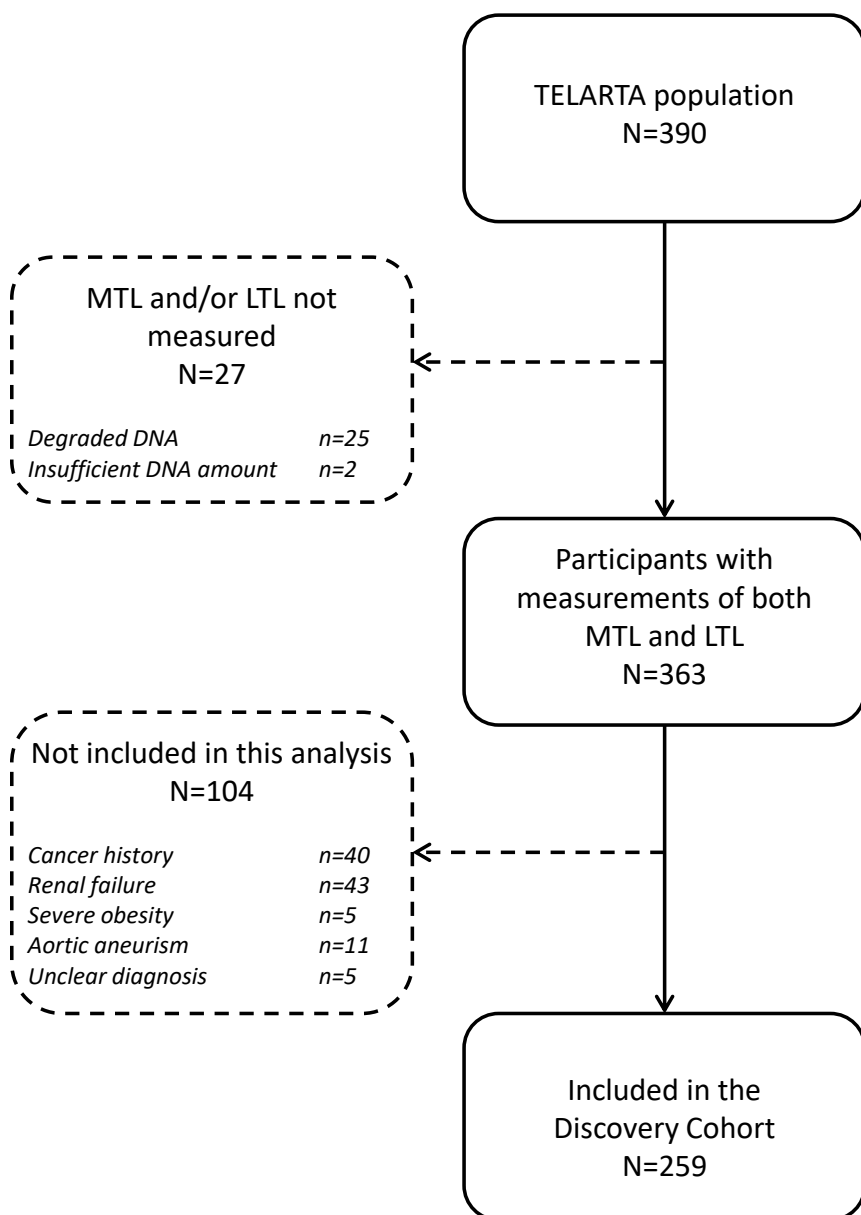
