Supplemental Material

Association of Accelerated Phenotypic Aging, Genetic Risk, and Lifestyle with Progression of Type 2 Diabetes: A Prospective Study Using Multi-State Model

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Assessment of Phenotypic Age Acceleration

Phenotypic age was calculated based on chronological age and 9 biomarkers, including albumin, creatinine, glucose, [log] C-reactive protein [CRP], lymphocyte percent, mean cell volume, red blood cell distribution width, alkaline phosphatase, and white blood cell count. The formula for phenotypic age is as follows:

$$\begin{aligned} xb = &-19.907 - 0.0336 \times Albumin + 0.0095 \times Creatinine + 0.1953 \times Glucose \\ &+ 0.0954 \times LnCRP - 0.0120 \times Lymphocyte\ Percentage \\ &+ 0.0268 \times Mean\ Cell\ Volume + 0.3306 \times Erythrocyte\ Distribution\ Width \\ &+ 0.00188 \times Alkaline\ Phosphatase + 0.0554 \times Leukocyte\ Count \\ &+ 0.0804 \times chronological\ age \end{aligned}$$

$$Phenotypic\ age = 141.50225 + \frac{ln\left(-0.00553 * ln\left(1 - \left(1 - e^{-e^{xb}\left(exp\left(0.923124\right)-1\right)/0.0076927}\right)\right)\right)}{0.090165}$$

The continuous phenotypic age acceleration (PhenoAgeAccel) was the residual obtained from a linear model by regressing phenotypic age on chronological age.

Assessment of Lifestyle

Six lifestyle behaviors including smoking status, alcohol status, dietary habits, physical activity, sleep status, and body shape were considered to calculate healthy lifestyle scores. Each lifestyle was scored as healthy (1 point) if recommended targets were achieved: non-smokers, moderate drinking (no more than one drink/day for women and two drinks/day for men; one drink is measured as 8 g ethanol in the U.K.) on a relatively regular frequency, having a healthy diet (daily eating of fruits, vegetables, and non-daily eating red meats and processed meats), being physically active (≥75 minutes of vigorous activity per week or 150 minutes of moderate activity per week), having a health sleep duration (average 6-9 hours per week), and non-obesity (body mass index<30 kg/m^2). The overall healthy lifestyle score was the sum of individual scores of the six lifestyle behaviors, ranging from 0 to 6, with a higher score indicating a healthier lifestyle.

Calculation of population attributable fraction (PAF)

The PAF function be defined as:

$$PAF = 1 - \frac{\{1 - S_0(t \mid X = 0, Z)\}}{\{1 - S(t \mid X = 0, Z)\}}$$

where X is the binary exposure. The function $S_0(t \mid X = 0, Z)$ denotes the counterfactual survival function for the event if the exposure would have been eliminated from the population at baseline and $S(t \mid X = 0, Z)$ denotes the factual survival function, which are estimated using the Cox proportional hazards model adjusted for confounders Z. This estimate manifests the population attributable fraction for a time-to-event outcome under the hypothetical scenario where a binary exposure is eliminated from the population.

Table S1 Codes used in the UK Biobank to identify Type 2 diabetes and Diabetes complications.

Outcomes	Diagnostic criteria
Type 2 diabetes (T2D)	• Self-reported: 1223; • ICD-9: 250; • ICD-10: E11; • Other diagnostic criteria: Prevalent diabetes cases through baseline Hemoglobin A1c (HbA1c) ≥ 48 mmol/mol and the use of insulin or other hypoglycemic drugs before recruitment were excluded.
Diabetes complication	•
Diabetic eye diseases	• Self-reported: 1276; • ICD-10: E11.3, E14.3, H36.0, and H28.0.
Diabetic kidney diseases	• Self-reported: 1607. • ICD-10: E11.2, E14.2, N18.0, N18.3-5, N18.8, N18.9, and N08.3.
Diabetic neuropathy diseases	• Self-reported: 1468; • ICD-10: E11.4, E14,4, G59,0 , G63,2, and G99.0.
Cardiovascular diseases	• Self-reported: 1075 and 1081; • ICD-10: I21, I22, I23, I63, I64, and I20.0.
Peripheral vascular diseases	• ICD-10: E11.5, I73.8, I73.9.
Metabolic events	• E11.0, E11.1, E11.6 , and E11.8.

Table S2 International Classification of Diseases (ICD) codes used for identification of cause-specific mortality.

Cause of Death	ICD-10
Cancer	C00-C97
Cardiovascular disease (CVD)	I00-I99

Table S3 The definition and measurements of covariates.

Variables	Field-ID	Notes
Age	21022	This is a derived variable based on date of birth and date of attending an initial assessment center and refers to the age of the participant on the day they attended an Initial Assessment Centre, truncated to whole year.
Sex	31	Sex (male or female) acquired from central registry at recruitment.
Race	21000	White and non-white (including Mixed, Asian or Asian British, Black or Black British, Chinese, and other ethnic groups).
Household income	738	The average total household income before tax was categorized as <18,000, 18,000 to 30,999, 31,000 to 51,999, 52,000 to 100,000, or ⩾100,000.
Education	6138	Education level was categorized as high school or below and college degree or above.
Smoking status	20116	Including never, previous, current.
Drinking status	20117	Including never, previous, current.
Healthy diet	1349, 1369, 1379, 1389, 1329, 1339, 1458, 1289,1299, 1309, 1319	Red meat intake was calculated as the sum of beef, lamb, mutton, pork, and processed meat. Fish intake was calculated as the sum of oily fish and non-oily fish. Vegetable intake was calculated as the sum of cooked vegetable intake and raw vegetable intake. Fruit intake was calculated as the sum of fresh fruit intake and dried fruit intake. Each diet was scored as healthy (1 point) if red meat intake (< median), fish intake (≥ median), vegetable intake (≥ median), and fruit intake (≥ median). The healthy diet scores were summed, ranging from 0 to 4 and a healthy diet statue was defined as a score ≥ 3. Category: no or yes
Physical activity	22032	Physical activity was classified into three groups according to International Physical Activity Questionnaire (IPAQ): high, moderate, and low.
Obesity status	23104	BMI was calculated by dividing weight (kg) by height (m) squared. Obese was defined as BMI ≥ 30 kg/m^2. Category: no or yes
Family history of T2D disease	20107, 20110, 20111	Family history of T2D was measured with screening questions: “Has/did your mother ever suffer from?”. Family history included the illness of father, mother, and siblings. Category: no or yes

Sleep status	1160	Sleep status was categorized into three groups, i.e., short sleep duration (<6 hours), normal sleep duration (6 to 9 hours), and long sleep duration (>9 hours).
Hypertension	93, 94, 6177	Systolic blood pressure and diastolic blood pressure was measured by automated device. The participants were classified as hypertension if their systolic blood pressure > 130 mmHg or diastolic blood pressure > 90 mmHg or ever had medication for blood pressure. Category: no or yes
High cholesterol	20002, 6153, 6177	High cholesterol was defined as a self-reported history of high cholesterol or taking medications. Category: no or yes
Cancer	40006, 40005, 41270, 41280, 40013, 40005, 41271, 41281, 20001, 20006	Cancer cases at baseline were identified from hospital inpatient data, cancer registries data, and self-reported data. Category: no or yes

Table S4 Comparison of characteristics between data with imputation and without imputation.

Characteristics	Data without imputation (n = 376,083)	Data with imputation (n = 376,083)
Age [years, median (IQR)]	57.0 (50.0-63.0)	57.0 (50.0-63.0)
Sex		
Female	208,244 (55.4)	208,244 (55.4)
Male	167,839 (44.6)	167,839 (44.6)
Race		
Non-white	33,072 (8.8)	33,239 (8.8)
White	341,340 (91.2)	342,844 (91.2)
Income		
<18,000	69,025 (21.4)	84,152 (22.4)
18,000 to 30,999	81,231 (25.2)	96,441 (25.6)
31,000 to 51,999	85,915 (26.6)	98,766 (26.3)
52,000 to 100,000	68,091 (21.1)	76,506 (20.3)
≥100,000	18,170 (5.6)	20,218 (5.4)
Education		
High school or below	186,837 (60.0)	232,728 (61.9)
College degree or above	124,588 (40.0)	143,355 (38.1)
Obese		
No	293,899 (78.1)	293,899 (78.1)
Yes	82,184 (21.9)	82,184 (21.9)
Smoke		
Never	208,691 (55.7)	209,664 (55.7)
Former	126,911 (33.9)	127,475 (33.9)
Current	38,762 (10.4)	38,944 (10.4)
Drink		
Never	15,430 (4.1)	15,473 (4.1)
Former	12,344 (3.3)	12,377 (3.3)
Current	347,464 (92.6)	348,233 (92.6)
Family history of T2D		
No	309,364 (82.3)	309,364 (82.3)
Yes	66,719 (17.7)	66,719 (17.7)
Physical activity IPAQ		
Low	52,434 (17.9)	68,002 (18.1)
Moderate	119,100 (40.7)	153,525 (40.8)
High	120,990 (41.4)	154,556 (41.1)
Healthy diet		
No	214,886 (59.6)	224,465 (59.7)
Yes	145,643 (40.4)	151,618 (40.3)

Sleep status		
Normal	347,958 (93.2)	350,279 (93.1)
Short	19,562 (5.2)	19,734 (5.2)
Long	5,993 (1.6)	6,070 (1.6)
Hypertension		
No	289,024 (76.9)	289,024 (76.9)
Yes	87,059 (23.1)	87,059 (23.1)
High cholesterol		
No	328,442 (87.3)	328,442 (87.3)
Yes	47,641 (12.7)	47,641 (12.7)
Cancer		
No	257,126 (68.4)	257,126 (68.4)
Yes	118,957 (31.6)	118,957 (31.6)

Data were presented as median (interquartile range, IQR) and frequency (%); numbers in parentheses for all variables represent column percentages.

Abbreviation: IPAQ, the International Physical Activity Questionnaire; T2D, type 2 diabetes.

