Supplementary methods

DFTJ cohort

Definition of obesity. Obesity status was classified based on body mass index (BMI) as underweight (BMI < 18.5), normal (18.5 ≤ BMI < 24), overweight (24 ≤ BMI < 28), and obesity (BMI ≥ 28) [24].

Definition of prevalent diseases. Hypertension was defined as a self-reported diagnosis of hypertension or anti-hypertensive medications usage or a measured systolic blood pressure (SBP) ≥140 mmHg or diastolic blood pressure (DBP) ≥90 mmHg. Dyslipidemia was defined as a self-reported diagnosis of dyslipidemia or lipid-lowering drugs usage or total cholesterol (TC) ≥6.22 mmol/L or triglyceride (TG) ≥2.26 mmol/L or high-density lipoprotein cholesterol (HDL-C) <1.04 mmol/L or low-density lipoprotein cholesterol (LDL-C) ≥4.14 mmol/L. Diabetes was defined as a self-reported diagnosis of diabetes or anti-diabetic medications usage or fasting blood glucose (FBG) ≥7.0 mmol/L or glycosylated hemoglobin A1c (HbA1c) ≥6.5 %. Cancers were defined based on medical records, and cardiovascular diseases were defined based on a self-reported physician diagnosis or medical records before the date of blood collection.

Definition of lifestyles. Lifestyle information was collected through face-to-face interviews conducted by trained interviewers using structured questionnaires. Smoking and drinking status were defined as category variables, while physical activity, diet, and sleep duration were defined as continuous variables with three ordered groups.

Questions about tobacco smoking included the age at initiation or cessation and the amount of tobacco smoked per day by current and former smokers. Smoking status was classified into three categories: never smoker, current smoker, and former smoker. A smoker was defined as an individual who had smoked for more than six months and consumed at least one cigarette per day. A former smoker was defined as someone who had ceased smoking for more than six months; otherwise, the individual was categorized as a never smoker.

Data on alcohol consumption included the age of initiation or cessation, drinking frequency, type of alcoholic beverage typically consumed, and volume of alcohol consumed per occasion. Drinking status was classified into three categories: never drinker, current drinker, and former drinker. A current drinker was defined as someone who had consumed alcohol for more than six months and drank at least once per week. A former drinker was someone who had stopped drinking for more than six months; otherwise, the individual was categorized as a never drinker.

Physical activity was assessed by inquiring about the frequency, type, and duration of activities performed weekly over the past six months. Types of exercise included walking, biking, dancing, tai chi, jogging, swimming, climbing stairs/mountains, and playing sports such as basketball, volleyball, or soccer. Physical activity was quantified by regular engagement in exercises lasting more than 20 minutes per session. Total weekly duration was calculated as duration (hours per session) multiplied by frequency (sessions per week). A cutoff of 7 hours per week was established, with participants engaging in more than 7 hours per week awarded 2 points. Those participating in more than 20 minutes per week were given 1 point, while others received 0 points[25].

Diet was evaluated based on the intake of three food components—vegetables, fruits, and

meat—as recommended in the 2013 American Heart Association guideline for lifestyle management to reduce cardiovascular risk[26]. A healthy diet was defined as consuming vegetables at least twice a day, fruits at least once a day, or meat less than once a day. Participants consuming at least two of these healthy dietary components were assigned 2 points. If only one component was met, 1 point was given; otherwise, participants received 0 points[27].

Nighttime sleep duration was categorized into three groups: optimal (6-8 hours/day, 2 point), intermediate (5-5.9 or 8.1-10 hours/day, 1 point), and poor (<5 or >10 hours/day, 0 point)[25].

Definition of family history. Family history of diseases was determined based on self-reported information regarding the occurrence of specific diseases in parents or siblings. Participants were specifically asked, "Has your father, mother, or sibling ever been diagnosed with IHD (ischemic heart disease) or stroke?"

UKB

***Definition of obesity*.** Obesity status was classified based on body mass index (BMI) as underweight (BMI < 18.5), normal (18.5 ≤ BMI < 25), overweight (25 ≤ BMI < 30), and obesity (BMI ≥ 30) [28].

Selection of major chronic diseases. Referred to 92 age-related diseases by Chang AY *et al*. [29], we selected major chronic diseases from top causes of disability-adjusted life-year (DALYs) for individuals aged 55+ globally, based on Global Burden of Disease Study from 1990 to 2021[30]. First, we included all cancers (level 2 cause in GDB) as a unique disease type. Next, among top 15 level 3 causes of DALYs, we excluded all cancer subtypes, disorders not related to age reported by Chang AY *et al*., communicable diseases, injuries, and diseases with case reports <500 in the UKB. Finally, we kept nine major chronic diseases: (1) all cancers; (2) IHD; (3) stroke; (4) chronic obstructive pulmonary disease (COPD); (5) diabetes; (6) Alzheimer's diseases and other dementias; (7) chronic kidney disease (CKD); (8) age-related and other hearing loss; (9) Cirrhosis and other chronic liver diseases.

Calculation of PhenoAge

The PhenoAge[4] is defined as:

$$\text{PhenoAge} = 141.50225 + \frac{\ln\left(-0.00553\times\ln\left(1-\text{CDF}(120,y_i)\right)\right)}{0.09165},$$

$$\ln\left(1-\text{CDF}(120,y_i)\right) = \frac{(-1.51714)\times\exp\left(-19.907+\sum_i b_i y_i\right)}{0.0076927},$$

where y_i and b_i represent the biomarker and corresponding coefficient, the detailed values of which are provided in **Additional File 1: Table S3**.

78 **Table S1. Characteristic of 36 clinical biomarkers in this study.**

Abbreviation	Biomarker	UKB Field ID	Skewness in DFTJ
Cardiometabolic traits			
BMI	Body-mass-index	21001	0.37
Waist	Waist circumference	48	0.23
SBP	Systolic blood pressure	4080	0.54
DBP	Diastolic blood pressure	4079	0.65
PP	Pressure pulse	4079,4080	0.74
FBG	Fasting blood glucose	30740 [a]	3.79
HDL-C	High-density lipoprotein cholesterol	30760	0.80
LDL-C	Low-density lipoprotein cholesterol	30780 [a]	0.46
TC	Total cholesterol	30690	0.48
TG	Triglyceride	30870	7.26
Hematological traits			
RBC	Red blood cell count	30010	0.09
MCV	Mean corpuscular volume	30040	-1.31
RDW	Red cell volume distribution width	30070	2.07
MCHC	Mean red blood cell hemoglobin concentration	30060	1.61
MCH	Mean red blood cell hemoglobin	30050	-1.24
HGB	Hemoglobin	30020	-0.22
HCT	Hematocrit	30030	-0.22
WBC	White cell count	30000	1.00
LYM	Lymphocyte proportion	30180	0.21
MONO	Monocyte proportion	30190	2.12
NEUT	Neutrophils proportion	30200	-0.11
EOS	Eosinophil proportion	30210	3.74
BASO	Basophil proportion	30220	2.05
PLT	Platelet count	30080	0.84
MPV	Mean platelet volume	30100	1.60
PDW	Platelet distribution width	30110	1.18
PCT	Plateletcrit	30090	0.97
Hepatic function			
AST	Aspartate aminotransferase	30650	12.78
ALP	Alkaline phosphatase	30610	11.17
ALT	Alanine aminotransferase	30620	7.80
TBIL	Total bilirubin	30840	3.09
DBIL	Direct bilirubin	30660	14.75
IDBIL	Indirect bilirubin	30840,30660	2.37
Renal function			
BUN	Blood urea nitrogen	30670	3.18
SCR	Serum creatinine	30700	14.60
SUA	Serum uric acid	30880	0.80

79 [a] UKB collected non-fasting blood glucose and LDL direct.

Table S2. Definition of cardiovascular diseases in the DFTJ cohort.

Disease	Definition	ICD-10 code
CVD	Cases of coronary heart disease, cerebrovascular disease, and peripheral artery disease, aortic atherosclerosis, and thoracoabdominal aortic aneurysm.	I00-I99
IHD	Cases of first occurrence of angina pectoris, myocardial infarction, other forms of acute or chronic heart disease, and cases of coronary revascularization procedures such as coronary artery bypass grafting or percutaneous transluminal coronary angioplasty during follow-up.	I20-I25
ACS	Acute myocardial infarction and unstable angina.	I20.0, I21
Stroke	Sudden or rapid onset of a typical neurological deficit of vascular origin that persisted more than 24 hours or till death.	I60, I61, I63, I64, I69.0, I69.1, I69.3, I69.4

Table S3. Model weights of PhenoAge calculation.

Abbreviation	Biomarker	Unit	Weight
Alb	Albumin	g/L	-0.0336
SCR	Serum creatinine	μmol/L	0.0095
BG	Blood glucose	mmol/L	0.1953
log CRP	C-reactive protein	mg/L	0.0954
LYM	Lymphocyte percentage	%	-0.0120
MCV	Mean corpuscular volume	fL	0.0268
RDW	Red cell volume distribution width	%	0.3306
ALP	Alkaline phosphatase	U/L	0.00188
WBC	White cell count	10^9/L	0.0554
CA	Chronological age	year	0.0804

Table S4. Comparison of biomarkers among different hospitals in the DFTJ cohort.