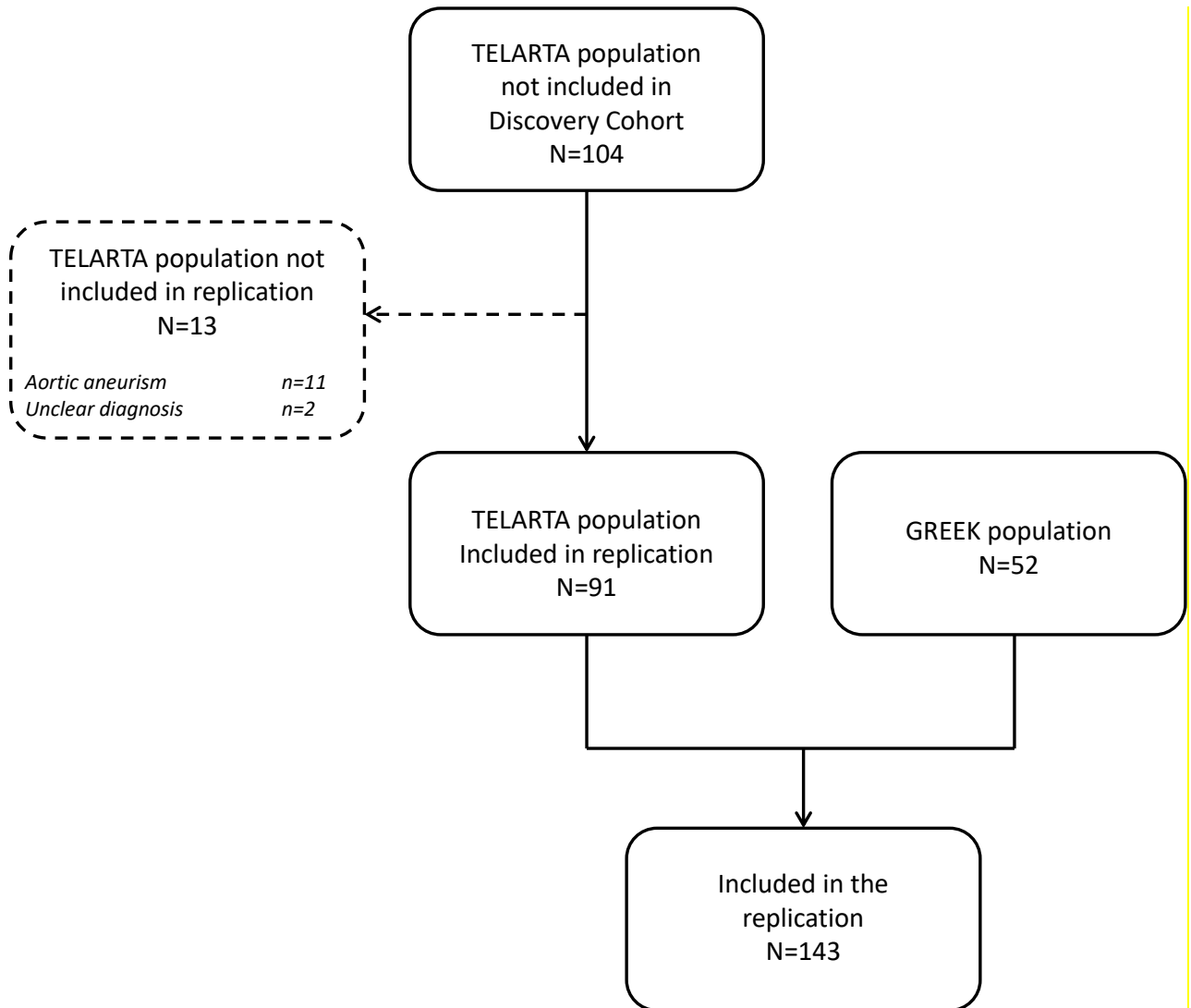


