Supplementary Materials
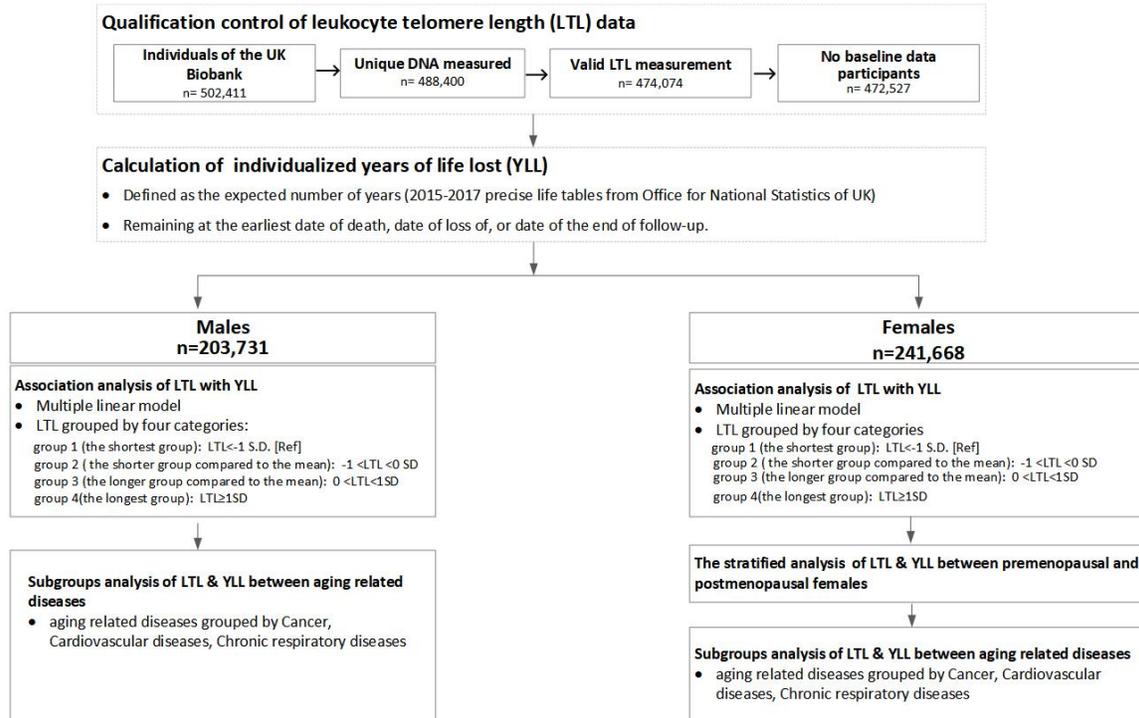
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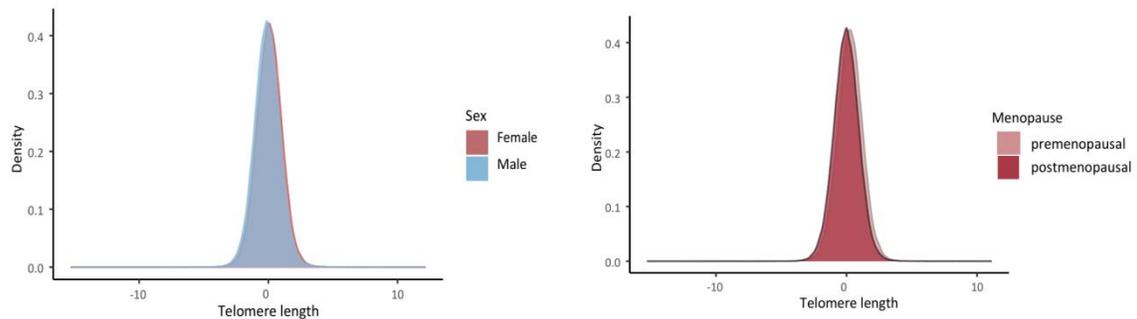
Appendix 1. Supplementary Figures