Table S5 Baseline characteristics of the participants stratified by PhenoAgeAccel categories

Characteristics	Biologically younger (*n* = 223,025)	Biologically older (*n* = 153,058)	*P* value[a]
Age [years, median (IQR)]	57.0 (49.0-63.0)	57.0 (50.0-63.0)	<0.001
Sex			<0.001
Female	121,300 (54.4)	86,944 (56.8)	
Male	101,725 (45.6)	66,114 (43.2)	
Race			0.001
Non-white	19,080 (8.6)	14,195 (9.3)	
White	203,945 (91.4)	138,863 (90.7)	
Income			<0.001
<18,000	44,138 (19.8)	40,097 (26.2)	
18,000 to 30,999	55,896 (25.1)	40,529 (26.5)	
31,000 to 51,999	60,303 (27.0)	38,554 (25.2)	
52,000 to 100,000	49,241 (22.1)	27,216 (17.8)	
≥100,000	13,447 (6.0)	6,662 (4.4)	
Education			<0.001
High school or below	133,255 (59.7)	99,686 (65.1)	
College degree or above	89,770 (40.3)	53,372 (34.9)	
Obese			<0.001
No	185,107 (83.0)	108,792 (71.1)	
Yes	37,918 (17.0)	44,266 (28.9)	
Smoke			<0.001
Never	130,790 (58.6)	78,872 (51.5)	
Former	77,419 (34.7)	50,088 (32.7)	
Current	14,816 (6.6)	24,098 (15.7)	
Drink			<0.001
Never	8,211 (3.7)	7,274 (4.8)	
Former	6,403 (2.9)	5,972 (3.9)	
Current	208,411 (93.4)	139,812 (91.3)	
Family history of T2D			<0.001
No	185,452 (83.2)	123,912 (81.0)	
Yes	37,573 (16.8)	29,146 (19.0)	
Physical activity IPAQ			<0.001
Low	37,550 (16.8)	29,871 (19.5)	
Moderate	91,029 (40.8)	62,564 (40.9)	
High	94,446 (42.3)	60,623 (39.6)	
Healthy diet			<0.001
No	127,897 (57.3)	96,319 (62.9)	
Yes	95,128 (42.7)	56,739 (37.1)	

Sleep status			<0.001
Normal	209,784 (94.1)	140,549 (91.8)	
Short	10,399 (4.7)	9,306 (6.1)	
Long	2,842 (1.3)	3,203 (2.1)	
Hypertension			<0.001
No	176,286 (79.0)	112,738 (73.7)	
Yes	46,739 (21.0)	40,320 (26.3)	
High cholesterol			<0.001
No	195,556 (87.7)	132,886 (86.8)	
Yes	27,469 (12.3)	20,172 (13.2)	
Cancer			<0.001
No	153,139 (68.7)	103,987 (67.9)	
Yes	69,886 (31.3)	49,071 (32.1)	

Data were presented as median (interquartile range, IQR) and frequency (%); numbers in parentheses for all variables represent column percentages.

[a]The one-way ANOVA test was used for continuous variables and the Chi-square test was used for remaining categorical variables.

Abbreviation: IPAQ, the International Physical Activity Questionnaire; T2D, type 2 diabetes.

Table S6 PhenoAgeAccel of participants stratified by lifestyle factors

Category	Total No.	No. of biological older participant (%)	Median (IQR) for PhenoAgeAccel
Healthy lifestyle score			
0	2,884	1,770 (61.37)	1.33 (-1.65,4.92)
1	21,670	11,832 (54.60)	0.51 (-2.42,3.91)
2	70,982	34,115 (48.06)	-0.21 (-2.95,2.99)
3	122,747	51,475 (41.94)	-0.85 (-3.50,2.12)
4	108,310	38,995 (36.00)	-1.47 (-4.03,1.39)
5	43,936	13,310 (30.29)	-2.02 (-4.51,0.68)
6	5,554	1,561 (28.11)	-2.40 (-4.75,0.41)
Lifestyle category[a]			
Unfavorable	24,554	13,602 (55.40)	0.60 (-2.32,4.05)
Intermediate	302,039	124,585 (41.25)	-0.93 (-3.59,2.08)
Favorable	49,490	14,871 (30.05)	-2.06 (-4.54,0.65)
Sleep score			
0	118,949	52,189 (43.88)	-0.68 (-3.43,2.49)
1	257,134	100,869 (39.23)	-1.13 (-3.76,1.81)
BMI score			
0	250,103	109,760 (43.89)	-0.64 (-3.28,2.37)
1	125,980	43,298 (34.37)	-1.73 (-4.37,1.27)
Drinking score			
0	208,244	86,944 (41.75)	-0.91 (-3.66,2.22)
1	167,839	66,114 (39.39)	-1.10 (-3.67,1.80)
Smoking score			
0	166,419	74,183 (44.58)	-0.59 (-3.35,2.54)
1	209,664	78,875 (37.62)	-1.30 (-3.89,1.61)
Diet score			
0	224,465	96,557 (43.02)	-0.74 (-3.43,2.32)
1	151,618	56,501 (37.27)	-1.37 (-3.99,1.59)
Physical activity score			
0	70,199	32,332 (46.06)	-0.44 (-3.22,2.82)
1	305,884	120,726 (39.47)	-1.12 (-3.76,1.85)

[a] Participants were divided into favorable (at least 5 healthy lifestyle factors), intermediate (2 or 4 healthy lifestyle factors), or unfavorable (0 or 1 healthy lifestyle factor) according to the number of healthy lifestyle factors.

Each lifestyle was scored as healthy (1 point) if recommended targets were achieved: non-smokers, non-drinkers, having a healthy diet (daily eating of fruits, vegetables, and non-daily eating red meats and processed meats), being physically active (⩾75 minutes of vigorous activity per week or 150 minutes of moderate activity per week), having a health sleep duration (average 6-9 hours per week), and non-obesity (body mass index<30 kg/m^2).

Abbreviation: IQR, interquartile range.

Table S7 Associations between PhenoAgeAccel and T2D, all-cause mortality and specific-cause mortality using Cox proportional hazard model.

Outcome	PhenoAgeAccel[a]	No. of cases/Total no.	Incidence/ 1,000 PYs	HR[b] (95% CI)
T2D	**Per 5 years increase**	17,615/376,083	3.58	1.34 (1.32,1.35)
	Category			
	Biologically younger	7,033/223,025	2.37	reference
	Biologically older	10,582/153,058	5.42	1.77 (1.71,1.82)
	Quantiles			
	Low	2,432/ 98,449	1.84	reference
	Intermediate	8,126/193,270	3.19	1.44 (1.37,1.50)
	High	7,057/ 84,364	6.67	2.46 (2.35,2.58)
	P for trend			<0.001
All-cause mortality	**Per 5 years increase**	28,373/376,083	5.65	1.32 (1.31,1.33)
	Category			
	Biologically younger	13,029/223,025	4.33	reference
	Biologically older	15,344/153,058	7.62	1.55 (1.51,1.58)
	Quantiles			
	Low	5,183/ 98,449	3.88	reference
	Intermediate	13,122/193,270	5.06	1.19 (1.16,1.23)
	High	10,068/ 84,364	9.17	1.96 (1.89,2.03)
	P for trend			<0.001
Cancer mortality	**Per 5 years increase**	14,723/376,083	2.93	1.26 (1.24,1.28)
	Category			
	Biologically younger	7,201/223,025	2.39	reference
	Biologically older	7,522/153,058	3.74	1.41 (1.36,1.46)
	Quantiles			
	Low	2,906/ 98,449	2.18	reference
	Intermediate	7,071/193,270	2.73	1.17 (1.12,1.22)
	High	4,746/ 84,364	4.32	1.71 (1.63,1.80)
	P for trend			<0.001
CVD mortality	**Per 5 years increase**	5,267/376,083	1.05	1.34 (1.32,1.37)
	Category			
	Biologically younger	2,239/223,025	0.74	reference
	Biologically older	3,028/153,058	1.50	1.68 (1.59,1.78)
	Quantiles			
	Low	816/ 98,449	0.61	reference
	Intermediate	2,423/193,270	0.94	1.34 (1.24,1.45)
	High	2,028/ 84,364	1.85	2.30 (2.11,2.50)
	P for trend			<0.001

[a]PhenoAgeAccel was classified into two groups: biologically younger (PhenoAgeAccel ≤0) and biologically older (PhenoAgeAccel >0). It was also divided into three quartile-based groups: low (bottom quantile), medium (quantiles 2-3), and high (top quantile).

[b]Cox proportional hazard regression model adjusted for age, sex, race, income, education, obesity status, smoking status, drinking status, physical activity, healthy diet, sleep status, hypertension, high cholesterol, and cancer.

Abbreviation: HR, hazard ratio; CI, confidence interval; PYs, person-years; T2D, type 2 diabetes; CVD, cardiovascular disease.

Table S8 Associations between PhenoAgeAccel and Diabetes complications in T2D population using Cox proportional hazard model.

Outcome	PhenoAgeAccel[a]	No. of cases/Total no.	Incidence/ 1,000 PYs	HR[b] (95% CI)
Diabetic eye diseases	**Per 5 years increase**	855/17,615	3.72	1.11 (1.05,1.18)
	Category			
	Biologically younger	342/ 733	3.69	reference
	Biologically older	513/10,582	3.74	1.10 (0.95, 1.26)
	Quantiles			
	Low	112/2,432	3.48	reference
	Intermediate	389/8,126	3.64	1.13 (0.92,1.40)
	High	354/7,057	3.90	1.31 (1.06,1.63)
	P for trend			0.007
Diabetic kidney diseases	**Per 5 years increase**	1,881/17,615	8.29	1.18 (1.14,1.22)
	Category			
	Biologically younger	671/ 733	7.31	reference
	Biologically older	1,210/10,582	8.96	1.26 (1.14, 1.38)
	Quantiles			
	Low	225/2,432	7.07	reference
	Intermediate	802/8,126	7.58	1.11 (0.96,1.29)
	High	854/7,057	9.57	1.45 (1.25,1.69)
	P for trend			<0.001
Diabetic neuropathy diseases	**Per 5 years increase**	228/17,615	0.98	1.24 (1.13,1.36)
	Category			
	Biologically younger	74/ 733	0.79	reference
	Biologically older	154/10,582	1.11	1.43 (1.08, 1.90)
	Quantiles			
	Low	30/2,432	0.92	reference
	Intermediate	92/8,126	0.85	0.95 (0.63,1.43)
	High	106/7,057	1.16	1.32 (0.87,1.99)
	P for trend			0.056
Cardiovascular diseases	**Per 5 years increase**	1,898/17,615	8.39	1.10 (1.06,1.14)
	Category			
	Biologically younger	710/ 733	7.78	reference
	Biologically older	1,188/10,582	8.80	1.17 (1.07, 1.29)
	Quantiles			
	Low	234/2,432	7.39	reference
	Intermediate	840/8,126	7.98	1.13 (0.98,1.31)
	High	824/7,057	9.22	1.36 (1.17,1.57)
	P for trend			<0.001

Peripheral vascular diseases	**Per 5 years increase**	536/17,615	2.32	1.24 (1.17,1.32)
	Category			
	Biologically younger	165/ 733	1.77	reference
	Biologically older	371/10,582	2.70	1.52 (1.26, 1.83)
	Quantiles			
	Low	56/2,432	1.73	reference
	Intermediate	207/8,126	1.93	1.14 (0.84,1.53)
	High	273/7,057	3.00	1.77 (1.32,2.37)
	P for trend			<0.001
Metabolic events	**Per 5 years increase**	226/17,615	0.98	1.18 (1.07,1.30)
	Category			
	Biologically younger	73/ 733	0.78	reference
	Biologically older	153/10,582	1.11	1.37 (1.03, 1.82)
	Quantiles			
	Low	24/2,432	0.74	reference
	Intermediate	90/8,126	0.84	1.12 (0.71,1.76)
	High	112/7,057	1.22	1.60 (1.02,2.52)
	P for trend			0.007
Diabetes complication	**Per 5 years increase**	4,524/17,615	20.82	1.13 (1.10,1.16)
	Category			
	Biologically younger	1702/ 733	19.32	reference
	Biologically older	2,822/10,582	21.84	1.17 (1.10, 1.25)
	Quantiles			
	Low	569/2,432	18.65	reference
	Intermediate	1,983/8,126	19.52	1.09 (0.99,1.20)
	High	1,972/7,057	23.14	1.35 (1.23,1.49)
	P for trend			<0.001

[a]PhenoAgeAccel was classified into two groups: biologically younger (PhenoAgeAccel ≤0) and biologically older (PhenoAgeAccel >0). It was also divided into three quartile-based groups: low (bottom quantile), medium (quantiles 2-3), and high (top quantile).