Biomarker[a]	Zhongxin	Tianai	Huaguo	Maojian
	n **= 5 588**	***n*** **= 1 728**	***n*** **= 4 398**	***n*** **= 4 190**
BMI	24.2 (3.22)	23.7 (2.99)	24.4 (3.29)	23.9 (3.36)
Waist	82.7 (9.11)	83.5 (8.57)	81.6 (9.07)	85.9 (9.69)
SBP	138 (23.2)	137 (21.3)	141 (22.7)	135 (21.1)
DBP	80.1 (13.3)	81.8 (11.8)	81.1 (12.8)	78.2 (11.4)
PP	58.3 (16.0)	55.4 (13.8)	60.0 (17.3)	57.2 (16.3)
HDL-C	1.42 (0.34)	1.53 (0.45)	1.55 (0.35)	1.28 (0.28)
LDL-C	2.79 (0.82)	2.57 (0.75)	2.81 (0.74)	3.19 (0.80)
log TG	0.84 (0.31)	0.95 (0.28)	0.91 (0.30)	0.83 (0.32)
TC	4.90 (0.98)	5.09 (0.89)	4.82 (0.96)	4.64 (0.89)
log FBG	1.94 (0.19)	1.95 (0.16)	1.92 (0.18)	1.84 (0.19)
WBC	5.51 (1.51)	4.67 (1.17)	5.80 (1.52)	6.31 (1.65)
LYM	30.3 (8.48)	32.7 (7.53)	32.2 (7.82)	32.9 (7.96)
log MONO	1.77 (0.42)	1.86 (0.20)	2.13 (0.21)	2.17 (0.21)
NEUT	60.5 (9.01)	58.7 (8.03)	57.5 (8.32)	56.5 (8.41)
log EOS	1.08 (0.48)	1.10 (0.45)	1.04 (0.47)	1.10 (0.47)
log BASO	0.85 (0.41)	0.51 (0.18)	0.41 (0.22)	0.37 (0.18)
RBC	4.54 (0.43)	4.59 (0.43)	4.44 (0.44)	4.58 (0.44)
MCV	91.0 (5.28)	90.0 (4.70)	93.0 (5.57)	92.5 (5.32)
log RDW	2.72 (0.11)	2.56 (0.05)	2.65 (0.07)	2.64 (0.06)
log MCHC	5.82 (0.03)	5.79 (0.03)	5.78 (0.03)	5.78 (0.03)
MCH	30.5 (2.04)	29.5 (1.80)	30.0 (2.00)	29.8 (1.99)
HGB	138 (14.1)	135 (12.7)	133 (13.4)	136 (13.4)
HCT	41.2 (3.94)	41.2 (3.66)	41.2 (3.72)	42.3 (3.65)
PLT	203 (53.5)	215 (51.3)	184 (48.5)	196 (51.2)
log MPV	2.17 (0.14)	2.22 (0.09)	2.43 (0.08)	2.45 (0.08)
PDW	18.3 (1.67)	16.5 (0.48)	12.8 (2.17)	12.9 (2.18)
PCT	0.16 (0.04)	0.17 (0.04)	0.19 (0.04)	0.21 (0.05)
log AST	3.14 (0.36)	3.50 (0.36)	3.15 (0.30)	3.04 (0.32)
log ALP	4.44 (0.29)	4.48 (0.28)	4.64 (0.28)	4.40 (0.26)
log ALT	2.98 (0.51)	3.32 (0.50)	2.94 (0.43)	2.87 (0.47)
log TBIL	2.59 (0.37)	2.60 (0.28)	2.83 (0.32)	2.91 (0.26)
log DBIL	1.60 (0.32)	1.43 (0.42)	1.87 (0.35)	1.82 (0.34)
log IDBIL	2.23 (0.41)	2.30 (0.33)	2.44 (0.30)	2.56 (0.26)
log BUN	1.82 (0.24)	1.94 (0.16)	1.74 (0.25)	1.83 (0.23)
log SCR	4.22 (0.27)	4.38 (0.20)	4.52 (0.18)	4.34 (0.21)
SUA	311 (85.7)	313 (74.8)	325 (84.7)	338 (82.4)

[a] Data are presented as mean (SD) for continuous variables. All biomarkers are significant different among hospitals by analysis of variance.

Table S5. Definition of major chronic diseases in the UKB.

Diseases [a]	ICD-10 [a]	Self-reported diseases [b]
All cancers	C00-C97	All items from Field 20001 in the UKB
Ischemic heart disease	I20-I25.9	heart/cardiac problem
Stroke	I60-I69.4	cerebrovascular disease
Chronic obstructive pulmonary disease	J41-J44.9	chronic obstructive airways disease/COPD
Diabetes mellitus	E08-E08.11, E08.3-E08.9, E10-E10.11, E10.3-E11.1, E11.3-E12.1, E12.3-E13.11, E13.3-E14.1, E14.3-E14.9	diabetes
Alzheimer's diseases and other dementias	F00-F02.0, F02.8-F06.2, G30-G31.1, G31.8-G32.89	dementia/Alzheimer's /cognitive impairment
Chronic kidney disease	D63.1, E08.2-E08.29, E10.2-E10.29, E11.2-E11.29, E12.2, E13.2-E13.29, E14.2, I12-I13.9, N02-N08.8, N15.0, N17-N19, P96.0-P96.0	renal/kidney failure, pyelonephritis, other renal/kidney problem
Age-related and other hearing loss	H74-H75.83, H90-H91, H91.1-H91.93, H94-H94.83, Q16-Q16.9	ear/vestibular disorder
Cirrhosis and other chronic liver diseases	I85-I85.9, I98.2-I98.2, K65.2-K65.2, K70-K77.8, R16-R18.9, Z52.6, Z94.4	hepatitis, liver failure/cirrhosis

[a] Definitions of the age-associated diseases in the UKB are referred to global disease burden (GDB) study [30].

[b] Self-reported non-cancer diseases and self-reported cancers are encoded using Data-Coding 6 and Data-Coding 3 in the UKB, respectively. Individuals with the corresponding self-reported diseases were removed for each chronic disease.

Table S6. Model weights of PAI calculation.

Biomarker	Unit	Optimal level [a]	Transformation [b]	Weight [c]	HR (95%CI) [d]	*P* [d]
Age	year		-	0.0959	1.10 (1.09, 1.11)	**3.49×10^{-170}**
log FBG	mmol/L	1.77	y_1	1.2841	3.61 (2.87, 4.55)	**9.36×10^{-28}**
	mmol/L		y_2	-0.7977	0.45 (0.22, 0.92)	**0.028**
log AST	μ/L	3.18	y_1	1.0251	2.79 (2.11, 3.67)	**3.39×10^{-13}**
	μ/L		y_2	-0.3121	0.73 (0.55, 0.97)	**0.030**
log SCR	μmol/L	4.32	y_1	0.8238	2.28 (1.80, 2.88)	**6.10×10^{-12}**
	μmol/L		y_2	-0.2870	0.75 (0.44, 1.29)	0.298
log ALP	μ/L	4.21	y_1	0.5364	1.71 (1.43, 2.05)	**6.75×10^{-9}**
	μ/L		y_2	-0.1347	0.87 (0.48, 1.60)	0.664
log RDW	%		-	2.0215	7.55 (3.73, 15.27)	**1.87×10^{-8}**
WBC	$10^{9/L}$	5.43	y_1	0.1025	1.11 (1.07, 1.15)	**1.88×10^{-8}**
	$10^{9/L}$		y_2	-0.0069	0.99 (0.89, 1.10)	0.897
log MONO	%	1.78	y_1	0.6061	1.83 (1.45, 2.31)	**3.18×10^{-7}**
	%		y_2	-0.0787	0.92 (0.59, 1.45)	0.733
SBP	mmHg		-	0.0062	1.01 (1.00, 1.01)	**3.07×10^{-6}**
BMI	kg/m^2	25.5	y_2	-0.0559	0.95 (0.92, 0.97)	**6.61×10^{-6}**
	kg/m^2		y_1	0.0231	1.02 (0.99, 1.05)	0.120
LYM	%	39.1	y_2	-0.0169	0.98 (0.98, 0.99)	**8.95×10^{-6}**
	%		y_1	0.0054	1.01 (0.99, 1.02)	0.526
log DBIL	μmol/L	1.237	y_1	0.4358	1.55 (1.27, 1.88)	**1.06×10^{-5}**
	μmol/L		y_2	-0.0620	0.94 (0.61, 1.44)	0.775
log ALT	μ/L	3.11	y_2	-0.4289	0.65 (0.54, 0.79)	**1.89×10^{-5}**
	μ/L		y_1	-0.4859	0.62 (0.48, 0.78)	**8.72×10^{-5}**
TC	mmol/L	5.52	y_2	-0.1640	0.85 (0.79, 0.92)	**3.35×10^{-5}**
	mmol/L		y_1	0.1202	1.13 (1.02, 1.24)	**0.015**
log BUN	mmol/L	1.63	y_1	0.4752	1.61 (1.23, 2.10)	**4.63×10^{-4}**
	mmol/L		y_2	-0.3725	0.69 (0.48, 0.99)	**0.042**
RBC	$10^{12}/L$	4.62	y_2	-0.1543	0.86 (0.72, 1.03)	0.094
	$10^{12}/L$		y_1	0.1565	1.17 (0.95, 1.44)	0.135
MCV	fL	89.4	y_1	0.0280	1.03 (0.99, 1.06)	0.100
	fL		y_2	-0.0269	0.97 (0.92, 1.03)	0.334
MCH	pg	29.3	y_2	0.1000	1.11 (0.97, 1.26)	0.142
	pg		y_1	0.0257	1.03 (0.94, 1.12)	0.552

[a] The cutoff points were determine using RCS curves for biomarkers with U-shaped relationships on mortality.