Supplementary Figure S1. Study design and workflow

Qualification control of leukocyte telomere length (LTL) data

| Individuals of the UK Biobank n= 502,411 | → | Unique DNA measured n= 488,400 | → | Valid LTL measurement n= 474,074 | → | No baseline data participants n= 472,527 |

Calculation of individualized years of life lost (YLL)
- Defined as the expected number of years (2015-2017 precise life tables from Office for National Statistics of UK)
- Remaining at the earliest date of death, date of loss of, or date of the end of follow-up.

Males
n=203,731

Association analysis of LTL with YLL
- Multiple linear model
- LTL grouped by four categories:

group 1 (the shortest group): LTL<-1 S.D. [Ref]
group 2 (the shorter group compared to the mean): -1 <LTL <0 SD
group 3 (the longer group compared to the mean): 0 <LTL<1SD
group 4(the longest group): LTL≥1SD

Subgroups analysis of LTL & YLL between aging related diseases
- aging related diseases grouped by Cancer, Cardiovascular diseases, Chronic respiratory diseases

Females
n=241,668

Association analysis of LTL with YLL
- Multiple linear model
- LTL grouped by four categories

group 1 (the shortest group): LTL<-1 S.D. [Ref]
group 2 (the shorter group compared to the mean): -1 <LTL <0 SD
group 3 (the longer group compared to the mean): 0 <LTL<1SD
group 4(the longest group): LTL≥1SD

The stratified analysis of LTL & YLL between premenopausal and postmenopausal females

Subgroups analysis of LTL & YLL between aging related diseases
- aging related diseases grouped by Cancer, Cardiovascular diseases, Chronic respiratory diseases

Supplementary Figure S2. Distribution of leukocyte telomere length

Appendix 2. Supplementary Tables

Supplementary table S1. Sex-specific baseline characteristics of participants with leukocyte telomere length