[b]Cox proportional hazard regression model adjusted for age, sex, race, income, education, obesity status, smoking status, drinking status, physical activity, healthy diet, sleep status, hypertension, high cholesterol, and cancer.

Abbreviation: HR, hazard ratio; CI, confidence interval; PYs, person-years.

Table S9 The Harrell's C-statistics and AUC of the PhenoAgeAccel and risk factors with the progression of T2D.

Variable combination	Harrell's C-statistics		AUC	
	Without PhenoAgeAccel	With PhenoAgeAccel	Without PhenoAgeAccel	With PhenoAgeAccel
Age				
Baseline to T2D	0.602	0.674	0.647	0.693
Baseline to Death	0.697	0.722	0.64	0.676
T2D to Complication	0.612	0.621	0.609	0.619
T2D to Death	0.625	0.638	0.603	0.616
Complication to Death	0.589	0.616	0.578	0.604
Age + sociodemographic factors[a]				
Baseline to T2D	0.685	0.724	0.676	0.709
Baseline to Death	0.716	0.735	0.664	0.692
T2D to Complication	0.621	0.629	0.616	0.625
T2D to Death	0.637	0.648	0.609	0.620
Complication to Death	0.606	0.627	0.592	0.612
Age + sociodemographic factors[a] + lifestyles[b]				
Baseline to T2D	0.764	0.778	0.712	0.728
Baseline to Death	0.734	0.746	0.683	0.701
T2D to Complication	0.631	0.635	0.624	0.630
T2D to Death	0.655	0.663	0.622	0.630
Complication to Death	0.622	0.636	0.607	0.620
Age + sociodemographic factors[a] + lifestyles[b] + [c]medical conditions				
Baseline to T2D	0.791	0.803	0.721	0.736
Baseline to Death	0.735	0.746	0.686	0.703
T2D to Complication	0.640	0.645	0.632	0.637
T2D to Death	0.655	0.663	0.619	0.627
Complication to Death	0.623	0.636	0.608	0.620

[a]Sociodemographic variables included sex, race, income, education, and family history of T2D.

[b]Lifestyles refers to obesity status, smoking status, drinking status, physical activity, diet, and sleep status.

[c]Medical conditions included hypertension, high cholesterol, and cancer.

Abbreviation: AUC, area under the curve; T2D, type 2 diabetes.

Table S10 Associations between Genetic risk and incident T2D using Cox proportional hazard model.

Genetic risk	No. of cases/Total no.	Incidence/ 1,000 PYs	HR[a] (95% CI)
Standard PRS			
Low genetic risk	2,255/92,508	1.84	reference
Medium genetic risk	8,087/185,014	3.33	1.70 (1.62,1.78)
High genetic risk	6,976/92,508	5.84	2.82 (2.69,2.95)
P for trend			<0.001
Standard PRS			
Low genetic risk	608/19,572	2.36	reference
Medium genetic risk	1,985/39,144	3.88	1.51 (1.38,1.66)
High genetic risk	1,703/19,572	6.78	2.50 (2.28,2.75)
P for trend			<0.001

[a]Cox proportional hazard regression model adjusted for age, sex, race, income, education, family history, obesity, smoking status, drinking status, physical activity, healthy diet, sleep status, hypertension, high cholesterol, cancer, genotyping batch, and genetic principal components.

Abbreviation: HR, hazard ratio; CI, confidence interval; PYs, person-years; T2D, type 2 diabetes; PRS, polygenic risk score.

Table S11 Additive interaction effect for PhenoAgeAccel and PRS.

	RERI[a] (95% CI)	*P* value	AP[a] (95% CI)	*P* value
Standard PRS				
Medium PRS× Biologically older	0.47 (0.32,0.63)	<0.001	0.15 (0.10,0.20)	<0.001
High PRS × Biologically older	0.89 (0.68,1.10)	<0.001	0.19 (0.14,0.23)	<0.001
Enhanced PRS				
Medium PRS× Biologically older	0.22 (-0.07,0.52)	0.067	0.08 (-0.03,0.19)	0.070
High PRS × Biologically older	0.73 (0.34,1.13)	<0.001	0.17 (0.08,0.26)	<0.001

[a]The 95% CIs of these interaction index were estimated by bootstrapping.

Abbreviation: T2D, type 2 diabetes; RERI, relative excess risk due to interaction; AP, attributable proportion due to interaction.

Table S12 Associations between Lifestyle and transitions from baseline, T2D, complication, to specific death using the multi-state model.

Transition	Lifestyle	No. of cases/Total no.	Incidence/ 1,000 PYs	HR[a] (95% CI)
Baseline to T2D	Favorable	2,182/102,505	1.59	Reference
	Intermediate	11,230/226,169	3.80	1.90 (1.82,1.99)
	Unfavorable	4,203/47,409	7.00	2.98 (2.83,3.14)
	P for trend			<0.001
Baseline to Death	Favorable	5,099/102,505	3.72	Reference
	Intermediate	15,791/226,169	5.34	1.29 (1.25,1.33)
	Unfavorable	4,733/47,409	7.88	1.78 (1.71,1.86)
	P for trend			<0.001
T2D to Complication	Favorable	517/2,182	49.80	Reference
	Intermediate	2,784/11,230	52.03	1.04 (0.94,1.14)
	Unfavorable	1,223/4,203	62.67	1.28 (1.15,1.42)
	P for trend			<0.001
T2D to Death	Favorable	177/2,182	17.05	Reference
	Intermediate	1,075/11,230	20.09	1.20 (1.02,1.41)
	Unfavorable	458/4,203	23.47	1.46 (1.22,1.74)
	P for trend			<0.001
Complication to Death	Favorable	97/517	56.72	Reference
	Intermediate	624/2,784	67.22	1.23 (0.99,1.53)
	Unfavorable	319/1,223	76.44	1.42 (1.13,1.79)
	P for trend			0.002

[a]Multi-state model adjusted for age, sex, race, income, education, family history, hypertension, high cholesterol, and cancer.

Abbreviation: HR, hazard ratio; CI, confidence interval; PYs, person-years; T2D, type 2 diabetes.

Table S13 Additive interaction effect for PhenoAgeAccel and lifestyle.

	RERI[a] (95% CI)	*P* value	AP[a] (95% CI)	*P* value
Baseline to T2D				
Intermediate lifestyle × Biologically older	0.69 (0.53,0.85)	<0.001	0.19 (0.14,0.23)	<0.001
Unfavorable lifestyle × Biologically older	1.50 (1.22,1.78)	<0.001	0.28 (0.23,0.32)	<0.001
Baseline to Death				
Intermediate lifestyle × Biologically older	0.39 (0.31,0.47)	<0.001	0.20 (0.16,0.25)	<0.001
Unfavorable lifestyle × Biologically older	0.87 (0.74,1.00)	<0.001	0.33 (0.29,0.37)	<0.001
T2D to Complication				
Intermediate lifestyle × Biologically older	0.10 (-0.09,0.28)	0.152	0.09 (-0.08,0.26)	0.160
Unfavorable lifestyle × Biologically older	0.03 (-0.20,0.26)	0.404	0.02 (-0.15,0.20)	0.405
T2D to Death				
Intermediate lifestyle × Biologically older	0.12 (-0.19,0.44)	0.222	0.10 (-0.16,0.35)	0.231
Unfavorable lifestyle × Biologically older	0.36 (-0.01,0.73)	0.029	0.22 (-0.02,0.47)	0.036
Complication to Death				
Intermediate lifestyle × Biologically older	0.30 (-0.11,0.71)	0.073	0.21 (-0.10,0.53)	0.094
Unfavorable lifestyle × Biologically older	0.49 (0.03,0.95)	0.019	0.30 (-0.01,0.60)	0.029

[a]The 95% CIs of these interaction index were estimated by bootstrapping.

Abbreviation: T2D, type 2 diabetes; RERI, relative excess risk due to interaction; AP, attributable proportion due to interaction.

Table S14 Sensitivity analysis excluding participants who entered different states on the same date.

Transition	PhenoAgeAccel[a]	No. of cases/Total no.	Incidence/ 1,000 PYs	HR[b] (95% CI)
Baseline to T2D	**Per 5 years increase**	15,958/374,426	3.25	1.34 (1.32,1.35)
	Category			
	Biologically younger	6,366/222,358	2.15	Reference
	Biologically older	9,592/152,068	4.93	1.78 (1.72,1.84)
	Quantiles			
	Low	2,192/98,209	1.66	Reference
	Intermediate	7,396/192,540	2.91	1.45 (1.38,1.52)
	High	6,370/83,677	6.06	2.48 (2.36,2.61)
	P for trend			<0.001
Baseline to Death	**Per 5 years increase**	25,623/374,426	5.22	1.32 (1.31,1.33)
	Category			
	Biologically younger	12,074/222,358	4.07	Reference
	Biologically older	13,549/152,068	6.97	1.53 (1.49,1.57)
	Quantiles			
	Low	4,861/98,209	3.68	Reference
	Intermediate	12,007/192,540	4.73	1.18 (1.15,1.23)
	High	8,755/83,677	8.32	1.93 (1.86,2.00)
	P for trend			<0.001
T2D to Complication	**Per 5 years increase**	2,924/15,958	35.21	1.12 (1.09,1.16)
	Category			
	Biologically younger	1,058/6,366	32.51	Reference
	Biologically older	1,866/9,592	36.95	1.19 (1.10,1.28)
	Quantiles			
	Low	336/2,192	29.81	Reference
	Intermediate	1,274/7,396	33.37	1.16 (1.03,1.31)
	High	1,314/6,370	39.13	1.43 (1.26,1.61)
	P for trend			<0.001
T2D to Death	**Per 5 years increase**	1,653/15,958	19.91	1.14 (1.09,1.18)
	Category			
	Biologically younger	612/6,366	18.81	Reference
	Biologically older	1,041/9,592	20.62	1.15 (1.04,1.28)
	Quantiles			
	Low	208/2,192	18.46	Reference
	Intermediate	698/7,396	18.28	1.04 (0.89,1.22)
	High	747/6,370	22.24	1.34 (1.15,1.57)
	P for trend			<0.001
Complication to Death	**Per 5 years increase**	651/2,924	72.80	1.13 (1.07,1.20)

Category			
Biologically younger	193/1,058	60.24	Reference
Biologically older	458/1,866	79.81	1.30 (1.10,1.55)
Quantiles			
Low	60/336	53.67	Reference
Intermediate	252/1,274	67.58	1.22 (0.92,1.63)
High	339/1,314	82.78	1.53 (1.15,2.02)
P for trend			<0.001

[a]PhenoAgeAccel was classified into two groups: biologically younger (PhenoAgeAccel ≤0) and biologically older (PhenoAgeAccel >0). It was also divided into three quartile-based groups: low (bottom quantile), medium (quantiles 2-3), and high (top quantile).

[b]Multi-state model adjusted for age, sex, race, income, education, family history, obesity, smoking status, drinking status, physical activity, healthy diet, sleep status, hypertension, high cholesterol, and cancer.

Abbreviation: HR, hazard ratio; CI, confidence interval; PYs, person-years; T2D, type 2 diabetes.

Table S15 Sensitivity analysis using time intervals of 0.5 year.