SUPPLEMENTAL MATERIAL

Online Figure I: Flow chart of the participants in the TELARTA project (Discovery Cohort).

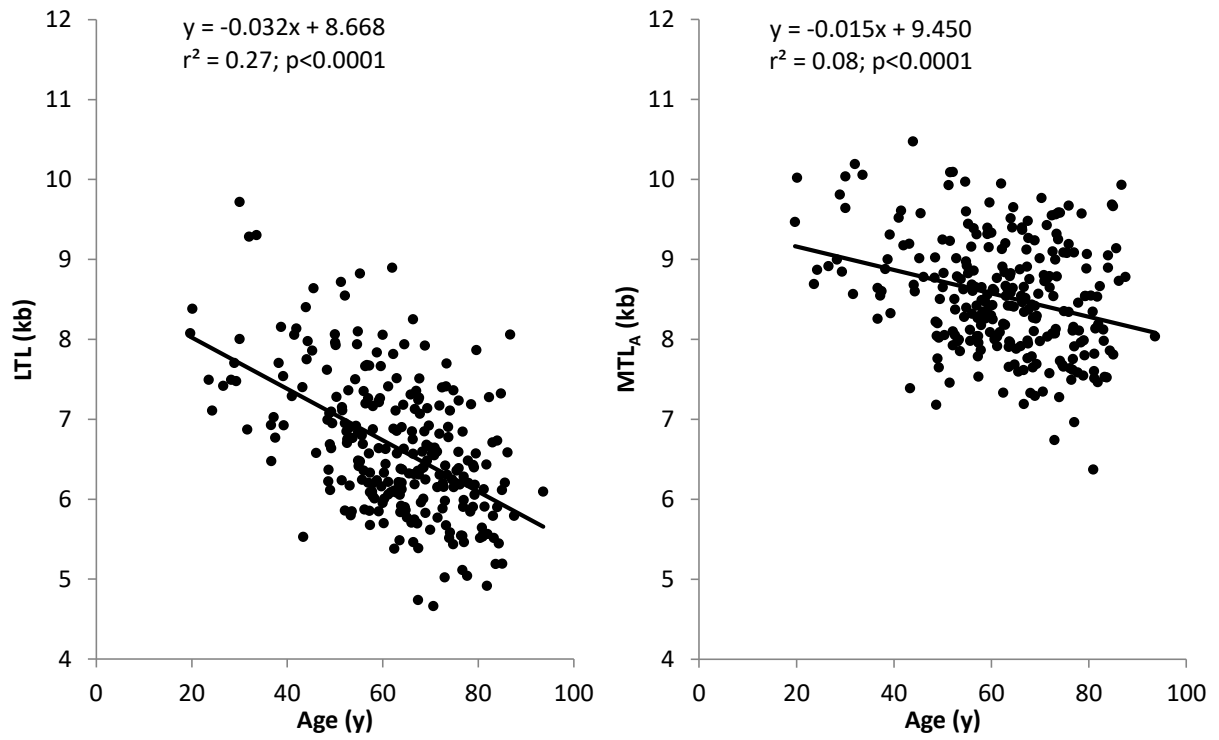


Online Figure II: Flow chart of the participants of the Replication Cohort.