Characteristics	Males(n=203,731)						Females(n=241,668)					
	LTL Increased Per S.D.	LTL < -1 S.D.[Ref.] n=35,907	-1 S.D. ≤ LTL < 0 S.D. n=76,106	0 S.D. ≤ LTL < 1 S.D. n=67,124	LTL ≥ 1 S.D. n=24,594	P	LTL Increased Per S.D.	LTL < -1 S.D.[Ref.] n=32,197	-1 S.D. ≤ LTL < 0 S.D. n=81,636	0 S.D. ≤ LTL < 1 S.D. n=88,100	LTL ≥ 1 S.D. n=39,735	P
LTL, mean (%)	-0.1 (1.0)	-1.6 (0.5)	-0.5 (0.3)	0.4 (0.3)	1.5 (0.5)	<0.001	0.1(1.0)	-1.5 (0.5)	-0.5 (0.3)	0.5 (0.3)	1.6 (0.5)	<0.001
Age, median (IQR: P_{25}, P_{75})	59.0 (51.1, 64.2)	61.8 (55.5, 65.9)	59.9 (52.4, 64.6)	57.4 (49.5, 63.1)	54.7 (47.3, 61.6)	<0.001	58.3 (50.8, 63.5)	60.9 (53.9, 65.2)	59.5 (52.1, 64.2)	57.5 (50.1, 62.9)	55.3 (48.2, 61.6)	<0.001
Age Group, N (%)						<0.001						<0.001
40-50	44,915 (22.0)	4,498 (12.5)	14,291 (18.8)	17,670 (26.3)	8,456 (34.4)		54626 (22.6)	4,898 (15.2)	15,666 (19.2)	21,762 (24.7)	12,300 (31.0)	
50-60	64,999 (31.9)	9,987 (27.8)	24,189 (31.8)	22,531 (33.6)	8,292 (33.7)		82,668 (34.2)	9,756 (30.3)	27,025 (33.1)	31,276 (35.5)	14,611 (36.8)	
60-70	93,817 (46.0)	21,422 (59.7)	37,626 (49.4)	26,923 (40.1)	7,846 (31.9)		104,374 (43.2)	17,543 (54.5)	38,945 (47.7)	35,062 (39.8)	12,824 (32.3)	
Smoking Status, N (%)						<0.001						<0.001
Never	98,308 (48.3)	15,639 (43.6)	35,918 (47.2)	33,782 (50.3)	12,969 (52.7)		140,999 (58.3)	17,964 (55.8)	47,135 (57.7)	51,909 (58.9)	23,991 (60.4)	
Former	79,779 (39.2)	15,284 (42.6)	30,619 (40.2)	25,147 (37.5)	8,729 (35.5)		78,130 (32.3)	10,869 (33.8)	26,678 (32.7)	28,267 (32.1)	12,316 (31.0)	
Current	24,914 (12.2)	4,835 (13.5)	9,282 (12.2)	7,984 (11.9)	2,813 (11.4)		21,684 (9.0)	3,218 (10.0)	7,515 (9.2)	7,653 (8.7)	3,298 (8.3)	
BMI(kg/m², median (IQR: P_{25}, P_{75})	6.8 (5.7, 7.9)	6.9 (5.9, 8.1)	6.8 (5.7, 7.9)	6.7 (5.6, 7.8)	6.6 (5.6, 7.7)	<0.001	26.1 (23.4, 29.6)	26.5(23.7, 30.1)	26.2 (23.6, 29.8)	26.0 (23.4, 29.5)	25.7 (23.1, 29.2)	<0.001
WBC(x10⁹/L), median (IQR: P_{25}, P_{75})	27.3 (25.0, 30.0)	27.5 (25.2, 30.3)	27.4 (25.1, 30.2)	27.3 (25.0, 30.0)	27.1 (24.8, 29.7)	<0.001	6.7 (5.7, 7.8)	6.8 (5.8, 7.9)	6.8 (5.7, 7.8)	6.7 (5.6, 7.7)	6.6 (5.6, 7.7)	<0.001