Transition	PhenoAgeAccel[a]	No. of cases/Total no.	Incidence/ 1,000 PYs	HR[b] (95% CI)
Baseline to T2D	**Per 5 years increase**	17,597/376,083	3.57	1.33 (1.32,1.35)
	Category			
	Biologically younger	7,026/223,025	2.36	Reference
	Biologically older	10,571/153,058	5.41	1.77 (1.71,1.82)
	Quantiles			
	Low	2,428/ 98,449	1.84	Reference
	Intermediate	8,122/193,270	3.19	1.44 (1.37,1.50)
	High	7,047/ 84,364	6.67	2.46 (2.35,2.58)
	P for trend			<0.001
Baseline to Death	**Per 5 years increase**	25,629/376,083	5.20	1.32 (1.30,1.33)
	Category			
	Biologically younger	12,076/223,025	4.06	Reference
	Biologically older	13,553/153,058	6.94	1.53 (1.49,1.57)
	Quantiles			
	Low	4,862/ 98,449	3.68	Reference
	Intermediate	12,008/193,270	4.72	1.18 (1.15,1.23)
	High	8,759/ 84,364	8.28	1.92 (1.85,1.99)
	P for trend			<0.001
T2D to Complication	**Per 5 years increase**	4,494/ 17,597	53.42	1.09 (1.06,1.11)
	Category			
	Biologically younger	1,691/7,026	51.33	Reference
	Biologically older	2,803/ 10,571	54.76	1.10 (1.04,1.17)
	Quantiles			
	Low	563/2,428	49.35	Reference
	Intermediate	1,976/8,122	51.16	1.07 (0.97,1.18)
	High	1,955/7,047	57.33	1.24 (1.13,1.36)
	P for trend			<0.001
T2D to Death	**Per 5 years increase**	1,722/ 17,597	20.47	1.14 (1.09,1.18)
	Category			
	Biologically younger	639/7,026	19.40	Reference
	Biologically older	1,083/ 10,571	21.16	1.15 (1.04,1.27)
	Quantiles			
	Low	217/2,428	19.02	Reference
	Intermediate	722/8,122	18.69	1.03 (0.89,1.20)
	High	783/7,047	22.96	1.34 (1.15,1.57)
	P for trend			<0.001
Complication to Death	**Per 5 years increase**	1,022/4,494	68.11	1.14 (1.09,1.19)
	Category			
	Biologically younger	314/1,691	56.37	Reference

	Biologically older	708/2,803	75.04	1.31 (1.15,1.51)
	Quantiles			
	Low	104/563	51.99	Reference
	Intermediate	392/1,976	60.89	1.13 (0.91,1.41)
	High	526/1,955	80.09	1.50 (1.21,1.86)
	P for trend			<0.001

[a]PhenoAgeAccel was classified into two groups: biologically younger (PhenoAgeAccel ≤0) and biologically older (PhenoAgeAccel >0). It was also divided into three quartile-based groups: low (bottom quantile), medium (quantiles 2-3), and high (top quantile).

[b]Multi-state model adjusted for age, sex, race, income, education, family history, obesity, smoking status, drinking status, physical activity, healthy diet, sleep status, hypertension, high cholesterol, and cancer.

Abbreviation: HR, hazard ratio; CI, confidence interval; PYs, person-years; T2D, type 2 diabetes.

Table S16 Sensitivity analysis using time intervals of 1 year.

Transition	PhenoAgeAccel[a]	No. of cases/Total no.	Incidence/ 1,000 PYs	HR[b] (95% CI)
Baseline to T2D	**Per 5 years increase**	17,576/376,083	3.57	1.33 (1.32,1.35)
	Category			
	Biologically younger	7,019/223,025	2.36	Reference
	Biologically older	10,557/153,058	5.41	1.77 (1.71,1.82)
	Quantiles			
	Low	2,425/ 98,449	1.83	Reference
	Intermediate	8,114/193,270	3.19	1.44 (1.37,1.50)
	High	7,037/ 84,364	6.66	2.46 (2.34,2.58)
	P for trend			<0.001
Baseline to Death	**Per 5 years increase**	25,639/376,083	5.21	1.32 (1.30,1.33)
	Category			
	Biologically younger	12,079/223,025	4.06	Reference
	Biologically older	13,560/153,058	6.94	1.53 (1.49,1.57)
	Quantiles			
	Low	4,863/ 98,449	3.68	Reference
	Intermediate	12,011/193,270	4.72	1.18 (1.15,1.23)
	High	8,765/ 84,364	8.29	1.92 (1.85,1.99)
	P for trend			<0.001
T2D to Complication	**Per 5 years increase**	4,466/ 17,576	52.63	1.08 (1.06,1.11)
	Category			
	Biologically younger	1,683/ 7,019	50.63	Reference
	Biologically older	2,783/ 10,557	53.92	1.10 (1.03,1.17)
	Quantiles			
	Low	559/ 2,425	48.54	Reference
	Intermediate	1,965/ 8,114	50.44	1.07 (0.98,1.18)
	High	1,942/ 7,037	56.48	1.24 (1.13,1.37)
	P for trend			<0.001
T2D to Death	**Per 5 years increase**	1,729/ 17,576	20.38	1.14 (1.09,1.18)
	Category			
	Biologically younger	640/7,019	19.25	Reference
	Biologically older	1,089/ 10,557	21.10	1.15 (1.04,1.27)
	Quantiles			
	Low	218/2,425	18.93	Reference
	Intermediate	725/8,114	18.61	1.04 (0.89,1.21)
	High	786/7,037	22.86	1.35 (1.15,1.57)
	P for trend			<0.001
Complication to Death	**Per 5 years increase**	1,005/4,466	67.64	1.14 (1.09,1.19)
	Category			
	Biologically younger	310/1,683	56.11	Reference

	Biologically older	695/2,783	74.47	1.32 (1.15,1.51)
	Quantiles			
	Low	102/559	51.68	Reference
	Intermediate	386/1,965	60.57	1.14 (0.91,1.42)
	High	517/1,942	79.40	1.50 (1.21,1.86)
	P for trend			<0.001

[a]PhenoAgeAccel was classified into two groups: biologically younger (PhenoAgeAccel ≤0) and biologically older (PhenoAgeAccel >0). It was also divided into three quartile-based groups: low (bottom quantile), medium (quantiles 2-3), and high (top quantile).

[b]Multi-state model adjusted for age, sex, race, income, education, family history, obesity, smoking status, drinking status, physical activity, healthy diet, sleep status, hypertension, high cholesterol, and cancer.

Abbreviation: HR, hazard ratio; CI, confidence interval; PYs, person-years; T2D, type 2 diabetes.

Table S17 Sensitivity analysis using time intervals of 3 year.

Transition	PhenoAgeAccel[a]	No. of cases/Total no.	Incidence/ 1,000 PYs	HR[b] (95% CI)
Baseline to T2D	**Per 5 years increase**	17,486/376,083	3.55	1.33 (1.31,1.34)
	Category			
	Biologically younger	6,988/223,025	2.35	Reference
	Biologically older	10,498/153,058	5.38	1.76 (1.71,1.82)
	Quantiles			
	Low	2,411/ 98,449	1.82	Reference
	Intermediate	8,081/193,270	3.18	1.44 (1.37,1.51)
	High	6,994/ 84,364	6.62	2.45 (2.34,2.57)
	P for trend			<0.001
Baseline to Death	**Per 5 years increase**	25,664/376,083	5.21	1.32 (1.30,1.33)
	Category			
	Biologically younger	12,084/223,025	4.07	Reference
	Biologically older	13,580/153,058	6.96	1.53 (1.49,1.57)
	Quantiles			
	Low	4,864/ 98,449	3.68	Reference
	Intermediate	12,021/193,270	4.72	1.19 (1.15,1.23)
	High	8,779/ 84,364	8.31	1.93 (1.86,2.00)
	P for trend			<0.001
T2D to Complication	**Per 5 years increase**	4,352/ 17,486	49.70	1.08 (1.06,1.11)
	Category			
	Biologically younger	1,642/6,988	47.76	Reference
	Biologically older	2,710/ 10,498	50.96	1.11 (1.04,1.18)
	Quantiles			
	Low	542/2,411	45.49	Reference
	Intermediate	1,923/8,081	47.82	1.09 (0.99,1.20)
	High	1,887/6,994	53.26	1.26 (1.14,1.39)
	P for trend			<0.001
T2D to Death	**Per 5 years increase**	1,753/ 17,486	20.02	1.14 (1.10,1.18)
	Category			
	Biologically younger	650/6,988	18.91	Reference
	Biologically older	1,103/ 10,498	20.74	1.15 (1.05,1.28)
	Quantiles			
	Low	221/2,411	18.55	Reference
	Intermediate	734/8,081	18.25	1.04 (0.89,1.20)
	High	798/6,994	22.52	1.35 (1.16,1.57)
	P for trend			<0.001
Complication to Death	**Per 5 years increase**	956/4,352	68.16	1.14 (1.08,1.19)
	Category			
	Biologically younger	295/1,642	56.74	Reference

	Biologically older	661/2,710	74.88	1.30 (1.13,1.50)
	Quantiles			
	Low	98/542	53.91	Reference
	Intermediate	367/1,923	60.45	1.09 (0.87,1.37)
	High	491/1,887	80.00	1.45 (1.16,1.81)
	P for trend			<0.001

[a]PhenoAgeAccel was classified into two groups: biologically younger (PhenoAgeAccel ≤0) and biologically older (PhenoAgeAccel >0). It was also divided into three quartile-based groups: low (bottom quantile), medium (quantiles 2-3), and high (top quantile).

[b]Multi-state model adjusted for age, sex, race, income, education, family history, obesity, smoking status, drinking status, physical activity, healthy diet, sleep status, hypertension, high cholesterol, and cancer.

Abbreviation: HR, hazard ratio; CI, confidence interval; PYs, person-years; T2D, type 2 diabetes.