[b] Given biomarker i, $y_{i1} = max(y_i - \tilde{y}_i, 0)$, and $y_{i2} = min(y_i - \tilde{y}_i, 0)$, where y_i and $\tilde{y}_i$ denotes the original value and the optimal level, respectively.

[c] Weight indicates the effect size per unit change of each biomarker on the mortality risk.

[d] HR (95% CI) indicates the hazard ratio (95% CI) per unit change of each biomarker on the mortality risk. $P < 0.05$ are labeled in bold.

Table S7. HRs of ΔPAI and ΔPhenoAge on mortality in the DFTJ testing set.

Model	Variable	HR per SD (95% CI)	*P* [a]
Full set			
ΔPAI + CA	ΔPAI	1.77 (1.68, 1.87)	**4.0×10^{-101}**
ΔPhenoAge + CA	ΔPhenoAge	1.49 (1.42, 1.55)	**3.8×10^{-72}**
ΔPAI + ΔPhenoAge + CA	ΔPAI	1.70 (1.57, 1.84)	**1.2×10^{-38}**
	ΔPhenoAge	1.05 (0.98, 1.13)	0.186
CA	CA	2.82 (2.62, 3.03)	**1.3×10^{-177}**
Only female			
ΔPAI + CA	ΔPAI	1.76 (1.61, 1.92)	**4.5×10^{-36}**
ΔPhenoAge + CA	ΔPhenoAge	1.46 (1.35, 1.58)	**1.0×10^{-22}**
ΔPAI + ΔPhenoAge + CA	ΔPAI	1.78 (1.54, 2.05)	**1.9×10^{-15}**
	ΔPhenoAge	0.99 (0.86, 1.14)	0.893
CA	CA	2.90 (2.59, 3.24)	**4.0×10^{-77}**
Only male			
ΔPAI + CA	ΔPAI	1.72 (1.61, 1.84)	**2.0×10^{-54}**
ΔPhenoAge + CA	ΔPhenoAge	1.47 (1.39, 1.56)	**7.4×10^{-40}**
ΔPAI + ΔPhenoAge + CA	ΔPAI	1.61 (1.46, 1.77)	**6.5×10^{-21}**
	ΔPhenoAge	1.09 (1.00, 1.19)	0.061
CA	CA	2.65 (2.40, 2.93)	**4.1×10^{-81}**

[a] $P < 0.05$ are labeled in bold.

Table S8. Predictive performance of single biomarker in the DFTJ testing set.

Biomarker	C-index		ΔC [a]			6-year
	Estimate	SE	Estimate	Z score	*P*	AUC
CA	0.771	0.008	Reference			0.766
log MONO	0.772	0.008	<0.001	0.902	0.184	0.764
MCH	0.772	0.008	0.001	1.268	0.102	0.768
MCV	0.773	0.008	0.001	1.592	0.056	0.767
SBP	0.774	0.008	0.003	2.195	0.014	0.767
BMI	0.774	0.008	0.003	2.081	0.019	0.771
log ALT	0.775	0.008	0.004	2.788	**0.003**	0.768
log AST	0.775	0.008	0.004	3.229	**6.21×10^{-4}**	0.769
TC	0.777	0.008	0.006	3.273	**5.33×10^{-4}**	0.771
log DBIL	0.777	0.008	0.006	2.824	**0.002**	0.768
RBC	0.777	0.008	0.006	3.694	**1.10×10^{-4}**	0.773
WBC	0.777	0.008	0.006	3.108	**9.41×10^{-4}**	0.771
log ALP	0.777	0.008	0.006	2.502	0.006	0.775
log FBG	0.778	0.008	0.007	3.304	**4.76×10^{-4}**	0.777
log BUN	0.779	0.008	0.008	3.701	**1.07×10^{-4}**	0.776
LYM	0.781	0.008	0.009	3.584	**1.69×10^{-4}**	0.774
log SCR	0.781	0.008	0.009	2.825	**0.002**	0.778
log RDW	0.781	0.008	0.010	4.469	**3.93×10^{-6}**	0.767
ΔPAI	0.816	0.008	0.045	8.666	**2.24×10^{-18}**	0.807

[a] The increase in C-index (ΔC) were assessed using Z-score tests and one-sided *P* value. $P < 0.0028$ (0.05/18) are labeled in bold.

Table S9. Predictive performance of mortality in the DFTJ testing set using mixed-effect Cox model.

Evaluation metric		PAI	PhenoAge	CA
Full set				
C-index		0.816 (0.796, 0.837)	0.801 (0.780, 0.821)	0.775 (0.755, 0.796)
AUC	1-year	0.839 (0.787, 0.887)	0.828 (0.774, 0.877)	0.771 (0.707, 0.837)
	3-year	0.819 (0.794, 0.844)	0.813 (0.788, 0.836)	0.774 (0.746, 0.802)
	6-year	0.806 (0.789, 0.824)	0.787 (0.769, 0.806)	0.757 (0.736, 0.775)
Calibration	Slope	1.02 (0.97, 1.07)	1.36 (1.30, 1.42)	0.97 (0.91, 1.04)
	Intercept	-0.02 (-0.07, 0.03)	-0.34 (-0.40, -0.28)	0.03 (-0.03, 0.09)
Only female				
C-index		0.840 (0.804, 0.876)	0.829 (0.793, 0.865)	0.808 (0.772, 0.844)
AUC	1-year	0.899 (0.835, 0.946)	0.910 (0.860, 0.950)	0.812 (0.719, 0.901)
	3-year	0.840 (0.801, 0.875)	0.849 (0.813, 0.882)	0.789 (0.746, 0.836)
	6-year	0.855 (0.830, 0.882)	0.842 (0.814, 0.870)	0.823 (0.794, 0.851)
Calibration	Slope	1.07 (1.03, 1.10)	1.56 (1.42, 1.71)	1.07 (0.99, 1.14)
	Intercept	-0.06 (-0.10, -0.03)	-0.55 (-0.69, -0.41)	-0.07 (-0.14, 0.01)
Only male				
C-index		0.760 (0.735, 0.785)	0.737 (0.712, 0.762)	0.710 (0.685, 0.735)
AUC	1-year	0.765 (0.667, 0.853)	0.723 (0.619, 0.815)	0.710 (0.601, 0.799)
	3-year	0.774 (0.735, 0.811)	0.754 (0.716, 0.788)	0.727 (0.687, 0.761)
	6-year	0.740 (0.715, 0.765)	0.709 (0.681, 0.737)	0.673 (0.646, 0.700)
Calibration	Slope	1.03 (0.98, 1.08)	1.20 (1.05, 1.35)	0.96 (0.86, 1.06)
	Intercept	-0.03 (-0.07, 0.02)	-0.19 (-0.33, -0.05)	0.04 (-0.05, 0.13)

All estimates were presented as mean (95% CI).

Table S10. HRs of ΔPAI and ΔPhenoAge on mortality in the DFTJ testing set using mixed-effect Cox model.

Model	Variable	HR per SD (95% CI)	*P* [a]
Full set			
ΔPAI + CA	ΔPAI	1.77 (1.68, 1.87)	**4.2×10^{-101}**
ΔPhenoAge + CA	ΔPhenoAge	1.49 (1.43, 1.56)	**2.4×10^{-70}**
ΔPAI + ΔPhenoAge + CA	ΔPAI	1.70 (1.57, 1.84)	**1.2×10^{-38}**
	ΔPhenoAge	1.05 (0.98, 1.13)	0.186
CA	CA	2.80 (2.61, 3.00)	**2.0×10^{-177}**
Only female			
ΔPAI + CA	ΔPAI	1.76 (1.61, 1.92)	**4.6×10^{-36}**
ΔPhenoAge + CA	ΔPhenoAge	1.47 (1.36, 1.59)	**3.0×10^{-23}**
ΔPAI + ΔPhenoAge + CA	ΔPAI	1.78 (1.54, 2.05)	**1.9×10^{-15}**
	ΔPhenoAge	0.99 (0.86, 1.14)	0.894
CA	CA	2.89 (2.58, 3.23)	**1.9×10^{-76}**
Only male			
ΔPAI + CA	ΔPAI	1.71 (1.60, 1.84)	**1.5×10^{-52}**
ΔPhenoAge + CA	ΔPhenoAge	1.47 (1.39, 1.56)	**6.0×10^{-37}**
ΔPAI + ΔPhenoAge + CA	ΔPAI	1.61 (1.46, 1.78)	**7.5×10^{-21}**
	ΔPhenoAge	1.08 (0.99, 1.19)	0.086
CA	CA	2.64 (2.39, 2.92)	**6.0×10^{-82}**

[a] $P < 0.05$ are labeled in bold.

Table S11. Associations between ΔPAI and incident CVD and its subtypes.