Townsend Deprivation Index, N (%)						0.007						<0.001
Quintile 1	42,718 (21.0)	7,524 (21.0)	16,056 (21.1)	13,985 (20.8)	5,153 (21.0)		50,160 (20.8)	6,504 (20.2)	16,815 (20.6)	18,605 (21.1)	8,236 (20.7)	
Quintile 2-4	122,546 (60.2)	21,396 (59.6)	46,032 (60.5)	40,377 (60.2)	14,741 (59.9)		148,354 (61.4)	19,778 (61.4)	50,092 (61.4)	53,936 (61.2)	24,548 (61.8)	
Quintile 5	38,218 (18.8)	6,949 (19.4)	13,923 (18.3)	12,674 (18.9)	4,672 (19.0)		42,877 (17.7)	5,890 (18.3)	14,644 (17.9)	15,450 (17.5)	6,893 (17.3)	
Education, N (%)						<0.001						<0.001
College/University	67,772 (33.3)	10,493 (29.2)	24,263 (31.9)	23,569 (35.1)	9,447 (38.4)		74,673 (30.9)	8,430 (26.2)	23,683 (29.0)	28,426 (32.3)	14,134 (35.6)	
Other	98,517 (48.4)	17,091 (47.6)	36,953 (48.6)	32,567 (48.5)	11,906 (48.4)		123,505 (51.1)	16,240 (50.4)	41,789 (51.2)	45,305 (51.4)	20,171 (50.8)	
Alcohol, N (%)						<0.001						<0.001
Never	32,695 (16.0)	5,761 (16.0)	12,211 (16.0)	10,790 (16.1)	3,933 (16.0)		10,842 (4.5)	1,573 (4.9)	3,808 (4.7)	3,806 (4.3)	1,655 (4.2)	
Former	66,408 (32.6)	11,616 (32.4)	24,528 (32.2)	22,030 (32.8)	8,234 (33.5)		8,790 (3.6)	1,334 (4.1)	2,951 (3.6)	3,127 (3.5)	1,378 (3.5)	
Current	73,731 (36.2)	12,694 (35.4)	27,638 (36.3)	24,426 (36.4)	8,973 (36.5)		221,821 (91.8)	29,261 (90.9)	74,795 (91.6)	81,091 (92.0)	36,674 (92.3)	
Physical Activity, N (%)						0.018						<0.001
Low	3,588 (1.8)	635 (1.8)	1,342 (1.8)	1,169 (1.7)	442 (1.8)		34,766 (14.4)	4,477 (13.9)	11,879 (14.6)	12,606 (14.3)	5,804 (14.6)	
Moderate	6,769 (3.3)	1,289 (3.6)	2,556 (3.4)	2,136 (3.2)	788 (3.2)		81,067 (33.5)	10,403 (32.3)	27,151 (33.3)	29,948 (34.0)	13,565 (34.1)	
High	193,192 (94.8)	33,941 (94.5)	72,150 (94.8)	63,764 (95.0)	23,337 (94.9)		72,716 (30.1)	9,414 (29.2)	24,314 (29.8)	26,683 (30.3)	12,305 (31.0)	
Menopausal Status, N (%)						-						<0.001
Pre	-	-	-	-	-		148,260 (61.3)	22,190 (68.9)	52,952 (64.9)	52,129 (59.2)	20,989 (52.8)	
Post	-	-	-	-	-		54,935 (22.7)	5,142 (16.0)	16,040 (19.6)	21,703 (24.6)	12,050 (30.3)	