Table S18 Sensitivity analysis excluding events occurred in the first two-year of follow-up

Transition	PhenoAgeAccel[a]	No. of cases/Total no.	Incidence/ 1,000 PYs	HR[b] (95% CI)
Baseline to T2D	**Per 5 years increase**	16,128/373,156	3.28	1.33 (1.31,1.34)
	Category			
	Biologically younger	6,544/222,057	2.20	Reference
	Biologically older	9,584/151,099	4.91	1.73 (1.67,1.78)
	Quantiles			
	Low	2,246/ 98,102	1.70	Reference
	Intermediate	7,537/192,126	2.96	1.44 (1.37,1.51)
	High	6,345/ 82,928	6.01	2.41 (2.29,2.53)
	P for trend			<0.001
Baseline to Death	**Per 5 years increase**	24,183/373,156	4.91	1.29 (1.28,1.30)
	Category			
	Biologically younger	11,595/222,057	3.90	Reference
	Biologically older	12,588/151,099	6.45	1.49 (1.45,1.53)
	Quantiles			
	Low	4,700/ 98,102	3.56	Reference
	Intermediate	11,452/192,126	4.50	1.17 (1.13,1.21)
	High	8,031/ 82,928	7.61	1.84 (1.77,1.91)
	P for trend			<0.001
T2D to Complication	**Per 5 years increase**	4,033/ 16,128	58.31	1.08 (1.05,1.11)
	Category			
	Biologically younger	1,565/6,544	56.42	Reference
	Biologically older	2,468/9,584	59.59	1.09 (1.02,1.16)
	Quantiles			
	Low	514/2,246	54.39	Reference
	Intermediate	1,822/7,537	56.30	1.08 (0.97,1.19)
	High	1,697/6,345	62.05	1.23 (1.11,1.36)
	P for trend			<0.001
T2D to Death	**Per 5 years increase**	1,528/ 16,128	22.09	1.14 (1.09,1.18)
	Category			
	Biologically younger	578/6,544	20.84	Reference
	Biologically older	950/9,584	22.94	1.16 (1.04,1.29)
	Quantiles			
	Low	196/2,246	20.74	Reference
	Intermediate	646/7,537	19.96	1.02 (0.87,1.20)
	High	686/6,345	25.08	1.36 (1.15,1.60)
	P for trend			<0.001
Complication to Death	**Per 5 years increase**	905/4,033	72.38	1.17 (1.11,1.22)
	Category			
	Biologically younger	286/1,565	58.98	Reference

	Biologically older	619/2,468	80.87	1.36 (1.18,1.57)
	Quantiles			
	Low	98/514	57.55	Reference
	Intermediate	353/1,822	63.38	1.07 (0.85,1.34)
	High	454/1,697	86.78	1.48 (1.18,1.85)
	P for trend			<0.001

[a]PhenoAgeAccel was classified into two groups: biologically younger (PhenoAgeAccel ≤0) and biologically older (PhenoAgeAccel >0). It was also divided into three quartile-based groups: low (bottom quantile), medium (quantiles 2-3), and high (top quantile).

[b]Multi-state model adjusted for age, sex, race, income, education, family history, obesity, smoking status, drinking status, physical activity, healthy diet, sleep status, hypertension, high cholesterol, and cancer.

Abbreviation: HR, hazard ratio; CI, confidence interval; PYs, person-years; T2D, type 2 diabetes.

Table S19 Sensitivity analysis excluding events occurred in the first five-year of follow-up

Transition	PhenoAgeAccel[a]	No. of cases/Total no.	Incidence/ 1,000 PYs	HR[b] (95% CI)
Baseline to T2D	**Per 5 years increase**	12,870/366,173	2.63	1.31 (1.30,1.33)
	Category			
	Biologically younger	5,316/219,280	1.80	Reference
	Biologically older	7,554/146,893	3.90	1.70 (1.64,1.76)
	Quantiles			
	Low	1,820/ 97,092	1.38	Reference
	Intermediate	6,107/189,009	2.41	1.45 (1.38,1.53)
	High	4,943/ 80,072	4.73	2.36 (2.23,2.49)
	P for trend			<0.001
Baseline to Death	**Per 5 years increase**	20,458/366,173	4.18	1.27 (1.25,1.28)
	Category			
	Biologically younger	10,046/219,280	3.39	Reference
	Biologically older	10,412/146,893	5.38	1.43 (1.39,1.47)
	Quantiles			
	Low	4,116/ 97,092	3.12	Reference
	Intermediate	9,765/189,009	3.85	1.14 (1.10,1.19)
	High	6,577/ 80,072	6.29	1.74 (1.67,1.81)
	P for trend			<0.001
T2D to Complication	**Per 5 years increase**	3,009/ 12,870	68.63	1.07 (1.03,1.10)
	Category			
	Biologically younger	1,197/ 5,316	66.52	Reference
	Biologically older	1,812/ 7,554	70.11	1.09 (1.01,1.17)
	Quantiles			
	Low	394/ 1,820	64.97	Reference
	Intermediate	1,398/ 6,107	66.92	1.08 (0.97,1.21)
	High	1,217/ 4,943	72.07	1.20 (1.07,1.34)
	P for trend			<0.001
T2D to Death	**Per 5 years increase**	1,196/ 12,870	27.28	1.15 (1.10,1.21)
	Category			
	Biologically younger	456/ 5,316	25.34	Reference
	Biologically older	740/ 7,554	28.63	1.18 (1.05,1.33)
	Quantiles			
	Low	151/ 1,820	24.90	Reference
	Intermediate	518/ 6,107	24.80	1.05 (0.88,1.26)
	High	527/ 4,943	31.21	1.39 (1.15,1.67)
	P for trend			<0.001
Complication to Death	**Per 5 years increase**	645/ 3,009	82.24	1.18 (1.11,1.26)
	Category			
	Biologically younger	212/ 1,197	67.16	Reference

	Biologically older	433/ 1,812	92.39	1.38 (1.16,1.63)
	Quantiles			
	Low	76/ 394	69.54	Reference
	Intermediate	257/ 1,398	70.08	1.02 (0.78,1.32)
	High	312/ 1,217	101.21	1.48 (1.14,1.91)
	P for trend			<0.001

[a]PhenoAgeAccel was classified into two groups: biologically younger (PhenoAgeAccel ≤0) and biologically older (PhenoAgeAccel >0). It was also divided into three quartile-based groups: low (bottom quantile), medium (quantiles 2-3), and high (top quantile).

[b]Multi-state model adjusted for age, sex, race, income, education, family history, obesity, smoking status, drinking status, physical activity, healthy diet, sleep status, hypertension, high cholesterol, and cancer.

Abbreviation: HR, hazard ratio; CI, confidence interval; PYs, person-years; T2D, type 2 diabetes.

Table S20 Sensitivity analysis excluding participants with cancer at baseline.

Transition	PhenoAgeAccel[a]	No. of cases/Total no.	Incidence/ 1,000 PYs	HR[b] (95% CI)
Baseline to T2D	**Per 5 years increase**	13,780/257,126	4.10	1.34 (1.32,1.36)
	Category			
	Biologically younger	5,585/153,139	2.74	Reference
	Biologically older	8,195/103,987	6.18	1.75 (1.69,1.82)
	Quantiles			
	Low	1,955/ 67,611	2.16	Reference
	Intermediate	6,403/132,518	3.68	1.42 (1.35,1.50)
	High	5,422/ 56,997	7.58	2.42 (2.29,2.55)
	P for trend			<0.001
Baseline to Death	**Per 5 years increase**	17,445/257,126	5.19	1.28 (1.27,1.30)
	Category			
	Biologically younger	8,527/153,139	4.19	Reference
	Biologically older	8,918/103,987	6.72	1.45 (1.41,1.50)
	Quantiles			
	Low	3,428/ 67,611	3.78	Reference
	Intermediate	8,469/132,518	4.86	1.20 (1.15,1.25)
	High	5,548/ 56,997	7.76	1.77 (1.69,1.85)
	P for trend			<0.001
T2D to Complication	**Per 5 years increase**	3,600/ 13,780	56.34	1.08 (1.05,1.11)
	Category			
	Biologically younger	1,376/5,585	54.29	Reference
	Biologically older	2,224/8,195	57.69	1.09 (1.01,1.16)
	Quantiles			
	Low	470/1,955	52.70	Reference
	Intermediate	1,585/6,403	53.74	1.04 (0.94,1.16)
	High	1,545/5,422	60.62	1.20 (1.08,1.34)
	P for trend			<0.001
T2D to Death	**Per 5 years increase**	1,284/ 13,780	20.10	1.12 (1.07,1.18)
	Category			
	Biologically younger	500/5,585	19.73	Reference
	Biologically older	784/8,195	20.34	1.09 (0.98,1.23)
	Quantiles			
	Low	169/1,955	18.95	Reference
	Intermediate	557/6,403	18.89	1.05 (0.88,1.25)
	High	558/5,422	21.89	1.31 (1.10,1.57)
	P for trend			<0.001
Complication to Death	**Per 5 years increase**	791/3,600	65.04	1.11 (1.06,1.17)
	Category			
	Biologically younger	242/1,376	52.81	Reference

Biologically older	549/2,224	72.43	1.37 (1.17,1.60)
Quantiles			
Low	80/470	47.25	Reference
Intermediate	312/1,585	59.73	1.26 (0.98,1.61)
High	399/1,545	76.07	1.60 (1.25,2.05)
P for trend			<0.001

[a]PhenoAgeAccel was classified into two groups: biologically younger (PhenoAgeAccel ≤0) and biologically older (PhenoAgeAccel >0). It was also divided into three quartile-based groups: low (bottom quantile), medium (quantiles 2-3), and high (top quantile).

[b]Multi-state model adjusted for age, sex, race, income, education, family history, obesity, smoking status, drinking status, physical activity, healthy diet, sleep status, hypertension, and high cholesterol.

Abbreviation: HR, hazard ratio; CI, confidence interval; PYs, person-years; T2D, type 2 diabetes.

Table S21 Sensitivity analysis excluding participants without complete data of covariates.

Transition	PhenoAgeAccel[a]	No. of cases/Total no.	Incidence/ 1,000 PYs	HR[b] (95% CI)
Baseline to T2D	**Per 5 years increase**	8,311/226,038	2.78	1.35 (1.33,1.37)
	Category			
	Biologically younger	3,543/139,106	1.90	Reference
	Biologically older	4,768/ 86,932	4.24	1.75 (1.68,1.83)
	Quantiles			
	Low	1,213/ 62,736	1.43	Reference
	Intermediate	3,955/116,820	2.55	1.48 (1.39,1.58)
	High	3,143/ 46,482	5.31	2.59 (2.42,2.77)
	P for trend			<0.001
Baseline to Death	**Per 5 years increase**	12,509/226,038	4.19	1.32 (1.30,1.34)
	Category			
	Biologically younger	6,328/139,106	3.40	Reference
	Biologically older	6,181/ 86,932	5.50	1.51 (1.45,1.56)
	Quantiles			
	Low	2,626/ 62,736	3.11	Reference
	Intermediate	5,978/116,820	3.86	1.18 (1.12,1.23)
	High	3,905/ 46,482	6.60	1.93 (1.83,2.03)
	P for trend			<0.001
T2D to Complication	**Per 5 years increase**	1,904/8,311	47.34	1.08 (1.04,1.12)
	Category			
	Biologically younger	776/3,543	46.71	Reference
	Biologically older	1,128/4,768	47.78	1.08 (0.98,1.18)
	Quantiles			
	Low	261/1,213	45.75	Reference
	Intermediate	860/3,955	45.33	1.02 (0.88,1.17)
	High	783/3,143	50.37	1.21 (1.05,1.40)
	P for trend			<0.001
T2D to Death	**Per 5 years increase**	748/8,311	18.60	1.12 (1.05,1.19)
	Category			
	Biologically younger	305/3,543	18.36	Reference
	Biologically older	443/4,768	18.77	1.10 (0.95,1.28)
	Quantiles			
	Low	93/1,213	16.30	Reference
	Intermediate	341/3,955	17.98	1.16 (0.92,1.46)
	High	314/3,143	20.20	1.46 (1.15,1.85)
	P for trend			<0.001
Complication to Death	**Per 5 years increase**	380/1,904	58.73	1.17 (1.09,1.26)
	Category			
	Biologically younger	122/776	45.94	Reference

Biologically older	258/1,128	67.62	1.58 (1.26,1.97)
Quantiles			
Low	43/261	44.50	Reference
Intermediate	145/860	51.25	1.15 (0.81,1.63)
High	192/783	71.77	1.70 (1.20,2.39)
P for trend			<0.001

[a]PhenoAgeAccel was classified into two groups: biologically younger (PhenoAgeAccel ≤0) and biologically older (PhenoAgeAccel >0). It was also divided into three quartile-based groups: low (bottom quantile), medium (quantiles 2-3), and high (top quantile).

