

Table S1. Relationship between MI/ACS and epigenetic age acceleration, per 1 year increment of the difference between baseline EA minus CA in men and women (men $n=171$, women, $n=135$).

Measure of epigenetic age	n, case/control	Model1	Model2	Model3
		OR (95%CI)	OR (95%CI)	OR (95%CI)
Men				
ΔAHR , per 1 year	67/104	1.000 (0.93-1.08)	1.006 (0.93-1.08)	1.000 (0.92-1.08)
	p-value for trends	0.994	0.880	0.993
ΔAHn , per 1 year	67/104	0.995 (0.92-1.08)	1.000 (0.92-1.09)	1.000 (0.91-1.09)
	p-value for trends	0.903	0.992	0.991
ΔAPh , per 1 year	67/104	1.035 (0.98-1.09)	1.026 (0.971-1.09)	1.026 (0.96-1.09)
	p-value for trends	0.239	0.401	0.426
ΔASB , per 1 year	67/104	0.986 (0.89-1.09)	0.989 (0.89-1.09)	0.988 (0.89-1.10)
	p-value for trends	0.782	0.831	0.825
Women				
ΔAHR , per 1 year	62/73	1.008 (0.93-1.09)	1.013 (0.93-1.10)	1.037 (0.95-1.14)
	p-value for trends	0.994	0.763	0.435
ΔAHn , per 1 year	62/73	1.009 (0.93-1.10)	1.016 (0.94-1.10)	1.033 (0.94-1.13)
	p-value for trends	0.824	0.708	0.492
ΔAPh , per 1 year	62/73	1.008 (0.95-1.07)	1.004 (0.95-1.06)	1.008 (0.94-1.8
	p-value for trends	0.788	0.904	0.806
ΔASB , per 1 year	62/73	0.999 (0.91-1.10)	1.005 (0.91-1.8)	1.031 (0.92-1.15)
	p-value for trends	0.980	0.926	0.592

ΔAHR – difference between EA by Horvath and chronological age; ΔAHn – difference between EA by Hannum and chronological age; ΔAPh – difference between Phenotypic EA and chronological age; ΔASB – difference between Skin and Blood EA and chronological age; OR – odds ratio ratio; CI – confidence interval; Model 1: age-adjusted; Model 2: adjusted for age and sex; Model 2:– adjusted for age, and smoking; model 3: adjusted for age, smoking, SBP, TC, BMI and education.

Table S2. Distribution of baseline covariates among cases of incident MI/ACS and expanded control(cases, n = 129 and controls, n =265).

Covariates	Cases (incident MI/ACS)	Expanded controls	p-value
Observed	129	265	
Age at baseline, years (mean, SD)	59.8 (6.87)	57.4 (6.95)	<0.001
Females (%)	62 (48.1)	155 (58.5)	0.051
Systolic blood pressure, mmHg (mean, SD)	151.6 (26.93)	136.7 (23.10)	<0.001
Diastolic blood pressure, mmHg (mean, SD)	92.3 (14.36)	86.5 (12.55)	<0.001
Body mass index, kg/sqm (mean, SD)	28.8 (5.73)	27.83 (4.83)	0.073
Waist/hip ratio, unit (mean, SD)	0.90 (0.077)	0.88 (0.032)	0.006
Total cholesterol mmol/l (mean, SD)	6.61 (1.27)	6.44 (1.26)	0.210
LDL cholesterol, mmol/l (mean, SD)	4.32 (1.14)	4.19 (1.12)	0.287
Glucose, plasma, mmol/l mean, SD)	6.41 (2.29)	5.82 (0.92)	<0.001
Hypertension (%)	96(74.4)	136 (51.3)	<0.001
HT treatment (among HT), (%)	46 (47.9)	55 (40.4)	0.001
Diabetes mellitus type 2 (%)	24(18.9)	16 (6.3)	<0.001
DM2 treatment (among DM2), (%)	8 (33.3)	5.(31.3)	0.840
Frequency of drinking (%)			
Non-drinkers	24 (18.6)	28 (10.6)	
< 1/month	55 (42.6)	116 (43.8)	0.125
1-3/month	25 (19.4)	50 (18.9)	
1-4/week	22 (17.1)	67 (25.3)	
5+/week	3 (2.3)	4 (1.5)	
Smoking (%)			
Never smoking	75 (58.1)	163 (61.5)	0.006
Former smoking	10 (7.8)	44 (16.6)	
Present smoker	27 (20.9)	58 (21.9)	
Married (%)	96 (74.4)	192 (72.5)	0.680
University education (%)	27 (20.9)	89 (33.6)	<0.001
Difference EA-chronological age by four measures:			
Δ AHr, year	0.055 (5.35)	1.213 (4.92)	0.034
Δ AHn, year	-2.702 (5.36)	-1.831 (4.64)	0.098
Δ APh, year	-8.945 (6.43)	-8.977 (6.01)	0.960
Δ ASB, year	-2.551 (4.06)	-1.551 (3.50)	0.012

SD – standard deviation; EA- epigenetic age; CVD – cardiovascular disease

^a ANOVA or Chi-square test.