Disease	Variable [a]	Base model		Full model	
		HR (95% CI)	*P* [b]	HR (95% CI)	*P* [b]
CVD	Continuous	1.18 (1.13, 1.24)	**7.41×10^{-14}**	1.11 (1.06, 1.17)	**1.82×10^{-5}**
	Q2	0.99 (0.87, 1.13)	0.906	0.96 (0.84, 1.10)	0.568
	Q3	1.08 (0.95, 1.23)	0.257	1.00 (0.88, 1.15)	0.961
	Q4	1.42 (1.25, 1.62)	**4.57×10^{-8}**	1.23 (1.07, 1.41)	**0.003**
IHD	Continuous	1.13 (1.07, 1.18)	**5.56×10^{-6}**	1.06 (1.00, 1.12)	0.052
	Q2	0.95 (0.82, 1.09)	0.463	0.92 (0.80, 1.06)	0.264
	Q3	1.00 (0.87, 1.15)	0.987	0.93 (0.80, 1.08)	0.332
	Q4	1.26 (1.09, 1.45)	**0.001**	1.09 (0.94, 1.26)	0.269
ACS	Continuous	1.22 (1.12, 1.34)	**8.01×10^{-6}**	1.14 (1.03, 1.25)	**0.009**
	Q2	1.05 (0.80, 1.38)	0.705	1.02 (0.78, 1.35)	0.863
	Q3	1.18 (0.90, 1.54)	0.227	1.09 (0.83, 1.43)	0.545
	Q4	1.44 (1.11, 1.88)	**0.006**	1.21 (0.92, 1.61)	0.177
Stroke	Continuous	1.40 (1.28, 1.52)	**2.22×10^{-14}**	1.31 (1.19, 1.44)	**1.58×10^{-8}**
	Q2	1.22 (0.88, 1.69)	0.225	1.16 (0.83, 1.60)	0.385
	Q3	1.56 (1.14, 2.12)	**0.005**	1.41 (1.03, 1.93)	**0.031**
	Q4	2.35 (1.76, 3.13)	**5.13×10^{-9}**	1.97 (1.46, 2.67)	**1.04×10^{-5}**

[a] Continuous group indicates that ΔPAI is analyzed as a continuous variable. Q2-4 groups indicate that quartile 2-4 groups of ΔPAI are compared with the quartile 1 group (the lowest).

[b] $P < 0.05$ are labeled in bold.

Table S12. Basic characteristics of the UKB.

Variable [a]	Survival *n*=277 283	Death *n*=19 648	*P* [b]
Sex, female (%)	137 684 (49.7)	6 746 (34.3)	**<0.001**
Age, years	55.8 (8.13)	61.7 (6.43)	**<0.001**
BMI, kg/m^2	27.3 (4.64)	28.4 (5.37)	**<0.001**
Townsend's index	-1.39 (3.03)	-0.79 (3.34)	**<0.001**
Ethnic, British (%)	243 773 (87.9)	17 789 (90.5)	**<0.001**
Smoking status, n (%)			**<0.001**
Current	25 580 (9.23)	3 623 (18.4)	
Former	94 774 (34.2)	8 460 (43.1)	
Never	155 663 (56.1)	7 402 (37.7)	
Prefer not to answer	1266 (0.46)	163 (0.83)	
Drinking status, n (%)			**<0.001**
Current	256 902 (92.6)	17 567 (89.4)	
Former	8 604 (3.10)	1 132 (5.76)	
Never	11 147 (4.02)	877 (4.46)	
Prefer not to answer	630 (0.23)	72 (0.37)	

[a] Data are presented as mean (SD) for continuous variables and number (percentage) for categorical variables.

[b] *P* for values between death events and survivals are derived from Student's t test for continuous variables, and Chi-square test for the categorical variables.

Table S13. Comparison of biomarkers between the DFTJ cohort and the UKB.

Biomarker [a]	Survival			Death		
	DFTJ *n* = 26 133	UKB *n* = 277 283	*P* [b]	DFTJ *n* = 2 530	UKB *n* = 19 648	*P* [b]
Age	62.6 (7.93)	55.8 (8.13)	**<0.001**	70.4 (7.82)	61.7 (6.43)	**<0.001**
BMI	24.3 (3.26)	27.3 (4.64)	**<0.001**	24.2 (3.64)	28.4 (5.37)	**<0.001**
SBP	133 (21.1)	139 (19.4)	**<0.001**	137 (21.7)	145 (20.6)	**<0.001**
log BG	1.86 (0.20)	1.79 (0.13)	**<0.001**	1.89 (0.27)	1.83 (0.18)	**<0.001**
TC	4.99 (0.97)	5.63 (1.11)	**<0.001**	4.92 (1.09)	5.36 (1.22)	**<0.001**
WBC	5.83 (1.56)	6.77 (1.71)	**<0.001**	6.37 (1.85)	7.36 (2.01)	**<0.001**
LYM	32.4 (8.23)	28.9 (7.28)	**<0.001**	30.3 (9.08)	26.9 (7.87)	**<0.001**
log MONO	1.96 (0.31)	2.05 (0.29)	**<0.001**	2.00 (0.31)	2.08 (0.32)	**<0.001**
RBC	4.56 (0.44)	4.56 (0.41)	0.939	4.53 (0.54)	4.55 (0.44)	0.085
MCV	91.1 (5.15)	91.2 (4.42)	**0.012**	91.5 (5.75)	92.2 (5.20)	**<0.001**
log RDW	2.65 (0.09)	2.67 (0.06)	**<0.001**	2.67 (0.09)	2.69 (0.07)	**<0.001**
MCH	29.9 (1.96)	31.5 (1.76)	**<0.001**	30.0 (2.22)	31.8 (2.03)	**<0.001**
log DBIL	1.56 (0.40)	1.01 (0.23)	**<0.001**	1.57 (0.44)	1.04 (0.26)	**<0.001**
log ALT	3.03 (0.48)	3.11 (0.44)	**<0.001**	2.99 (0.55)	3.14 (0.45)	**<0.001**
log AST	3.16 (0.34)	3.27 (0.26)	**<0.001**	3.18 (0.44)	3.33 (0.33)	**<0.001**
log ALP	4.47 (0.29)	4.38 (0.27)	**<0.001**	4.53 (0.34)	4.45 (0.29)	**<0.001**
log SCR	4.35 (0.24)	4.28 (0.19)	**<0.001**	4.48 (0.33)	4.33 (0.23)	**<0.001**
log BUN	1.74 (0.26)	1.83 (0.20)	**<0.001**	1.78 (0.34)	1.87 (0.25)	**<0.001**

[a] Data are presented as mean (SD) for continuous variables.

[b] *P* values between the DFTJ cohort and the UKB are derived from Student's *t* test.

Table S14. Evaluation of discrimination and calibration for PAI, PhenoAge, and CA in the UKB.

Evaluation metric		PAI	PhenoAge	CA
Full set				
C-index		0.749 (0.746, 0.752)	0.743 (0.739, 0.746)	0.706 (0.702, 0.709)
AUC	1-year	0.761 (0.735, 0.789)	0.755 (0.729, 0.782)	0.666 (0.641, 0.691)
	3-year	0.754 (0.744, 0.765)	0.750 (0.739, 0.761)	0.683 (0.671, 0.693)
	6-year	0.744 (0.737, 0.750)	0.741 (0.734, 0.748)	0.688 (0.681, 0.695)
	12-year	0.759 (0.755, 0.763)	0.754 (0.750, 0.758)	0.714 (0.710, 0.717)
Calibration	Slope	1.01 (0.99, 1.02)	1.12 (1.09, 1.15)	1.02 (0.97, 1.07)
	Intercept	-0.01 (-0.02, 0.01)	-0.11 (-0.14, -0.08)	-0.02 (-0.07, 0.03)
Only female				
C-index		0.731 (0.725, 0.737)	0.724 (0.718, 0.730)	0.700 (0.694, 0.706)
AUC	1-year	0.764 (0.715, 0.812)	0.759 (0.712, 0.806)	0.668 (0.610, 0.720)
	3-year	0.726 (0.704, 0.746)	0.722 (0.700, 0.741)	0.674 (0.653, 0.693)
	6-year	0.714 (0.701, 0.726)	0.713 (0.701, 0.724)	0.675 (0.664, 0.688)
	12-year	0.736 (0.730, 0.742)	0.731 (0.724, 0.738)	0.704 (0.697, 0.710)
Calibration	Slope	1.00 (0.97, 1.03)	1.07 (1.03, 1.11)	1.01 (0.94, 1.08)
	Intercept	0.00 (-0.03, 0.03)	-0.07 (-0.11, -0.03)	-0.01 (-0.07, 0.06)
Only male				
C-index		0.749 (0.745, 0.753)	0.740 (0.736, 0.744)	0.705 (0.701, 0.709)
AUC	1-year	0.748 (0.716, 0.778)	0.737 (0.705, 0.767)	0.659 (0.624, 0.692)
	3-year	0.756 (0.743, 0.769)	0.748 (0.735, 0.762)	0.681 (0.668, 0.695)
	6-year	0.748 (0.740, 0.755)	0.741 (0.733, 0.749)	0.690 (0.681, 0.698)
	12-year	0.763 (0.759, 0.767)	0.755 (0.750, 0.759)	0.716 (0.711, 0.721)
Calibration	Slope	1.00 (0.98, 1.02)	1.12 (1.08, 1.15)	1.02 (0.97, 1.06)
	Intercept	0.00 (-0.02, 0.01)	-0.11 (-0.14, -0.08)	-0.02 (-0.06, 0.03)

136 **Table S15. HRs of ΔPAI and ΔPhenoAge on mortality in the UKB.**

Model	Variable	HR per SD (95% CI)	*P*
Full set			
ΔPAI + CA	ΔPAI	1.61 (1.59, 1.63)	$<1\times10^{-300}$
ΔPhenoAge + CA	ΔPhenoAge	1.47 (1.46, 1.48)	$<1\times10^{-300}$
ΔPAI + ΔPhenoAge + CA	ΔPAI	1.43 (1.41, 1.46)	$<1\times10^{-300}$
	ΔPhenoAge	1.15 (1.14, 1.17)	7.2×10^{-81}
CA	CA	2.37 (2.33, 2.41)	$<1\times10^{-300}$
Only females			
ΔPAI + CA	ΔPAI	1.55 (1.52, 1.58)	$<1\times10^{-300}$
ΔPhenoAge + CA	ΔPhenoAge	1.44 (1.41, 1.46)	$<1\times10^{-300}$
ΔPAI + ΔPhenoAge + CA	ΔPAI	1.36 (1.32, 1.40)	4.9×10^{-97}
	ΔPhenoAge	1.18 (1.15, 1.21)	3.4×10^{-36}
CA	CA	2.30 (2.23, 2.37)	$<1\times10^{-300}$
Only males			
ΔPAI + CA	ΔPAI	1.59 (1.57, 1.61)	$<1\times10^{-300}$
ΔPhenoAge + CA	ΔPhenoAge	1.44 (1.43, 1.46)	$<1\times10^{-300}$
ΔPAI + ΔPhenoAge + CA	ΔPAI	1.46 (1.43, 1.49)	4.7×10^{-306}
	ΔPhenoAge	1.11 (1.09, 1.13)	8.8×10^{-26}
CA	CA	2.37 (2.32, 2.42)	$<1\times10^{-300}$