[b]Multi-state model adjusted for age, sex, race, income, education, family history, obesity, smoking status, drinking status, physical activity, healthy diet, sleep status, hypertension, high cholesterol, and cancer.

Abbreviation: HR, hazard ratio; CI, confidence interval; PYs, person-years; T2D, type 2 diabetes.

Table S22 Sensitivity analysis adjusting for usage of cholesterol and blood pressure medication or the taking of exogenous hormones

Transition	PhenoAgeAccel[a]	No. of cases/Total no.	Incidence/ 1,000 PYs	HR[b] (95% CI)
Baseline to T2D	**Per 5 years increase**	17,615/376,083	3.58	1.33 (1.32, 1.35)
	Category			
	Biologically younger	7,033/223,025	2.37	Reference
	Biologically older	10,582/153,058	5.42	1.74 (1.69, 1.80)
	Quantiles			
	Low	2,432/98,449	1.84	Reference
	Intermediate	8,126/193,270	3.19	1.32 (1.26, 1.38)
	High	7,057/84,364	6.67	2.44 (2.33, 2.56)
	P for trend			<0.001
Baseline to Death	**Per 5 years increase**	25,623/376,083	5.2	1.31 (1.30, 1.33)
	Category			
	Biologically younger	12,074/223,025	4.06	Reference
	Biologically older	13,549/153,058	6.94	1.53 (1.49, 1.57)
	Quantiles			
	Low	4,861/98,449	3.68	Reference
	Intermediate	12,007/193,270	4.72	1.18 (1.14, 1.22)
	High	8,755/84,364	8.28	2.03 (1.96, 2.11)
	P for trend			<0.001
T2D to Complication	**Per 5 years increase**	4,524/17,615	54.24	1.09 (1.06, 1.12)
	Category			
	Biologically younger	1,702/7,033	52.14	Reference
	Biologically older	2,822/10,582	55.6	1.11 (1.04, 1.18)
	Quantiles			
	Low	569/2,432	50.36	Reference
	Intermediate	1,983/8,126	51.79	1.07 (0.98, 1.18)
	High	1,972/7,057	58.32	1.25 (1.14, 1.37)
	P for trend			<0.001
T2D to Death	**Per 5 years increase**	1,710/17,615	20.5	1.13 (1.09, 1.18)
	Category			
	Biologically younger	635/7,033	19.45	Reference
	Biologically older	1,075/10,582	21.18	1.14 (1.03, 1.26)
	Quantiles			
	Low	215/2,432	19.03	Reference
	Intermediate	719/8,126	18.78	1.04 (0.89, 1.22)
	High	776/7,057	22.95	1.35 (1.16, 1.58)
	P for trend			<0.001
Complication to Death	**Per 5 years increase**	1,040/4,524	68.58	1.13 (1.08, 1.18)
	Category			

Biologically younger	320/1,702	56.8	Reference
Biologically older	720/2,822	75.53	1.27 (1.11, 1.46)
Quantiles			
Low	107/569	52.37	Reference
Intermediate	396/1,983	61.24	1.14 (0.92, 1.41)
High	537/1,972	80.67	1.51 (1.22, 1.87)
P for trend			<0.001

[a]PhenoAgeAccel was classified into two groups: biologically younger (PhenoAgeAccel ≤0) and biologically older (PhenoAgeAccel >0). It was also divided into three quartile-based groups: low (bottom quantile), medium (quantiles 2-3), and high (top quantile).

[b]Multi-state model adjusted for age, sex, race, income, education, family history, obesity, smoking status, drinking status, physical activity, healthy diet, sleep status, hypertension, high cholesterol, cancer, and usage of cholesterol and blood pressure medication or the taking of exogenous hormones.

Abbreviation: HR, hazard ratio; CI, confidence interval; PYs, person-years; T2D, type 2 diabetes.

Table S23 Sensitivity analysis adjusting for systolic blood pressure, HbA1C, glucose, and total cholesterol

Transition	PhenoAgeAccel[a]	No. of cases/Total no.	Incidence/ 1,000 PYs	HR[b] (95% CI)
Baseline to T2D	**Per 5 years increase**	17,615/376,083	3.58	1.13 (1.11, 1.15)
	Category			
	Biologically younger	7,033/223,025	2.37	Reference
	Biologically older	10,582/153,058	5.42	1.48 (1.43, 1.53)
	Quantiles			
	Low	2,432/98,449	1.84	Reference
	Intermediate	8,126/193,270	3.19	1.32 (1.26, 1.38)
	High	7,057/84,364	6.67	1.87 (1.78, 1.96)
	P for trend			<0.001
Baseline to Death	**Per 5 years increase**	25,623/376,083	5.2	1.34 (1.32, 1.35)
	Category			
	Biologically younger	12,074/223,025	4.06	Reference
	Biologically older	13,549/153,058	6.94	1.57 (1.53, 1.61)
	Quantiles			
	Low	4,861/98,449	3.68	Reference
	Intermediate	12,007/193,270	4.72	1.22 (1.18, 1.26)
	High	8,755/84,364	8.28	2.03 (1.96, 2.11)
	P for trend			<0.001
T2D to Complication	**Per 5 years increase**	4,524/17,615	54.24	1.12 (1.09, 1.15)
	Category			
	Biologically younger	1,702/7,033	52.14	Reference
	Biologically older	2,822/10,582	55.6	1.13 (1.06, 1.21)
	Quantiles			
	Low	569/2,432	50.36	Reference
	Intermediate	1,983/8,126	51.79	1.09 (1.00, 1.20)
	High	1,972/7,057	58.32	1.31 (1.19, 1.45)
	P for trend			<0.001
T2D to Death	**Per 5 years increase**	1,710/17,615	20.5	1.23 (1.18, 1.28)
	Category			
	Biologically younger	635/7,033	19.45	Reference
	Biologically older	1,075/10,582	21.18	1.27 (1.14, 1.41)
	Quantiles			
	Low	215/2,432	19.03	Reference
	Intermediate	719/8,126	18.78	1.14 (0.97, 1.33)
	High	776/7,057	22.95	1.64 (1.40, 1.93)
	P for trend			<0.001
Complication to Death	**Per 5 years increase**	1,040/4,524	68.58	1.21 (1.16, 1.27)
	Category			

Biologically younger	320/1,702	56.8	Reference
Biologically older	720/2,822	75.53	1.46 (1.27, 1.68)
Quantiles			
Low	107/569	52.37	Reference
Intermediate	396/1,983	61.24	1.22 (0.98, 1.52)
High	537/1,972	80.67	1.79 (1.43, 2.23)
P for trend			<0.001

[a]PhenoAgeAccel was classified into two groups: biologically younger (PhenoAgeAccel ≤0) and biologically older (PhenoAgeAccel >0). It was also divided into three quartile-based groups: low (bottom quantile), medium (quantiles 2-3), and high (top quantile).

[b]Multi-state model adjusted for age, sex, race, income, education, family history, obesity, smoking status, drinking status, physical activity, healthy diet, sleep status, hypertension, high cholesterol, cancer, systolic blood pressure, HbA1C, glucose, and total cholesterol.

Abbreviation: HR, hazard ratio; CI, confidence interval; PYs, person-years; T2D, type 2 diabetes.

Table S24 The coefficients of each biomarkers for PhenoAge after re-training using UK Biobank with 5-fold cross-validation.

Biomarkers	Coefficients in NHANES	Coefficients in UK Biobank					
		CV1	CV2	CV3	CV4	CV5	Mean
Albumin (g/L)	-0.0336	-0.0341	-0.0361	-0.0345	-0.0348	-0.0345	-0.0348
Creatinine (umol/L)	0.0095	0.0086	0.0087	0.0088	0.0087	0.0091	0.0088
Glucose (mmol/L)	0.1953	0.1387	0.1411	0.1404	0.1435	0.1407	0.1409
log C-reactive protein (CRP) (mg/L)	0.0954	0.1312	0.1236	0.1319	0.1241	0.1259	0.1274
Lymphocyte percentage (%)	-0.0120	-0.0166	-0.0168	-0.0172	-0.0163	-0.0174	-0.0169
Mean corpuscular volume (fL)	0.0268	0.0549	0.055	0.0545	0.0548	0.0548	0.0548
Red blood cell distribution width (RDW)	0.3306	0.3014	0.2964	0.3053	0.3033	0.3075	0.3028
Alkaline phosphatase (U/L)	0.0019	0.0049	0.0049	0.0046	0.0047	0.0051	0.0049
White blood cell count (10^9 cells/L)	0.0554	0.0833	0.0812	0.0795	0.0819	0.0813	0.0814
Age at recruitment (years)	0.0804	0.0866	0.0858	0.0858	0.0866	0.0864	0.0862

Abbreviation: NHANES, National Health and Nutrition Examination Survey; CV, cross-validation.

The UK Biobank was randomly split into five equal sets, each 4 of the 5 folds was treated as training data to calculate the new coefficients of biomarkers, using a parametric proportional hazards model based on the Gompertz distribution.

Table S25 Sensitivity analysis using recalculated PhenoAgeAccel derived from UK Biobank

Transition	PhenoAgeAccel[a]	No. of cases/Total no.	Incidence/ 1,000 PYs	HR[b] (95% CI)
Baseline to T2D	**Per 5 years increase**	17,892/381,848	3.58	1.28 (1.26, 1.29)
	Category			
	Biologically younger	6,542/220,143	2.23	Reference
	Biologically older	11,350/161,705	5.49	1.70 (1.64, 1.76)
	Quantiles			
	Low	2,285/100,288	1.7	Reference
	Intermediate	8,220/195,604	3.19	1.42 (1.35, 1.49)
	High	7,387/85,956	6.86	2.26 (2.15, 2.37)
	P for trend			<0.001
Baseline to Death	**Per 5 years increase**	25,931/381,848	5.19	1.30 (1.29, 1.31)
	Category			
	Biologically younger	11,445/220,143	3.91	Reference
	Biologically older	14,486/161,705	7.01	1.43 (1.39, 1.47)
	Quantiles			
	Low	4,804/100,288	3.58	Reference
	Intermediate	11,715/195,604	4.55	1.15 (1.11, 1.19)
	High	9,412/85,956	8.74	1.93 (1.86, 2.00)
	P for trend			<0.001
T2D to Complication	**Per 5 years increase**	4,606/17,892	54.45	1.15 (1.13, 1.18)
	Category			
	Biologically younger	1,435/6,542	45.96	Reference
	Biologically older	3,171/11,350	59.42	1.09 (1.01, 1.17)
	Quantiles			
	Low	462/2,285	41.63	Reference
	Intermediate	1,994/8,220	51.38	1.26 (1.14, 1.40)
	High	2,150/7,387	61.98	1.59 (1.43, 1.76)
	P for trend			<0.001
T2D to Death	**Per 5 years increase**	1,737/17,892	20.53	1.16 (1.12, 1.20)
	Category			
	Biologically younger	569/6,542	18.22	Reference
	Biologically older	1,168/11,350	21.88	1.18 (1.05, 1.33)
	Quantiles			
	Low	197/2,285	17.75	Reference
	Intermediate	742/8,220	19.12	1.11 (0.95, 1.30)
	High	798/7,387	23.01	1.40 (1.19, 1.65)
	P for trend			<0.001
Complication to Death	**Per 5 years increase**	1,053/4,606	68.01	1.16 (1.11, 1.21)
	Category			
	Biologically younger	270/1,435	57.62	Reference

Biologically older	783/3,171	72.52	1.38 (1.16, 1.63)
Quantiles			
Low	92/462	61.3	Reference
Intermediate	363/1,994	54.18	0.86 (0.69, 1.09)
High	598/2,150	82.12	1.31 (1.04, 1.64)
P for trend			<0.001

[a]PhenoAgeAccel was classified into two groups: biologically younger (PhenoAgeAccel ≤0) and biologically older (PhenoAgeAccel >0). It was also divided into three quartile-based groups: low (bottom quantile), medium (quantiles 2-3), and high (top quantile).

