.4, 1533.2)	0.347
LTL (continuous)								
LTL	-1043.3 (-1576.0, -510.6)	<0.001	329.7 (-161.4, 820.9)	0.188	-713.6 (-1538.0, 110.9)	0.09	-1.64 (-87.78, 84.51)	0.97
Sex	11837.9 (6774.1, 16901.8)	<0.001	-28201.6 (-32870.9, -23532.9)	<0.001	-16363.7 (-24200.8, -8526.7)		806.4 (-12.5, 1625.3)	0.054
Interaction	282.4 (-499.9, 1064.7)	0.479	-781.7 (-1503.1, -60.4)	0.034	-499.3 (-1710.0, 711.5)	0.419	88.4 (-38.1, 214.9)	0.171

Linear regression models were used and adjusted for age, ethnicity, qualifications, Townsend deprivation index, smoking status, alcohol intake frequency, body mass index, Apolipoprotein E  $\epsilon$ 4, family history of dementia, white blood cell count, hypertension, hypercholesterolemia and hyperglycemia.

Abbreviations: LTL, leukocyte telomere length.

**Table S7: Interaction between leukocyte telomere length and APOE ε4 on brain volume.**

	White matter volume		Gray matter volume		Total brain volume		White matter hyperintensity volumes	
	β (95% CI)	P	β (95% CI)	P	β (95% CI)	P	β (95% CI)	P
LTL tertile								
Highest	0 (Ref.)		0 (Ref.)		0 (Ref.)		0 (Ref.)	
Medial	-1884.2 (-33014.7, -753.7)	0.001	-576.3 (-1618.7, 466.1)	0.279	-2460.6 (-4210.1, -711.0)	0.006	153.2 (-29.7, 336.2)	0.101
Lowest	-1074.6 (-2191.6, 42.3)	0.059	-86.4 (-1116.4, 943.6)	0.869	-1161.1 (-2889.8, 567.6)	0.188	123.1 (-57.6, 303.9)	0.182
APOE 4 carrier	-299.3 (-1792.4, 1193.8)	0.694	-600.2 (-1977.1, 776.6)	0.393	-899.6 (-3210.4, 1411.2)	0.445	266.5 (24.9, 508.1)	0.031
Interaction								
Medial LTL tertile * APOE 4 carrier	-198.8 (-2308.5, 1910.9)	0.853	797.4 (-1147.9, 2742.8)	0.422	598.7 (-2666.3, 3863.7)	0.719	-62.0 (-403.4, 279.4)	0.722
Lowest LTL tertile * APOE 4 carrier	539.1 (-1572.3, 2650.5)	0.617	226.1 (-1720.9, 2173.0)	0.820	765.2 (-2502.4, 4032.9)	0.646	-195.8 (-537.5, 145.9)	0.261
LTL (continuous)								
LTL	-917.7 (-1383.4, -452.1)		-47.4 (-476.8, 382.0)	0.829	-965.2 (-1685.9, -244.4)	0.009	57.6 (-17.8, 132.9)	0.134
APOE 4 carrier	-123.1 (-5702.6, 5456.4)	0.966	373.6 (-4771.7, 5519.0)	0.887	250.7 (-8384.9, 8886.2)	0.955	247.4 (-1150.4, 655.6)	0.591
Interaction	12.4 (-846.4, 871.1)	0.977	99.0 (-692.9, 890.9)	0.806	111.4 (-1217.7, 144.6)	0.869	-66.8 (-205.8, 72.1)	0.346

Linear regression models were used and adjusted for age, sex, ethnicity, qualifications, Townsend deprivation index, smoking status, alcohol intake frequency, body mass index, family history of dementia, white blood cell count, hypertension, hypercholesterolemia and hyperglycemia.

Abbreviations: LTL, leukocyte telomere length; APOE 4, Apolipoprotein E ε4.