Table S3. Relationship between MI/ACS and epigenetic age acceleration, per 1 year increment of the difference between baseline EA minus CA in the expanded sample (cases, n = 129 and controls, n =265).

Measure of epigenetic age	n, case/ control	Model1	Model2	Model3	Model4
		OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
Δ AHr, per 1 year	129/177	0.98	0.969	0.971	0.971
		(0.94-1.03)	(0.92-1.06)	(0.93-1.02)	(0.92-1.02)
	p-value for trends	0.391	0.193	0.230	0.258
Δ AHn, per 1 year	129/177	0.996	0.979	0.984	0.995
		(0.95-1.05)	(0.93-1.03)	(0.93-1.04)	(0.94-1.05)
	p-value for trends	0.886	0.413	0.554	0.860
Δ APh, per 1 year	129/177	1.014	1.005	1.000	0.998
		(0.98-1.05)	(0.97-1.04)	(0.961-1.04)	(0.96-1.04)
	p-value for trends	0.439	0.809	0.988	0.923
Δ ASB, per 1 year	129/177	0.950	0.938	0.947	0.949
		(0.89-1.01)	(0.88-1.00)	(0.89-1.1	(0.88-1.02)
	p-value for trends	0.096	0.055	0.088	0.135

Δ AHr – difference between EA by Horvath and chronological age; Δ AHn – difference between EA by Hannum and chronological age; Δ APh – difference between Phenotypic EA and chronological age; Δ ASB – difference between Skin and Blood EA and chronological age; OR – odds ratio; CI – confidence interval;

Model 1: age-adjusted; Model 2: adjusted for age and sex; Model 3: adjusted for age, sex and smoking; Model 4: adjusted for age, sex, smoking, SBP, TC, BMI and education.

Table S4. Relationship between MI/ACS and epigenetic age acceleration in the expanded sample, by tertiles of the difference between baseline EA minus CA (cases, n=129 and controls, n=265).

Measure of epigenetic age	n, case/control	Tertiles	Absolute difference T1-T2 T2-T3	Model1	Model2	Model3	Model4
				OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
ΔAHR , year	129/265	T1 (ref)		1.0	1.0	1.0	1.0
		T2	5.31	0.68 (0.40-1.15)	0.64 (0.38-1.09)	0.61 (0.36-1.05)	0.66 (0.38-1.18)
		T3	5.48	0.86 (0.50-1.49)	0.79 (0.45-1.38)	0.80 (0.45-1.42)	0.83 (0.45-1.51)
		p-value for trend		0.540	0.366	0.395	0.489
ΔAHn , year	129/265	T1 (ref)		1.0	1.0	1.0	1.0
		T2	4.94	0.86 (0.50-1.46)	0.79 (0.46-1.36)	0.88 (0.51-1.53)	0.94 (0.52-1.69)
		TQ3	5.31	1.17 (0.65-2.09)	0.97 (0.53-1.78)	1.06 (0.57-1.96)	1.24 (0.64-2.40)
		p-value for trend		0.626	0.894	0.888	0.550
ΔAPh , year	129/265	T1 (ref)		1.0	1.0	1.0	1.0
		T2	6.34	0.97 (0.57-1.65)	0.96 (0.56-1.63)	0.98 (0.57-1.68)	0.95 (0.53-1.68)
		T3	7.03	1.42 (0.85-2.42)	1.26 (0.73-2.18)	1.24 (0.70-2.17)	1.10 (0.61-2.00)
		p-value for trend		0.197	0.415	0.472	0.768
ΔASB , year	129/265	T1 (ref)		1.0	1.0	1.0	1.0
		T2	3.79	0.54 (0.32-0.93)	0.51 (0.30-0.88)	0.52 (0.29-0.89)	0.56 (0.32-1.00)
		T3	4.05	0.82 (0.48-1.38)	0.73 (0.42-1.25)	0.78 (0.45-1.35)	0.80 (0.44-1.44)
		p-value for trend		0.432	0.241	0.363	0.424

ΔAHR – difference between EA by Horvath and chronological age; ΔAHn – difference between EA by Hannum and chronological age; ΔAPh – difference between Phenotypic EA and chronological age; ΔASB – difference between Skin and Blood EA and chronological age; OR – odds ratio; CI – confidence interval;

Model 1: age-adjusted; Model 2: adjusted for age and sex; Model 3: adjusted for age, sex and smoking; Model 4: adjusted for age, sex, smoking, SBP, TC, BMI and education.