[b]Multi-state model adjusted for age, sex, race, income, education, family history, obesity, smoking status, drinking status, physical activity, healthy diet, sleep status, hypertension, high cholesterol, and cancer.

Abbreviation: HR, hazard ratio; CI, confidence interval; PYs, person-years; T2D, type 2 diabetes.

Table S26 Sensitivity analysis of joint effect between PhenoAgeAccel and lifestyle using lifestyle scores that do not include BMI

	No. of cases (Incidence per 1,000 PYs)	HR[a] (95% CI)	PAF%[b] (95% CI)
Baseline → T2D			
Favorable lifestyle			
Biologically younger	2,005 (2.08)	Reference	Reference
Biologically older	2,162 (4.47)	1.96 (1.85, 2.09)	5.9 (5.3, 6.4)
Intermediate lifestyle			
Biologically younger	4,383 (2.44)	1.29 (1.23, 1.36)	5.4 (4.3, 6.5)
Biologically older	6,853 (5.48)	2.64 (2.51, 2.78)	23.7 (22.6, 24.7)
Unfavorable lifestyle			
Biologically younger	645 (3.06)	1.75 (1.60, 1.92)	1.5 (1.2, 1.8)
Biologically older	1,567 (7.20)	3.77 (3.52, 4.04)	6.5 (6.1, 7.0)
Baseline → Death			
Favorable lifestyle			
Biologically younger	3,649 (3.79)	Reference	Reference
Biologically older	2,815 (5.82)	1.47 (1.40, 1.54)	3.4 (2.9, 3.9)
Intermediate lifestyle			
Biologically younger	7,408 (4.12)	1.24 (1.19, 1.29)	5.2 (4.3, 6.2)
Biologically older	8,700 (6.95)	2.06 (1.98, 2.14)	17.1 (16.2, 18.0)
Unfavorable lifestyle			
Biologically younger	1,017 (4.82)	1.66 (1.55, 1.78)	1.5 (1.3, 1.7)
Biologically older	2,034 (9.34)	3.28 (3.10, 3.47)	5.5 (5.2, 5.9)
T2D → Complication			
Favorable lifestyle			
Biologically younger	468 (48.87)	Reference	Reference
Biologically older	555 (52.16)	1.13 (1.00, 1.28)	1.1 (-0.1, 2.3)
Intermediate lifestyle			
Biologically younger	1,052 (52.06)	1.12 (1.00, 1.25)	2.0 (-0.1, 4.1)
Biologically older	1,797 (54.88)	1.25 (1.13, 1.39)	6.4 (3.3, 9.5)
Unfavorable lifestyle			
Biologically younger	182 (63.61)	1.52 (1.28, 1.81)	1.1 (0.6, 1.7)
Biologically older	470 (63.75)	1.64 (1.44, 1.88)	3.2 (2.3, 4.2)
T2D → Death			
Favorable lifestyle			
Biologically younger	171 (17.86)	Reference	Reference
Biologically older	198 (18.61)	1.11 (0.90, 1.36)	1.0 (-1.1, 3.2)
Intermediate lifestyle			
Biologically younger	408 (20.19)	1.20 (1.00, 1.44)	3.9 (0.1, 7.7)
Biologically older	686 (20.95)	1.35 (1.14, 1.60)	10.0 (4.7, 15.4)

Unfavorable lifestyle			
Biologically younger	56 (19.57)	1.32 (0.97, 1.80)	0.8 (-0.2, 1.8)
Biologically older	191 (25.91)	1.98 (1.60, 2.45)	5.4 (3.6, 7.3)
Complication → Death			
Favorable lifestyle			
Biologically younger	86 (54.64)	Reference	Reference
Biologically older	124 (66.81)	1.26 (0.96, 1.66)	2.3 (-0.6, 5.2)
Intermediate lifestyle			
Biologically younger	200 (57.96)	1.13 (0.88, 1.46)	2.1 (-2.4, 6.7)
Biologically older	451 (73.24)	1.48 (1.17, 1.87)	12.9 (5.5, 20.3)
Unfavorable lifestyle			
Biologically younger	34 (55.85)	1.17 (0.78, 1.75)	0.5 (-0.8, 1.8)
Biologically older	145 (95.49)	2.15 (1.63, 2.84)	7.2 (4.4, 10.1)

[a]Multi-state model adjusted for age, sex, race, income, education, family history, hypertension, high cholesterol, and cancer.

[b]PAFs at the median follow-up time of the study population were reported.

Abbreviation: HR, hazard ratio; CI, confidence interval; PYs, person-years; PAF, population attributable fraction; T2D, type 2 diabetes.

Table S27 Sensitivity analysis of joint effect between PhenoAgeAccel and lifestyle using reclassified lifestyle categories

	No. of cases (Incidence per 1,000 PYs)	HR[a] (95% CI)	PAF%[b] (95% CI)
Baseline → T2D			
Favorable lifestyle			
Biologically younger	555 (1.19)	Reference	Reference
Biologically older	500 (2.58)	1.96 (1.74,2.22)	1.4 (1.1, 1.7)
Intermediate lifestyle			
Biologically younger	4,261 (2.27)	1.83 (1.67,2.00)	10.6 (9.3, 11.8)
Biologically older	5,654 (4.87)	3.61 (3.30,3.94)	23.0 (21.9, 24.1)
Unfavorable lifestyle			
Biologically younger	2,217 (3.51)	2.79 (2.54,3.07)	7.8 (7.2, 8.4)
Biologically older	4,428 (7.40)	5.59 (5.11,6.11)	20.5 (19.7, 21.3)
Baseline → Death			
Favorable lifestyle			
Biologically younger	1,626 (3.49)	Reference	Reference
Biologically older	1,046 (5.39)	1.43 (1.32,1.54)	1.2 (0.9, 1.4)
Intermediate lifestyle			
Biologically younger	7,500 (4.00)	1.20 (1.14,1.27)	4.6 (3.3, 5.9)
Biologically older	7,584 (6.53)	1.92 (1.82,2.03)	13.8 (12.9, 14.8)
Unfavorable lifestyle			
Biologically younger	2,948 (4.67)	1.47 (1.38,1.56)	3.5 (2.9, 4.0)
Biologically older	4,919 (8.22)	2.68 (2.53,2.84)	12.0 (11.4, 12.6)
T2D → Complication			
Favorable lifestyle			
Biologically younger	141 (57.15)	Reference	Reference
Biologically older	130 (51.87)	0.96 (0.76,1.22)	-0.1 (-0.7, 0.5)
Intermediate lifestyle			
Biologically younger	992 (50.11)	0.92 (0.77,1.10)	-1.6 (-5.1, 2.0)
Biologically older	1,474 (54.73)	1.05 (0.88,1.25)	1.3 (-3.3, 5.8)
Unfavorable lifestyle			
Biologically younger	569 (54.82)	1.07 (0.89,1.29)	0.6 (-1.3, 2.5)
Biologically older	1,218 (57.13)	1.21 (1.01,1.44)	3.6 (0.0, 7.1)
T2D → Death			
Favorable lifestyle			
Biologically younger	47 (19.05)	Reference	Reference
Biologically older	46 (18.35)	0.96 (0.64,1.45)	-0.1 (-1.1, 1.0)
Intermediate lifestyle			
Biologically younger	391 (19.75)	1.09 (0.81,1.48)	1.8 (-4.6, 8.2)
Biologically older	561 (20.83)	1.23 (0.91,1.66)	5.9 (-2.3, 14.1)

Unfavorable lifestyle			
Biologically younger	197 (18.98)	1.13 (0.82,1.57)	1.3 (-2.0, 4.6)
Biologically older	468 (21.95)	1.47 (1.08,2.00)	8.4 (2.4, 14.3)
Complication → Death			
Favorable lifestyle			
Biologically younger	26 (53.59)	Reference	Reference
Biologically older	25 (56.07)	1.07 (0.62,1.85)	0.1 (-1.1, 1.4)
Intermediate lifestyle			
Biologically younger	189 (57.37)	1.15 (0.76,1.73)	2.2 (-4.6, 9.0)
Biologically older	362 (74.07)	1.50 (1.01,2.24)	11.0 (1.1, 21.0)
Unfavorable lifestyle			
Biologically younger	105 (56.64)	1.16 (0.75,1.79)	1.4 (-2.7, 5.4)
Biologically older	333 (79.30)	1.74 (1.16,2.60)	12.4 (4.4, 20.4)

[a]Multi-state model adjusted for age, sex, race, income, education, family history, hypertension, high cholesterol, and cancer.

[b]PAFs at the median follow-up time of the study population were reported.

Healthy lifestyle score was reclassified into three categories: favorable lifestyle (5-6), intermediate lifestyle (3-4), and unfavorable lifestyle (0-2).

Abbreviation: HR, hazard ratio; CI, confidence interval; PYs, person-years; PAF, population attributable fraction; T2D, type 2 diabetes.

Table S28 Sensitivity analysis using death caused by diabetes or diabetes complications.

Transition	PhenoAgeAccel[a]	No. of cases/Total no.	Incidence/ 1,000 PYs	HR[b] (95% CI)
Baseline to T2D	**Per 5 years increase**	17,615/376,083	3.58	1.34 (1.32,1.35)
	Category			
	Biologically younger	7,033/223,025	2.37	Reference
	Biologically older	10,582/153,058	5.42	1.77 (1.71,1.82)
	Quantiles			
	Low	2,432/98,449	1.84	Reference
	Intermediate	8,126/193,270	3.19	1.44 (1.37,1.50)
	High	7,057/84,364	6.67	2.46 (2.35,2.58)
	P for trend			<0.001
T2D to Complication	**Per 5 years increase**	4,523/17,615	54.23	1.09 (1.06,1.11)
	Category			
	Biologically younger	1,702/7,033	52.14	Reference
	Biologically older	2,821/10,582	55.58	1.10 (1.04,1.17)
	Quantiles			
	Low	569/2,432	50.36	Reference
	Intermediate	1,982/8,126	51.76	1.06 (0.97,1.17)
	High	1,972/7,057	58.32	1.24 (1.12,1.36)
	P for trend			<0.001
T2D to Death	**Per 5 years increase**	30/17,615	0.36	1.36 (1.04,1.77)
	Category			
	Biologically younger	11/7,033	0.34	Reference
	Biologically older	19/10,582	0.37	1.26 (0.59,2.69)
	Quantiles			
	Low	2/2,432	0.18	Reference
	Intermediate	13/8,126	0.34	2.07 (0.46,9.21)
	High	15/7,057	0.44	3.28 (0.74,14.63)
	P for trend			0.072
Complication to Death	**Per 5 years increase**	182/4,523	12	1.09 (0.98,1.22)
	Category			
	Biologically younger	59/1,702	10.47	Reference
	Biologically older	123/2,821	12.9	1.28 (0.93,1.75)
	Quantiles			
	Low	21/569	10.28	Reference
	Intermediate	68/1,982	10.52	1.06 (0.64,1.73)
	High	93/1,972	13.97	1.43 (0.88,2.32)
	P for trend			0.057

[a]PhenoAgeAccel was classified into two groups: biologically younger (PhenoAgeAccel ≤0) and biologically older (PhenoAgeAccel >0). It was also divided into three quartile-based groups: low (bottom quantile), medium (quantiles 2-3), and high (top quantile).