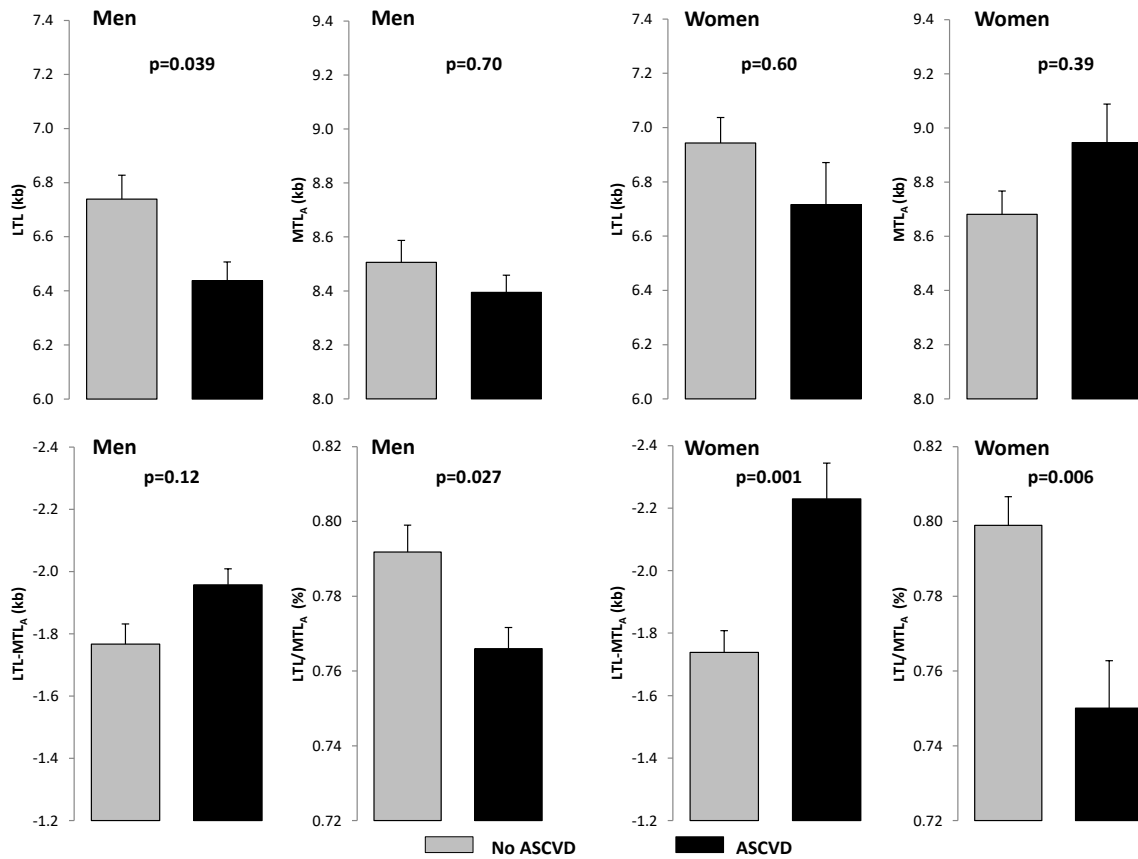
Online Figure III: Leukocyte telomere length and site-adjusted muscle telomere length versus age in the Discovery Cohort.

LTL= leukocyte telomere length; MTL_A = site-adjusted muscle telomere length adjusted for biopsy site.



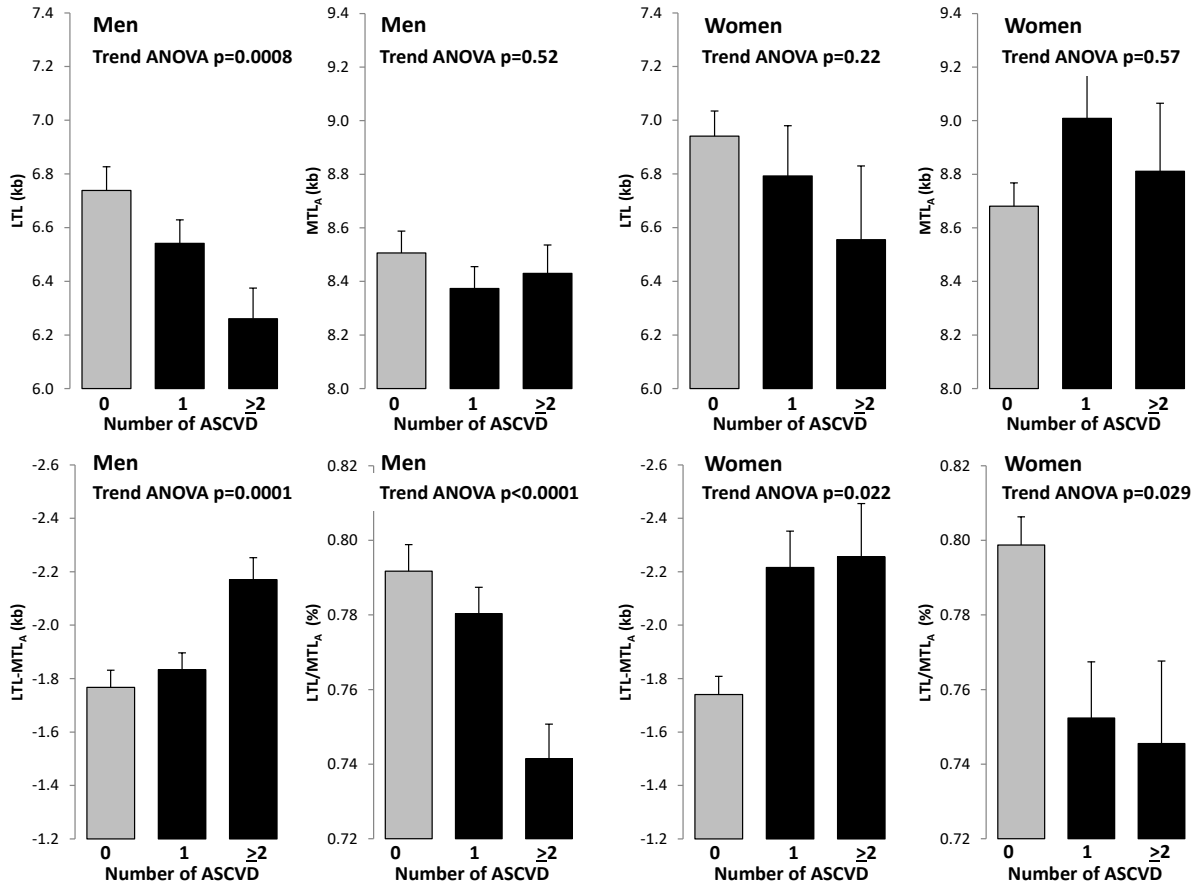
Online Figure IV: The four telomere length models in men and women of the Discovery Cohort.