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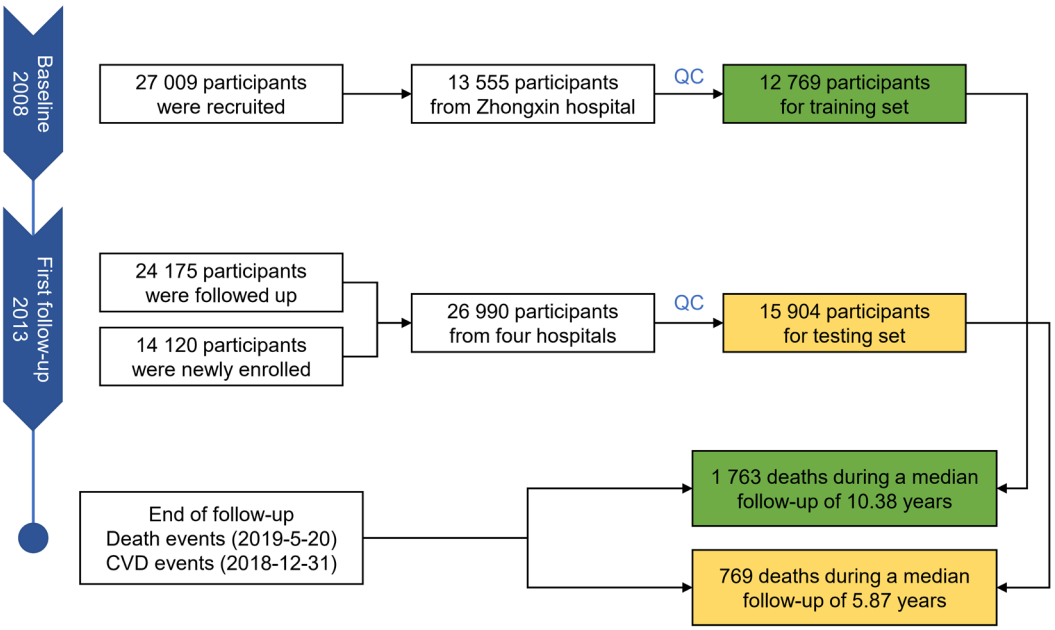


Figure S1. Timeline of the DFTJ cohort and flowchart of study participants.

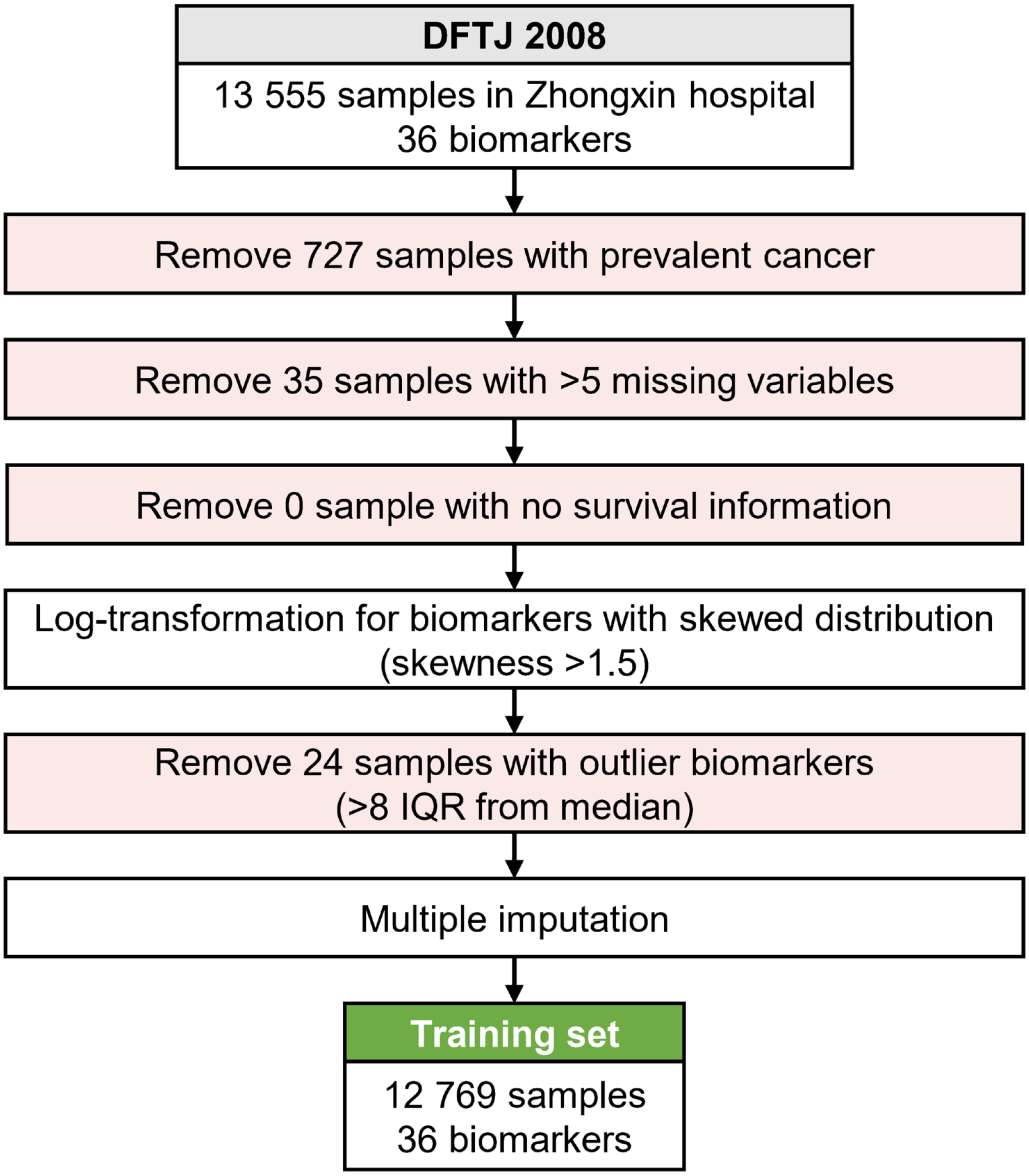
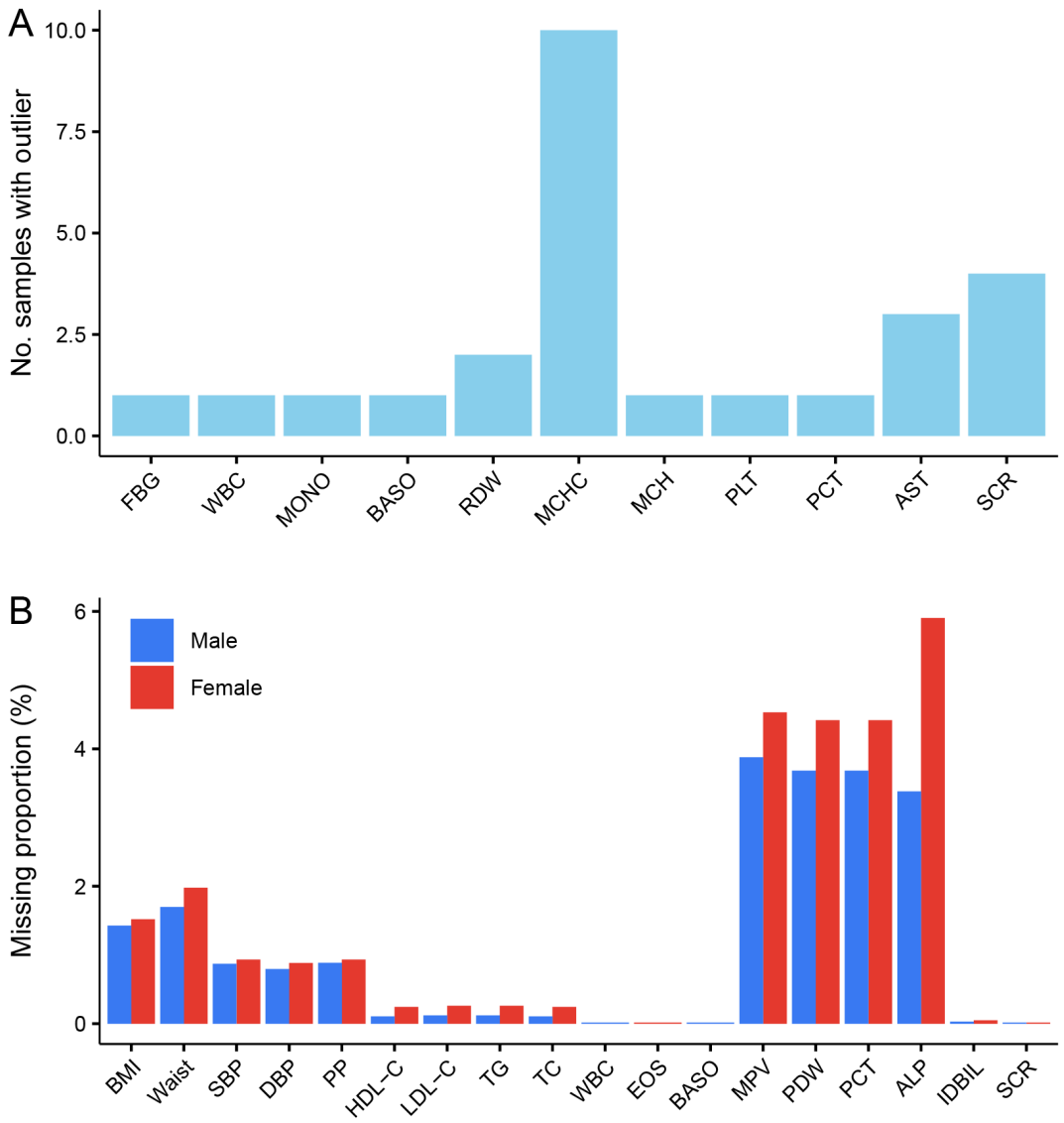


Figure S2. Quality control process in the DFTJ training dataset.