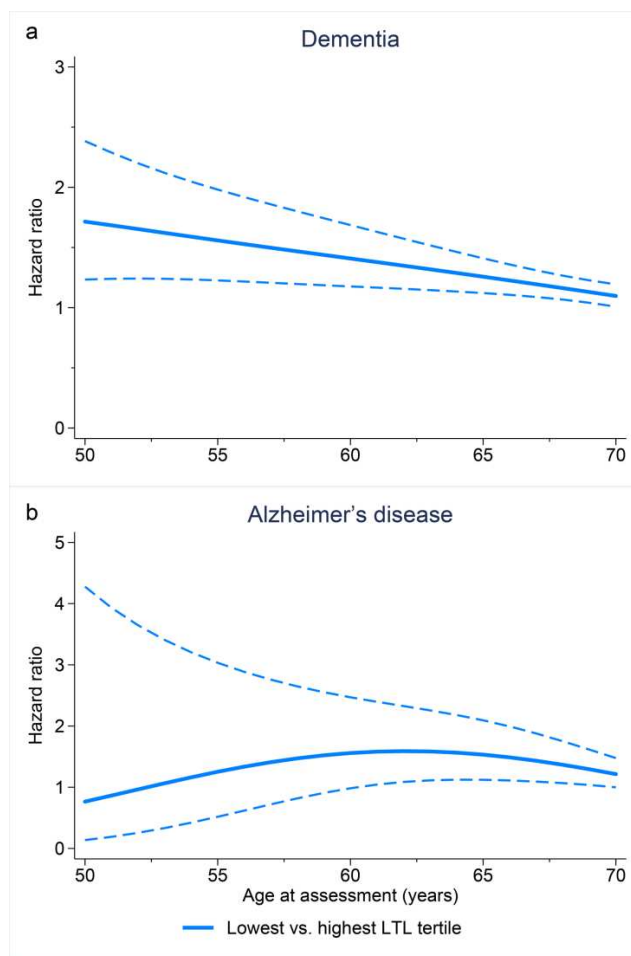


**Table S8:  $\beta$ -Coefficients and 95% confidence intervals (CIs) for the association between leukocyte telomere length (LTL) and brain volume after excluding prevalent dementia at baseline.**

Brain volume (mm <sup>3</sup> )	Multivariate adjusted *		
	$\beta$	(95% CI)	P value
<b>Total brain volume</b>			
Highest LTL tertile	0 (Ref.)	0 (Ref.)	
Medial LTL tertile	-852.8	-2424.6, 518.9	0.204
Lowest LTL tertile	-2318.7	-3812.2, -825.2	0.002
Per 1-SD reduction of LTL	-933.4	-1546.1, -320.7	0.003
<b>White matter volume</b>			
Highest LTL tertile	0 (Ref.)	0 (Ref.)	
Medial LTL tertile	-942.6	-1893.4, 8.1	0.052
Lowest LTL tertile	-1930.7	-2895.5, -965.8	<0.001
Per 1-SD reduction of LTL	-904.9	-1300.7, -509.1	<0.001
<b>Grey matter volume</b>			
Highest LTL tertile	0 (Ref.)	0 (Ref.)	
Medial LTL tertile	-10.2	-887.1, 866.7	0.982
Lowest LTL tertile	-388.0	-1277.9, 501.8	0.393
Per 1-SD reduction	-28.5	-393.6, 336.6	0.878
<b>White matter hyperintensity volume</b>			
Highest LTL tertile	0 (Ref.)	0 (Ref.)	
Medial LTL tertile	66.6	-86.5, 219.6	0.394
Lowest LTL tertile	126.7	-28.6, 282.0	0.110
Per 1-SD reduction of LTL	38.2	-25.5, 101.9	0.240

\*Linear regression models adjusted for age, sex, ethnicity, qualifications, Townsend deprivation index, smoking status, alcohol intake frequency, body mass index, Apolipoprotein E  $\epsilon$ 4, family history of dementia, white blood cell count, hypertension, hypercholesterolemia and hyperglycemia.

Abbreviations: LTL, leukocyte telomere length; SD, standard deviation.



**Figure S1: Age-dependent associations of leukocyte telomere length with risks of dementia and Alzheimer' disease.**

Flexible parametric survival models with leukocyte telomere length (LTL) as time-dependent variable were used to calculate HRs, considered attained age as timescale, and adjusted for sex, ethnicity, qualifications, Townsend deprivation index, smoking status, alcohol intake frequency, body mass index, Apolipoprotein E  $\epsilon$ 4, family history of dementia, white blood cell count, hypertension, hypercholesterolemia and hyperglycemia. LTL was categorized into according to the tertiles of T/S ratio.