LTL= leukocyte telomere length; MTL_A = site-adjusted muscle telomere length; ASCVD = atherosclerotic cardiovascular disease. Values are adjusted for age. Mean \pm SEM.



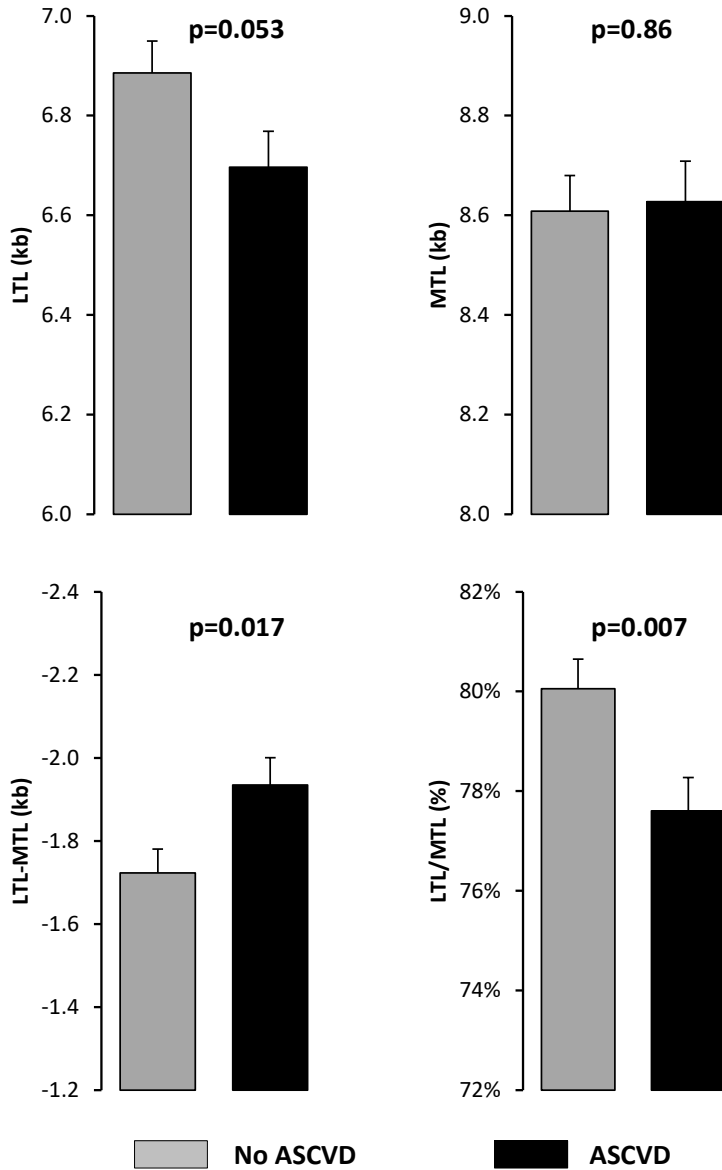
Online Figure V: The four telomere length models versus the number of atherosclerotic sites in the men and women of the Discovery Cohort.