Note. LTL, leukocyte telomere length; Individualized YLL, individualized expected years of life lost; 95%CI, 95% confidence interval; S.D., standard deviation; Ref., reference group; WBC, white blood cell count; BMI, body mass index

Supplementary table S2. Stratification analysis of covariates between leukocyte telomere length and individualized expected years of life lost Males

Stratification Analysis	LTL Increased Per S.D.			-1 S.D. ≤ LTL < 0 S.D.			0 S.D. ≤ LTL < 1 S.D.			LTL ≥ 1 S.D.		
	Individualized YLL (95%CI)	P	P het	Individualized YLL (95%CI)	P	P het	Individualized YLL (95%CI)	P	P het	Individualized YLL (95%CI)	P	P het
Age Groups			0.033			0.209			0.360			0.030
40-50	0.142(0.059, 0.222)	0.001		0.005(-0.283, 0.294)	0.974		0.242(-0.039, 0.520)	0.092		0.366(0.057, 0.675)	0.020	
50-60	0.005(-0.058, 0.069)	0.862		-0.178(-0.369, 0.013)	0.067		0.018(-0.173, 0.208)	0.855		-0.155(-0.391, 0.079)	0.192	
60-70	0.087(-0.043, 0.217)	0.186		0.157(-0.177, 0.492)	0.357		0.201(-0.154, 0.560)	0.267		0.096(-0.421, 0.611)	0.717	
BMI			0.040			0.945			0.019			0.256
<30	-1.017(-1.089, -0.945)	<0.001		-1.348(-1.577, -1.119)	<0.001		-2.546(-2.774, -2.311)	<0.001		-3.400(-3.671, -3.123)	<0.001	
≥30	-0.826(-0.953, -0.699)	<0.001		-1.311(-1.703, -0.918)	<0.001		-1.894(-2.292, -1.501)	<0.001		-2.939(-3.424, -2.425)	<0.001	
Smoking Status			<0.001			0.002			<0.001			<0.001
Never	-1.078(-1.162, -0.999)	<0.001		-1.489(-1.744, -1.235)	<0.001		-2.434(-2.688, -2.179)	<0.001		-3.687(-3.990, -3.330)	<0.001	
Former	-1.091(-1.213, -0.969)	<0.001		-1.737(-2.128, -1.341)	<0.001		-3.011(-3.408, -2.621)	<0.001		-3.615(-4.078, -3.109)	<0.001	
Current	-0.520(-0.685, -0.356)	<0.001		-0.476(-0.986, 0.027)	0.064		-1.325(-1.834, -0.816)	<0.001		-1.802(-2.431, -1.177)	<0.001	
Townsend Deprivation Index			0.002			0.102			0.016			0.005
Quintile 1	-1.131(-1.263, -0.999)	<0.001		-1.734(-2.159, -1.309)	<0.001		-2.853(-3.278, -2.428)	<0.001		-3.875(-4.375, -3.370)	<0.001	
Quintile 2-4	-0.933(-1.016, -0.856)	<0.001		-1.277(-1.527, -1.022)	<0.001		-2.252(-2.507, -2.002)	<0.001		-3.143(-3.446, -2.840)	<0.001	
Quintile 5	-0.846(-1.000, -0.699)	<0.001		-1.245(-1.724, -0.767)	<0.001		-2.233(-2.711, -1.754)	<0.001		-2.938(-3.515, -2.368)	<0.001	
Education			0.323			0.642			0.307			0.206
Other	-0.871(-0.956, -0.787)	<0.001		-1.252(-1.519, -0.986)	<0.001		-2.069(-2.335, -1.803)	<0.001		-2.868(-3.188, -2.547)	<0.001	
College/University	-0.924(-1.019, -0.828)	<0.001		-1.138(-1.454, -0.822)	<0.001		-2.253(-2.563, -1.943)	<0.001		-3.135(-3.499, -2.777)	<0.001	
Alcohol			0.137			0.62			0.277			0.139
Never	-1.508(-2.068, -0.949)	<0.001		-0.870(-2.700, 0.961)	0.352		-3.242(-5.06, -1.399)	<0.001		-5.182(-7.298, -3.059)	<0.001	
Former	-0.781(-1.195, -0.361)	<0.001		-0.787(-2.081, 0.501)	0.231		-1.440(-2.734, -0.117)	0.029		-2.396(-3.958, -0.834)	0.003	
Current	-0.959(-1.019, -0.894)	<0.001		-1.358(-1.561, -1.162)	<0.001		-2.383(-2.585, -2.180)	<0.001		-3.247(-3.485, -3.002)	<0.001	
Physical Activity			0.021			0.011			0.008			0.071
Low	-0.841(-0.996, -0.685)	<0.001		-0.766(-1.267, -0.271)	0.002		-1.976(-2.477, -1.480)	<0.001		-3.007(-3.600, -2.413)	<0.001	
Moderate	-1.087(-1.199, -0.980)	<0.001		-1.730(-2.084, -1.370)	<0.001		-2.793(-3.147, -2.439)	<0.001		-3.714(-4.134, -3.301)	<0.001	
High	-0.942(-1.040, -0.838)	<0.001		-1.370(-1.688, -1.058)	<0.001		-2.196(-2.514, -1.884)	<0.001		-3.224(-3.603, -2.851)	<0.001	

Note. LTL, leukocyte telomere length; Individualized YLL, individualized expected years of life lost; 95%CI, 95% confidence interval; S.D., standard deviation; WBC, white blood cell count; BMI, body mass index; reference group, the shortest group: LTL<-1 S.D.