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145 **Figure S3. Summary of quality control in the DFTJ training set.** (**A**) Number of samples with
146 outlier (> 8 IQR from median). (**B**) Missing proportion before imputation.

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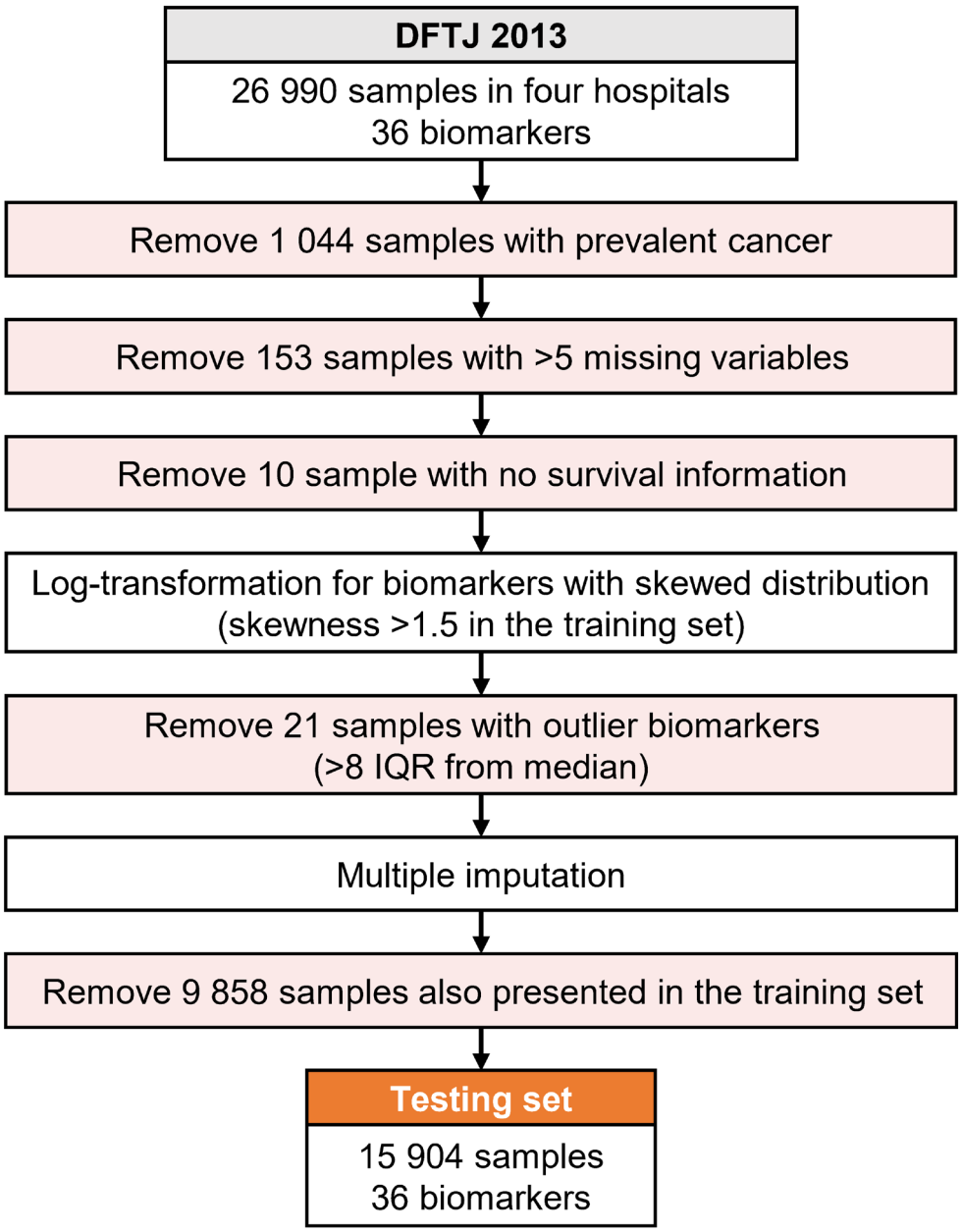

Figure S4. Quality control process in the DFTJ testing dataset.

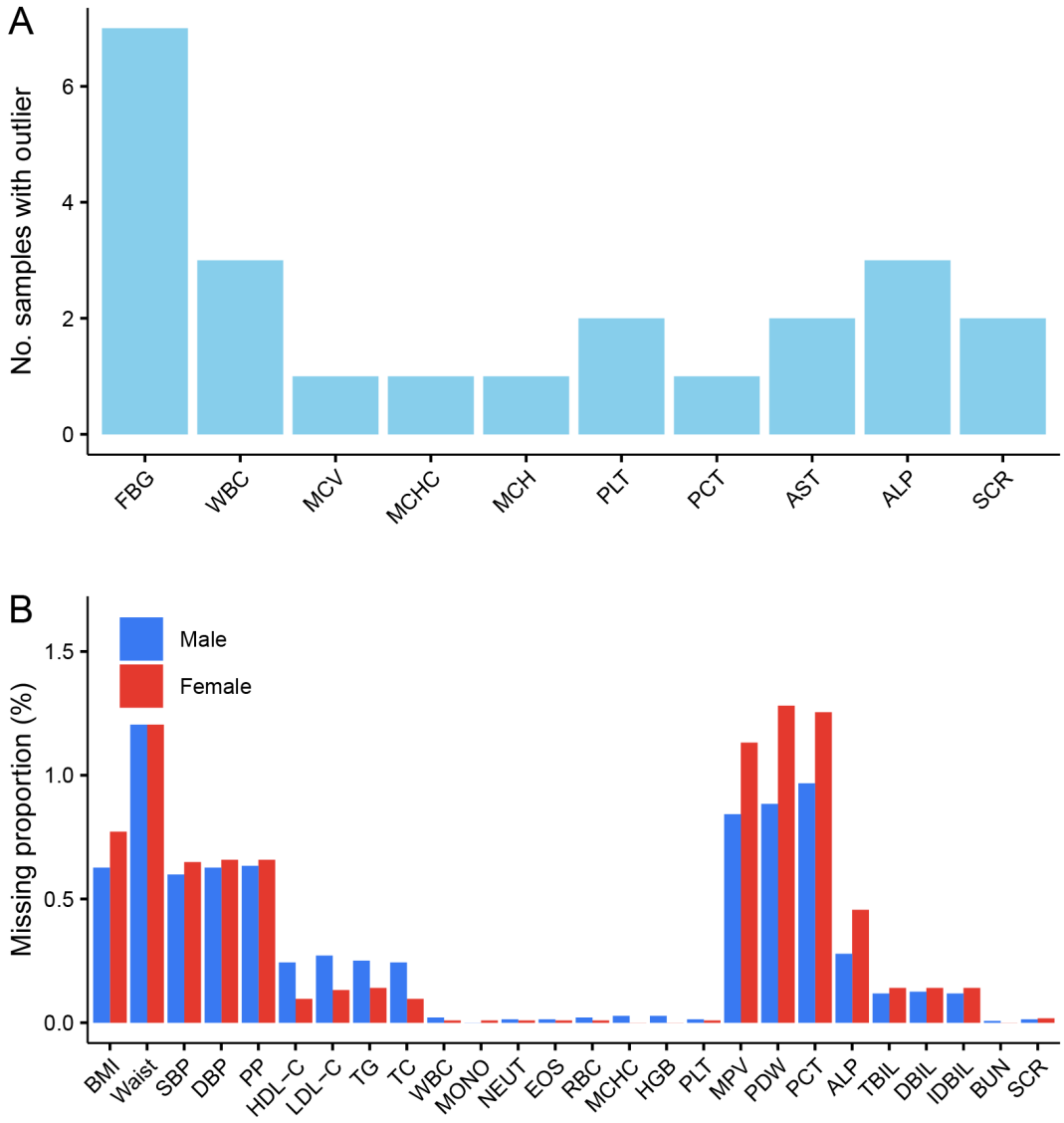

Figure S5. Summary of quality control in the DFTJ testing set. (**A**) Number of samples with outlier (> 8 IQR from median). (**B**) Missing proportion before imputation.