0 = Control; 1, one site; ≥ 2 , two or more sites. Values are adjusted for age. Mean \pm SEM.



Online Figure VI: The four telomere length models in the subjects of the Replication Cohort with and without atherosclerotic cardiovascular disease (ASCVD).

LTL= leukocyte telomere length; MTL= muscle telomere length; ACVD = atherosclerotic cardiovascular disease. Age and sex adjusted values. Mean \pm SEM.



Online Table I. Muscle telomere length (kb) in different biopsy sites in the Discovery Cohort.

Muscle tissue source	N	Least square mean	SE
Head & neck	35	8.412	0.117
Legs distal	11	8.244	0.206
Legs proximal	76	8.414	0.078
Abdominal and back	67	8.551	0.084
Pelvic cavity	20	8.574	0.152
Thorax	50	8.849	0.096

Least square mean estimates are from model with age, sex and biopsy site. Weighted mean muscle telomere length was 8.50 kb. Muscle telomere length varied significantly between tissues (**Online Table IIb**).

Online Table II. Age and sex effects on leukocyte telomere length (A) and muscle telomere length (B), and comparisons of TL attrition rates between leukocyte telomere length and muscle telomere length in a mixed model (C) in the Discovery Cohort.

A. LTL					
	Estimate	SE	F	df	p (> t)
Intercept	8.746	0.208			
Age (y)	-0.030	0.0033	82.7	1,256	<0.0001
Sex	-0.312	0.101	9.59	1,256	0.0022
B. MTL					
	Estimate	SE	F	df	p (> t)
Intercept	9.49	0.203			
Age (y)	-0.0124	0.0031	15.53	1,251	<0.0001
Sex	-0.317	0.0935	11.48	5,251	0.0008
Biopsy site			3.32	5,251	0.0063
C*. TL					
	Estimate	SE	F	df	p (> t)
Intercept	8.746	0.202			
Age (y)	-0.030	0.0032	88.31	1,337.1	<0.0001
Sex	-0.312	0.090	11.92	1,256	0.0006
Tissue	0.794	0.153	26.90	1,257	<0.0001
Tissue x Age	0.0174	0.0024	52.93	1,257	<0.0001

LTL: $r^2 = 0.299$. MTL: $r^2 = 0.177$.

C: Comparison of shortening rate between LTL and MTL using a mixed model with ‘individual’ as random effect. Coding of sex: women = 0, men = 1. Coding of tissue type: leukocytes = 0, muscle = 1.

LTL= leukocyte telomere length; MTL = muscle telomere length; df = degrees of freedom; SE = standard error; N = 271 individuals.

*Instead of defining tissue as a binary variable (leukocytes/muscle), the model can be extended by defining tissue as a factor with seven levels (six muscle types plus leukocytes). However, this model fitted markedly less well (current model: AIC=984; extended model: AIC=1046).

Online Table III. Odds ratios for atherosclerotic cardiovascular disease as the best model in Table 2 adjusted for potentially confounding variables (*italics*) in the Discovery Cohort.