Supplementary table S2. Stratification analysis of covariates between leukocytes telomere length and individualized expected years of life lost females

Stratification Analysis	LTL Increased Per S.D.			-1 S.D. ≤ LTL < 0 S.D.			0 S.D. ≤ LTL < 1 S.D.			LTL ≥ 1 S.D.		
	Individualized YLL (95%CI)	P	P het	Individualized YLL (95%CI)	P	P het	Individualized YLL (95%CI)	P	P het	Individualized YLL (95%CI)	P	P het
Age Groups			<0.001			0.229			0.094			<0.001
40-50	0.203(0.116, 0.290)	<0.001		0.301(-0.034, 0.636)	0.079		0.287(-0.037, 0.609)	0.082		0.817(0.475, 1.160)	<0.001	
50-60	0.021(-0.031, 0.076)	0.435		0.010(-0.171, 0.192)	0.908		0.113(-0.063, 0.291)	0.209		0.034(-0.165, 0.234)	0.743	
60-70	-0.069(-0.160, 0.002)	0.057		-0.046(-0.282, 0.180)	0.666		-0.141(-0.377, 0.097)	0.247		-0.370(-0.673, -0.067)	0.016	
BMI			0.310			0.875						0.816
<30	0.109(0.058, 0.161)	<0.001		-0.019(-0.193, 0.154)	0.832		0.045(-0.122, 0.212)	0.594	0.334	0.283(0.096, 0.469)	0.003	
≥30	0.049(-0.043, 0.148)	0.306		-0.049(-0.363, 0.271)	0.775		-0.129(-0.443, 0.185)	0.417		0.222(-0.135, 0.579)	0.224	
Smoking Status			<0.001			0.262						<0.001
Never	0.051(-0.006, 0.103)	0.074		-0.064(-0.270, 0.116)	0.436		-0.135(-0.321, 0.051)	0.162	<0.001	0.103(-0.103, 0.315)	0.331	
Former	0.039(-0.045, 0.122)	0.367		-0.064(-0.348, 0.225)	0.666		-0.109(-0.386, 0.174)	0.447		0.167(-0.148, 0.483)	0.297	
Current	0.606(0.440, 0.765)	<0.001		0.385(-0.135, 0.905)	0.149		1.169(0.655, 1.689)	<0.001		1.658(1.058, 2.258)	<0.001	
Townsend Deprivation Index			0.008			0.123						0.060
Quintile 1	-0.031(-0.124, 0.062)	0.520		0.099(-0.223, 0.414)	0.554		-0.291(-0.600, 0.025)	0.068	0.022	-0.049(-0.396, 0.303)	0.790	
Quintile 2-4	0.121(0.063, 0.178)	<0.001		-0.146(-0.336, 0.051)	0.145		0.000(-0.190, 0.190)	0.991		0.273(0.063, 0.482)	0.011	
Quintile 5	0.185(0.073, 0.297)	0.001		0.264(-0.119, 0.646)	0.178		0.396(0.020, 0.772)	0.038		0.633(0.204, 1.055)	0.004	
Education			0.001			0.895			0.094			0.031
Other	0.096(0.032, 0.153)	0.002		0.032(-0.172, 0.230)	0.766		0.051(-0.147, 0.249)	0.607		0.281(0.057, 0.505)	0.014	
College/University	0.248(0.172, 0.325)	<0.001		0.006(-0.261, 0.274)	0.954		0.331(0.070, 0.592)	0.013		0.681(0.395, 0.968)	<0.001	
Alcohol			0.304			0.293			0.086			0.590
Never	-0.037(-0.281, 0.208)	0.765		0.545(-0.300, 1.395)	0.205		0.031(-0.795, 0.857)	0.943		0.061(-0.863, 0.985)	0.897	
Former	0.253(-0.018, 0.524)	0.070		0.277(-0.641, 1.196)	0.553		0.992(0.092, 1.892)	0.031		0.746(-0.271, 1.763)	0.150	
Current	0.102(0.057, 0.147)	<0.001		-0.070(-0.229, 0.083)	0.368		-0.038(-0.191, 0.115)	0.625		0.268(0.096, 0.433)	0.002	
Physical Activity			<0.001			0.074			0.043			<0.001
Low	0.320(0.201, 0.445)	<0.001		0.414(-0.006, 0.828)	0.055		0.470(0.056, 0.884)	0.025		1.241(0.784, 1.705)	<0.001	
Moderate	0.051(-0.026, 0.128)	0.178		-0.154(-0.410, 0.102)	0.247		-0.141(-0.390, 0.115)	0.278		0.038(-0.237, 0.320)	0.774	
High	0.085(0.007, 0.163)	0.029		0.078(-0.195, 0.345)	0.582		0.091(-0.169, 0.358)	0.487		0.397(0.104, 0.689)	0.008	
Menopausal Status			<0.001			<0.001			<0.001			<0.001
Pre	-0.387(-0.446, -0.328)	<0.001		-0.320(-0.501, -0.135)	0.001		-0.741(-0.922, -0.560)	<0.001		-1.276(-1.490,-1.065)	<0.001	
Post	0.705(0.625, 0.785)	<0.001		0.750(0.474, 1.031)	<0.001		1.387(1.114, 1.660)	<0.001		2.285(1.986, 2.589)	<0.001	