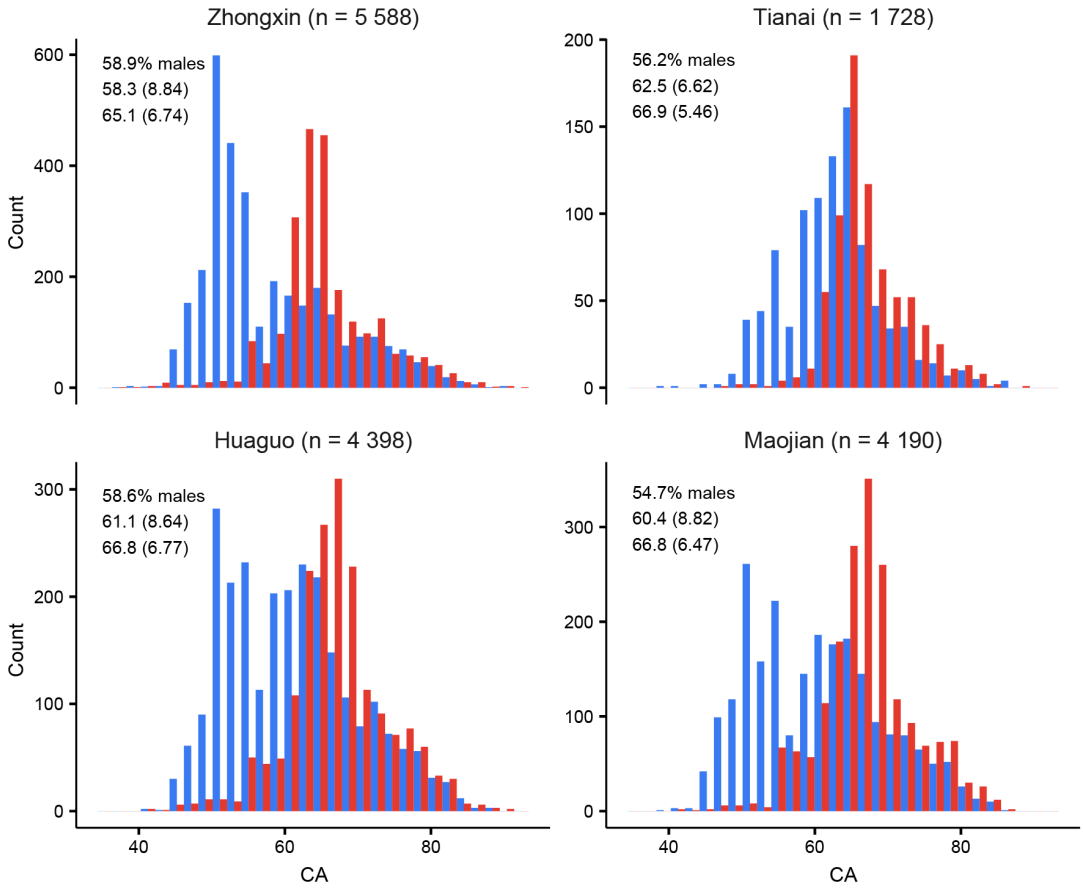

Figure S6. Joint distribution of CA and sex in the DFTJ testing set. Female and male samples are represented by red and blue bars, respectively.

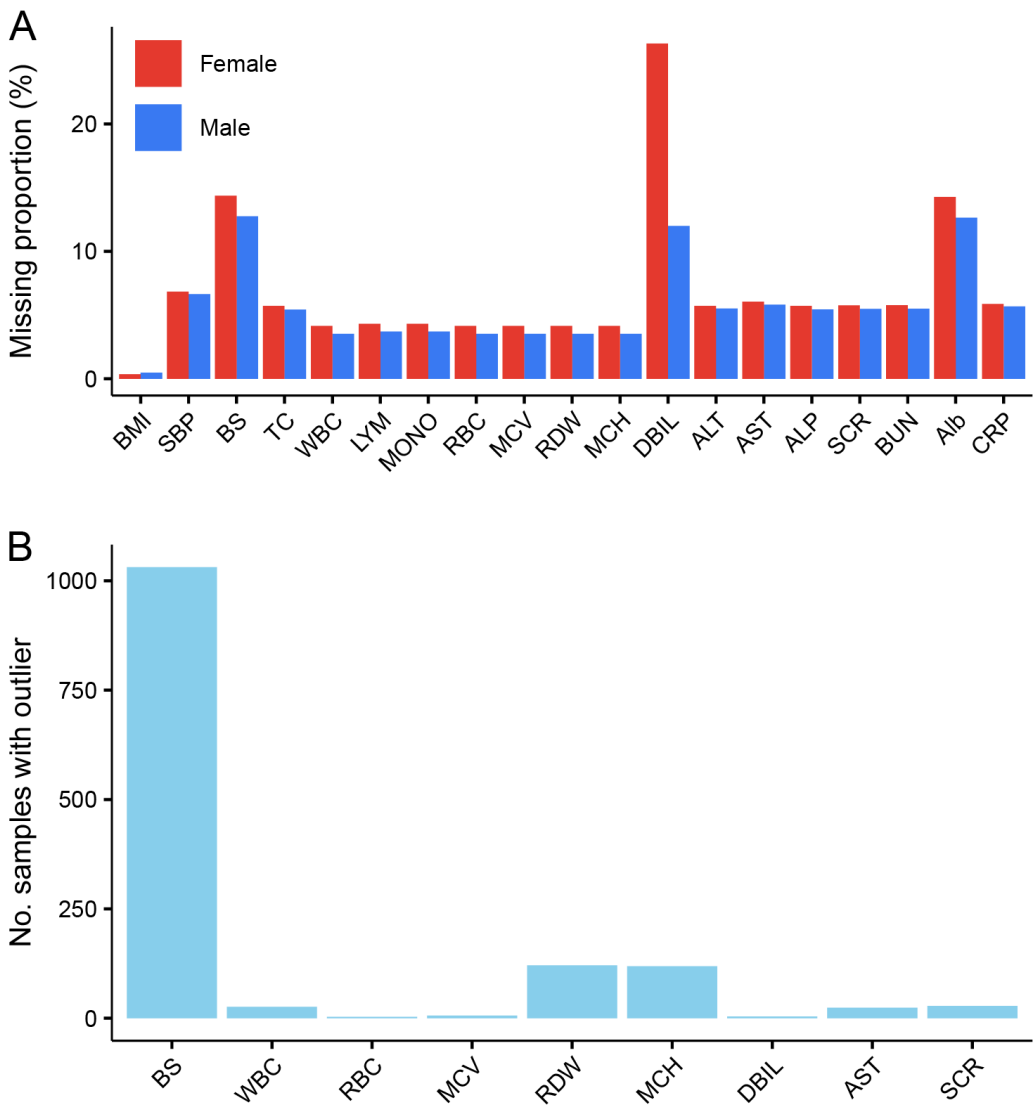

Figure S7 Missing proportion and the number of samples with outlier in the UKB. (**A**) Missing proportion before filtering samples with any missing variable. (**B**) Number of samples with outlier (> 8 IQR from median).