Variable	Odd's ratio	95% confidence interval		p
		lower limit	upper limit	
TL (Z-score)	0.571	0.383	0.833	0.0035
Age (years)	1.212	0.969	1.606	0.0988
Age squared	0.999	0.998	1.000	0.1588
Sex	2.834	1.359	6.067	0.0053
<i>Ever smoking</i>	5.148	2.608	10.544	<0.0001
<i>Hypertension</i>	2.587	1.269	5.384	0.0088
<i>Diabetes</i>	2.418	0.916	6.678	0.0749
<i>Dyslipidemia</i>	3.101	1.283	7.987	0.0115
<i>BMI</i>	0.868	0.794	0.944	0.0007

TL (LTL/MTL_A) was transformed to Z-scores. Coding of sex: women = 0, men = 1.

P-values based on likelihood-ratio tests.

LTL = leukocyte telomere length; MTL_A = muscle telomere length adjusted for muscle biopsy site; BMI = body mass index.

Online Table IV: The four telomere length models in age- and sex- matched pairs (N=79) with and without atherosclerotic cardiovascular disease (in the Discovery Cohort).

	Age (years)	LTL (kb)	MTL_A (kb)	LTL-MTL_A (kb)	LTL/MTL_A (%)
Control	64.5 ± 10.2	6.69 ± 0.68	8.48 ± 0.62	-1.79 ± 0.51	78.9 ± 5.8
ASCVD	64.6 ± 10.1	6.42 ± 0.84	8.42 ± 0.75	-2.00 ± 0.67	76.3 ± 7.4
ASCVD-Controls*	0.10 ± 0.73	-0.28 ± 1.06	-0.06 ± 1.03	-0.21 ± 0.81	-2.7 ± 9.0
Paired t-test	p = 0.21	p = 0.023	p = 0.59	p = 0.022	p = 0.0097

LTL = leukocyte telomere length; MTL_A = muscle telomere length adjusted for muscle biopsy site;
ASCVD = atherosclerotic cardiovascular disease.
*Mean of intra-pair differences

Online Table V: Odds ratios for men (A) and women (B) for atherosclerotic cardiovascular disease, age in the four telomere length models in the Discovery Cohort.

A. Men in Discovery Cohort (n=177).

Variable	LTL	MTL_A	LTL-MTL_A	LTL/MTL_A
	OR	OR	OR	OR
	95% CI	95% CI	95% CI	95% CI
	p	p	p	p
TL (Z-scores)	0.60 0.40, 0.88 0.0091	0.83 0.58, 1.16 0.27	0.76 0.53, 1.08 0.1332	0.68 0.47, 0.97 0.0338
Age (years)	1.32 1.05, 1.75 0.016	1.34 1.07, 1.78 0.0086	1.19 0.98, 1.51 0.0116	1.30 1.05, 1.72 0.0141
Age squared (years ² /100)	0.83 0.66, 0.99 0.034	0.82 0.66, 0.98 0.0276	0.83 0.67, 0.99 0.0325	0.83 0.68, 0.99 0.0338
AICc	221.59	227.19	226.14	223.89
ΔAICc	0	5.60	4.55	2.30

TL = telomere length; LTL = leukocyte telomere length; MTL_A = muscle telomere length adjusted for muscle biopsy site; ASCVD = atherosclerotic cardiovascular disease; OR = odds ratio; CI = confidence interval.

TLs were transformed to Z-scores. Age squared was divided by 100 to yield more informative estimates.

The best fitting model is indicated in bold. p-values based on likelihood-ratio tests. AICc represents Akaike's Information Criterion with a correction for finite sample sizes,¹⁹ while ΔAICc is relative to the best model (in bold).