Note. LTL, leukocyte telomere length; Individualized YLL, individualized expected years of life lost; 95%CI, 95% confidence interval; S.D., standard deviation; WBC, white blood cell count; BMI, body mass index; reference group, the shortest group: LTL<-1 S.D.

Supplementary table S3. Sensitivity analyses including participants with various ethnicity at baseline (*n*=216,391 males, *n*=256,086 females) for the associations between leukocyte telomere length and individualized expected years of life lost

Characteristic	Males		Females	
	Individualized YLL (95%CI)	*P*	Individualized YLL (95%CI)	*P*
LTL Increased Per S.D.	-0.947(-1.007, -0.886)		0.148(0.103, 0.193)	
LTL Groups				
LTL<-1 S.D.	Ref.	-	Ref.	-
-1 S.D.≤LTL<0 S.D.	-1.303(-1.496, -1.110)	<0.001	-0.013(-0.167, 0.135)	<0.001
0 S.D.≤LTL<1 S.D.	-2.352(-2.545, -2.159)	<0.001	0.064(-0.077, 0.212)	<0.000
LTL≥1 S.D.	-3.214(-3.437, -2.985)	<0.001	0.386(0.225, 0.553)	<0.001

Note. LTL, leukocyte telomere length; Individualized YLL, individualized expected years of life lost; 95%CI, 95% confidence interval; S.D., standard deviation; Ref, reference group; Fully-adjusted model: adjusted for age, ethnicity, menopausal status (females only), body mass index (BMI), smoking status, white cell count, townsend deprivation index, college degree, alcohol activity, physical activity and the interaction term of LTL with age.

Supplementary table S4. Sensitivity analyses including participants with various ethnicity at baseline (*n*= 155,150 postmenopausal females, *n*= 60,013 premenopausal females) for the associations between leukocyte telomere length and individualized expected years of life lost

Characteristics	Premenopausal Females		Postmenopausal Females	
	Individualized YLL (95%CI)	*P*	Individualized YLL (95%CI)	*P*
LTL Increased Per S.D.	0.787(0.711, 0.867)		-0.384(-0.444, -0.329)	
LTL Groups				
LTL<-1 S.D.	Ref.	-	Ref.	-
-1 S.D.≤LTL<0 S.D.	0.848(0.578, 1.118)	<0.001	-0.363(-0.542,-0.184)	<0.001
0 S.D.≤LTL<1 S.D.	1.575(1.312, 1.837)	<0.001	-0.773(-0.953,-0.594)	<0.000
LTL≥1 S.D.	2.541(2.252, 2.830)	<0.001	-1.294(-1.504,-1.089)	<0.001

Note. LTL, leukocyte telomere length; Individualized YLL, individualized expected years of life lost; 95%CI, 95% confidence interval; S.D., standard deviation; Ref, reference group; Fully-adjusted model: adjusted for age, ethnicity, menopausal status (females only), body mass index (BMI), smoking status, white cell count, townsend deprivation index, college degree, alcohol activity, physical activity and the interaction term of LTL with age.