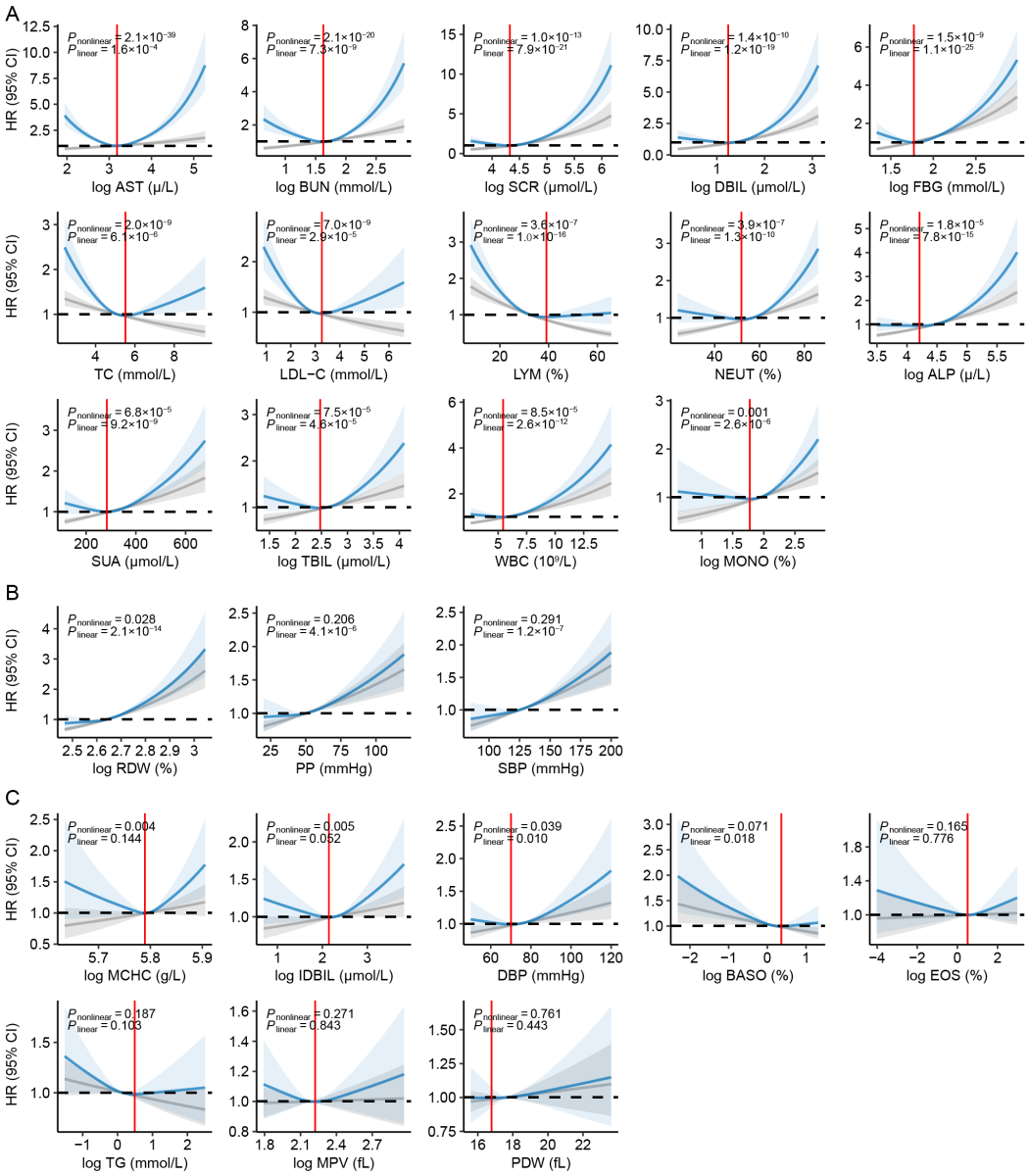

Figure S8. Nonlinear and linear associations between 25 clinical biomarkers and mortality in the DFTJ cohort. (A) Fourteen biomarkers have significant linear and nonlinear associations with mortality. **(B)** Three biomarkers have significant linear but insignificant nonlinear associations with mortality. **(C)** Eight biomarkers have insignificant linear and nonlinear associations with mortality. HRs and CIs in linear associations, represented by grey and the shaded areas, were estimated using Cox models. HRs and CIs in nonlinear associations, represented by blue and the shaded areas, were estimated using Cox models with cubic splines, adjusted for CA. The mean value of each biomarker was set as the reference to calculate HR. The vertical red line indicates the optimal level corresponding to the lowest HR in the RCS curve. *P* values from both nonlinear and linear models were listed at every panel.

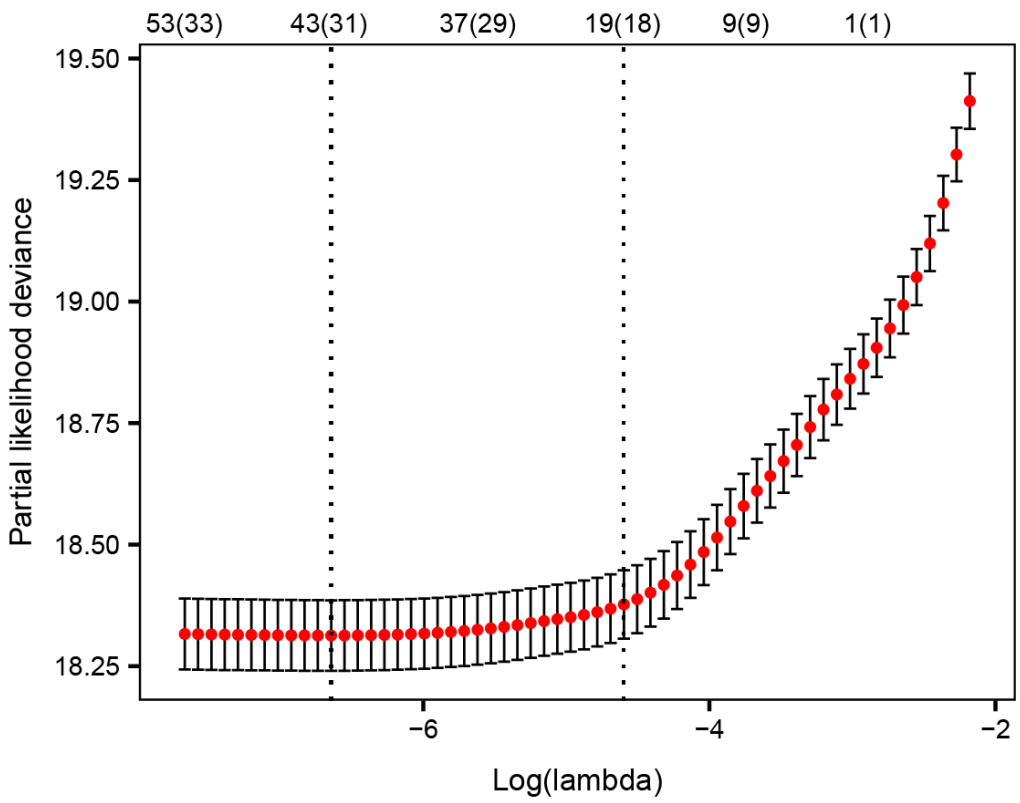

Figure S9. Regularization parameter (lambda) selection in cross validation. The red points and the vertical black lines represent the mean and one standard error of the partial likelihood deviance at each lambda value, respectively. The left vertical dotted line denotes the optimal lambda, minimizing the partial likelihood deviance. The right vertical dotted line marks the lambda chosen using the "one standard error" rule, which provides a more parsimonious model with an acceptable error margin. The numbers at the top indicate the number of selected predictors, while the numbers in parentheses represent the unique clinical biomarkers.

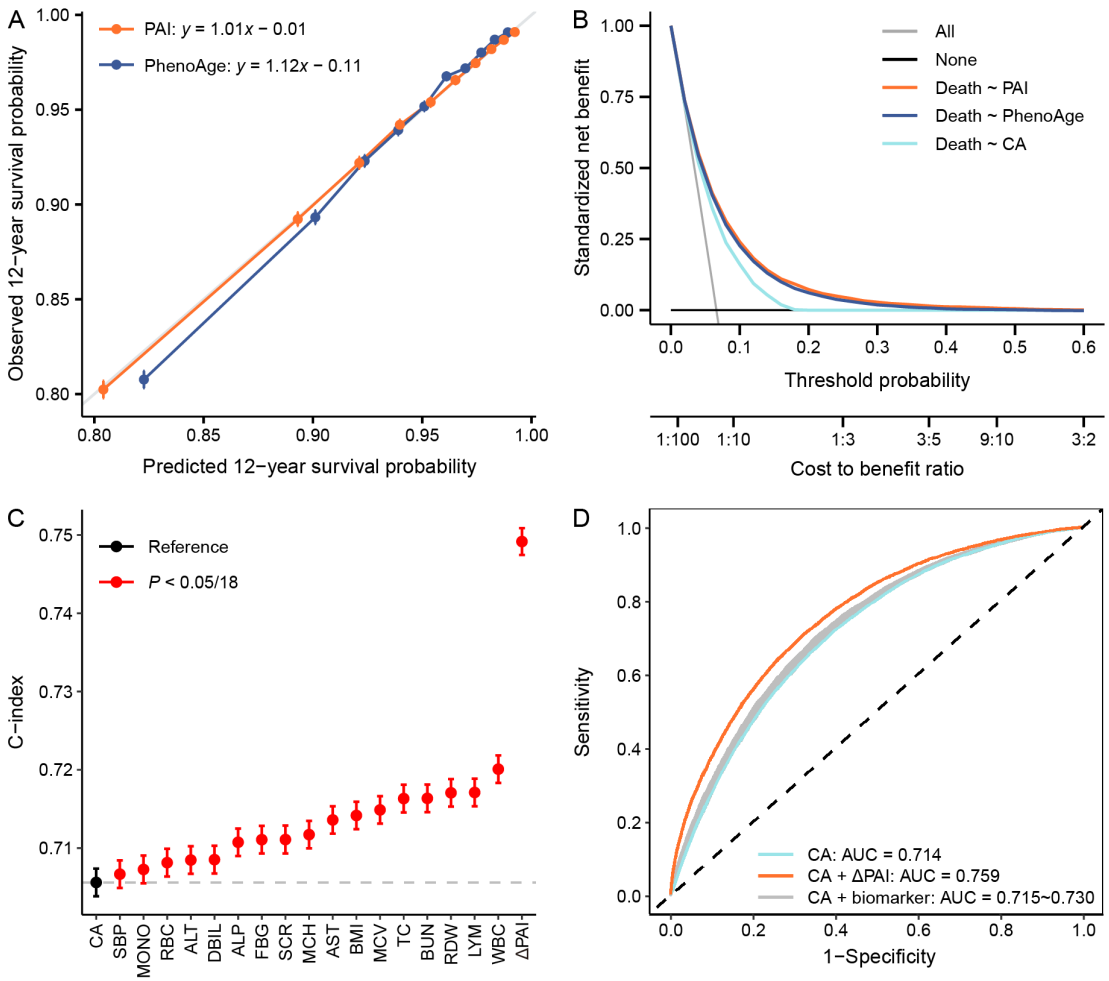

Figure S10. Prediction of mortality using PAI and ΔPAI in the UKB. (**A**) Calibration plot of the predicted and mean observed 12-year survival probability within each decile group, defined by the predicted 12-year survival probability. Vertical lines show the 95% CIs of the observed 12-year survival probability. Calibration slopes and intercepts are labeled in the equations in the legend. The grey line shows a perfect calibration scenario along the diagonal (y=x). (**B**) Decision curve analysis of mortality prediction models based on PAI, PhenoAge, and CA. For comparison, the grey and black lines indicate strategies assuming all or no individuals are treated. (**C**) C-index of models with CA as the only covariate (reference), as well as CA and biomarker/ΔPAI as covariates. Each dot indicates the C-index estimate, with vertical lines showing one standard error. The dashed line represents the C-index of the reference model. Models showing significant improvement over the reference model ($P < 0.05/18$) are highlighted in red. (**D**) The ROC curves at 12-year interval of models with CA (blue), CA and ΔPAI (orange), or CA and single biomarker (grey) as covariates.