B. Women in Discovery Cohort (n=83).

Variable	LTL	MTL_A	LTL-MTL_A	LTL/MTL_A
	OR	OR	OR	OR
	95% CI	95% CI	95% CI	95% CI
	p	p	p	p
TL (Z-scores)	0.75 0.36, 1.46 0.399	1.74 0.98, 3.21 0.059	0.42 0.20, 0.79 0.0006	0.39 0.18, 0.79 0.0075
Age (years)	1.33 0.96, 2.13 0.0923	1.50 1.04, 2.51 0.0243	1.39 0.99, 2.27 0.0556	1.35 0.98, 2.18 0.0736
Age squared (years ² /100)	0.82 0.58, 1.06 0.1554	0.76 0.51, 1.13 0.24	0.78 0.54, 1.03 0.0823	0.80 0.98, 1.04 0.0984
AICc	93.90	91.06	87.06	87.46
ΔAICc	6.84	4.00	0	0.40

TL = telomere length; LTL = leukocyte telomere length; MTL_A = muscle telomere length adjusted for muscle biopsy site; ASCVD = atherosclerotic cardiovascular disease; OR = odds ratio; CI = confidence interval.

TLs were transformed to Z-scores. Age squared was divided by 100 to yield more informative estimates.

The best fitting model is indicated in bold. p-values based on likelihood-ratio tests. AICc represents Akaike's Information Criterion with a correction for finite sample sizes,¹⁹ while ΔAICc is relative to the best model (in bold).

Online Table VI: Main characteristics of the Replication Cohort

Parameter	All	Control	ASCVD
Number (W/M)	143 (46/97)	80 (37/43)	63 (9/54)
Women (%)	32	46	14***
French/Greek (number)	91/52	50/30	41/22
Age (years)	56 ± 17	50 ± 17	65 ± 11***
Hypertension (%) †	49	41	59*
Diabetes (%) †	24	12	38***
Dyslipidemia †	24	16	33*
Smoking (%) §	49	39	60*
BMI (kg/m ²)	30.8 ± 10.1	32.2 ± 11.4	29.1 ± 7.9
Severe Obesity (%)	20	30	8**
Renal failure (%)	31	31	32
Cancer (%)	28	30	25

ASCVD: atherosclerotic cardiovascular disease; BMI : body mass index.

Data are expressed as mean ± SD; % or number.

*p < 0.05; ** p<0.01; *** p < 0.001 for ASCVD vs. No ASCVD.

† history of or specific treatment for this risk factor; § current and ex-smokers.

Severe Obesity: BMI > 40 kg/m²; Renal failure: glomerular filtration < 30 ml/min/1,73m²;

Cancer: active malignancy or history of chemotherapy/radiotherapy for cancer.

Online Table VII: Odds ratios for atherosclerotic cardiovascular disease, age and sex in the four telomere length models in the Replication Cohort.

Variable	LTL	MTL	LTL-MTL	LTL/MTL
	OR 95% CI p	OR 95% CI p	OR 95% CI p	OR 95% CI p
TL (Z-scores)	0.58 0.36, 0.91 0.0172	1.03 0.72, 1.47 0.88	0.60 0.40, 0.88 0.0088	0.56 0.36, 0.84 0.0042
Age (years)	1.21 1.01, 1.39 0.057	1.19 0.99, 1.50 0.067	1.19 0.98, 1.51 0.081	1.20 0.98, 1.51 0.077
Age squared (years ² /100)	0.88 0.72, 1.04 0.146	0.90 0.75, 1.07 0.24	0.90 0.74, 1.06 0.22	0.89 0.73, 1.06 0.19
Sex	2.69 1.16, 6.70 0.021	2.63 1.14, 6.51 0.023	3.20 1.34, 8.23 0.0081	3.13 1.32, 8.02 0.0088
AICc	204.44	210.09	203.24	201.90
Δ AICc	2.55	8.19	1.35	0

TL = telomere length; LTL = leukocyte telomere length; MTL = muscle telomere length; OR = odds ratio; CI = confidence interval.

TLs were transformed to Z-scores. Age squared was divided by 100 to yield more informative estimates. Coding of sex: women = 0, men = 1.

The best fitting model is indicated in bold. p-values based on likelihood-ratio tests. AICc represents Akaike's Information Criterion with a correction for finite sample sizes,¹⁹ while Δ AICc is relative to the best model (in bold).