[b]Multi-state model adjusted for age, sex, race, income, education, family history, obesity, smoking status, drinking status, physical activity, healthy diet, sleep status, hypertension, high cholesterol, and cancer.
Deaths caused by diabetic complications are defined according to ICD-10 and include the following events: diabetic eye diseases, diabetic kidney diseases, diabetic neuropathy diseases, cardiovascular diseases, peripheral vascular diseases, and metabolic events
Abbreviation: HR, hazard ratio; CI, confidence interval; PYs, person-years; T2D, type 2 diabetes.

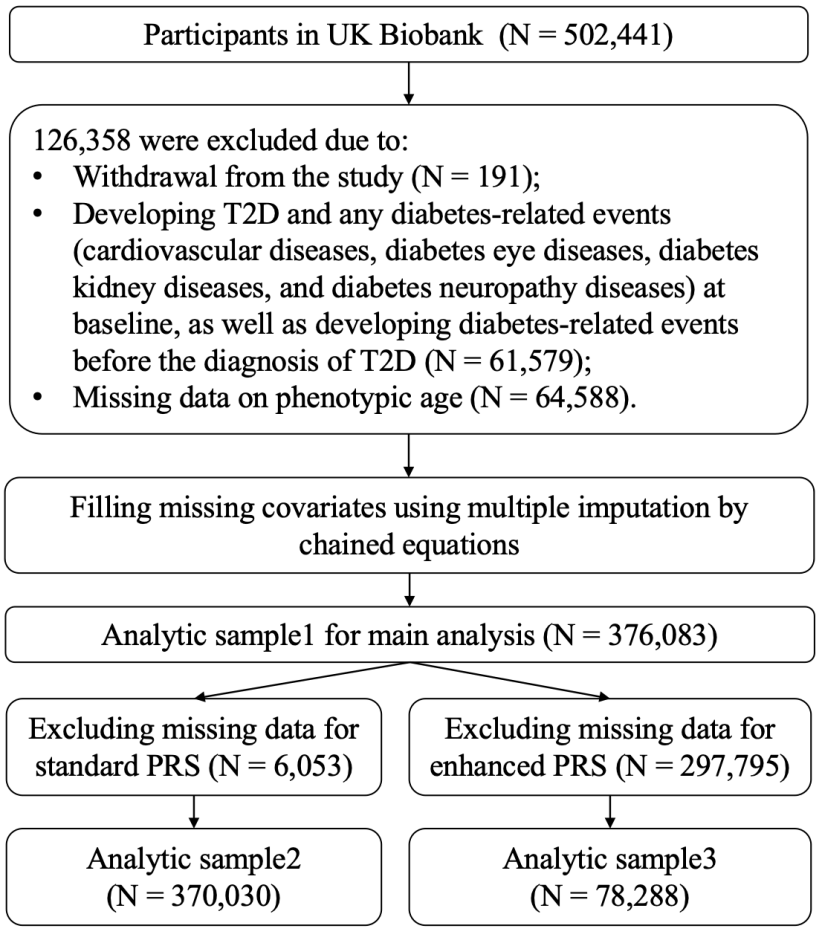

Fig. S1 The selection flow chart of the participants in this study.

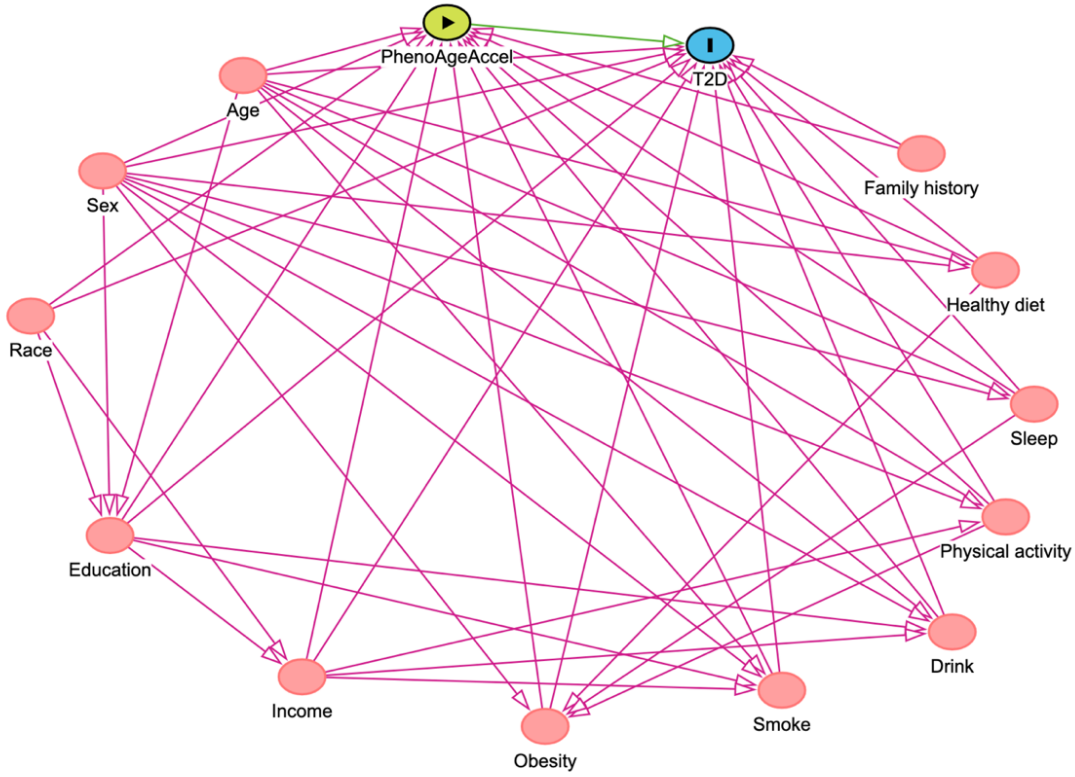

Fig. S2 Directed acyclic graph for the associations between PhenoAgeAccel and T2D.

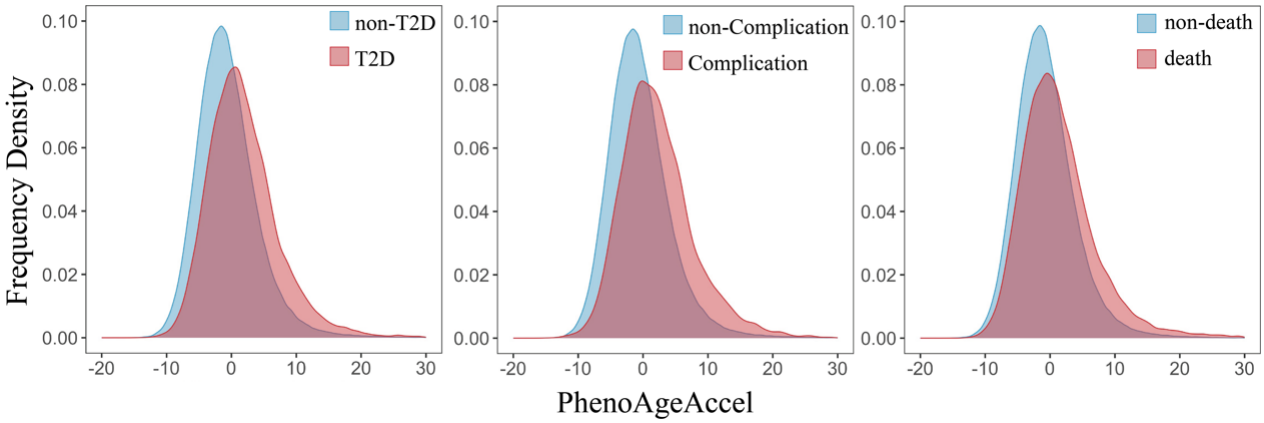

Fig. S3 The distribution of PhenoAgeAccel in the UK Biobank.

Abbreviation: T2D, type 2 diabetes.

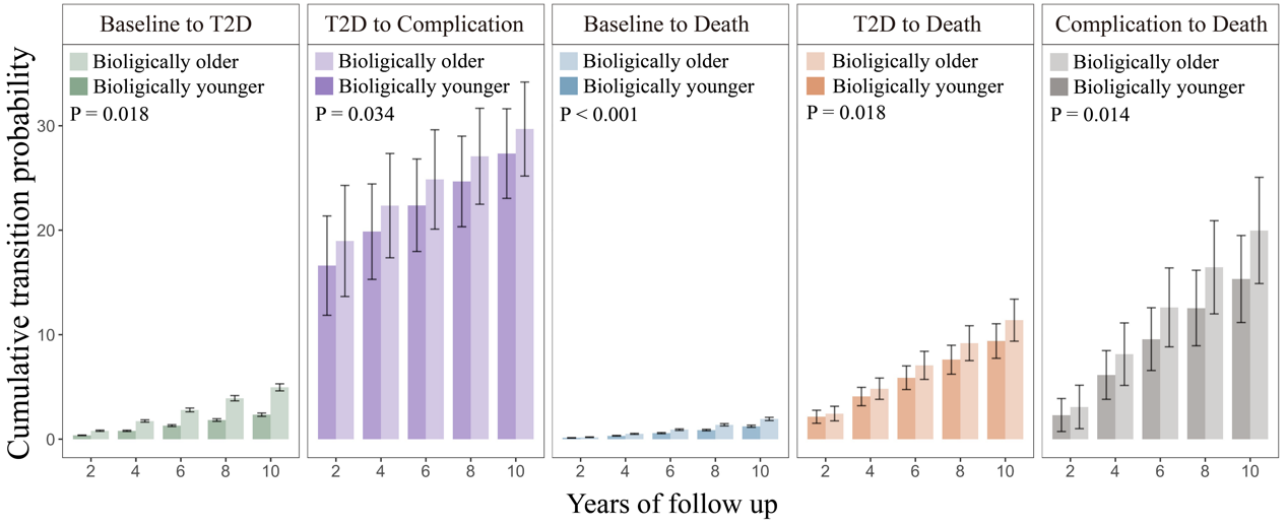

Fig. S4 Cumulative transition probability of five transitions of T2D for biologically younger and biologically older participants.

Multi-state model adjusted for age, sex, race, income, education, family history, obesity, smoking status, drinking status, physical activity, healthy diet, sleep status, hypertension, high cholesterol, and cancer.

The transition probability was estimated for biologically older and biologically younger hypothetical subjects (a 55-year-old male, White, with a household income of less than $18,000, an education level of high school or below, unhealthy lifestyles, no family history of T2D, no hypertension, no cholesterol issues, and no cancer).

Abbreviation: T2D, type 2 diabetes.

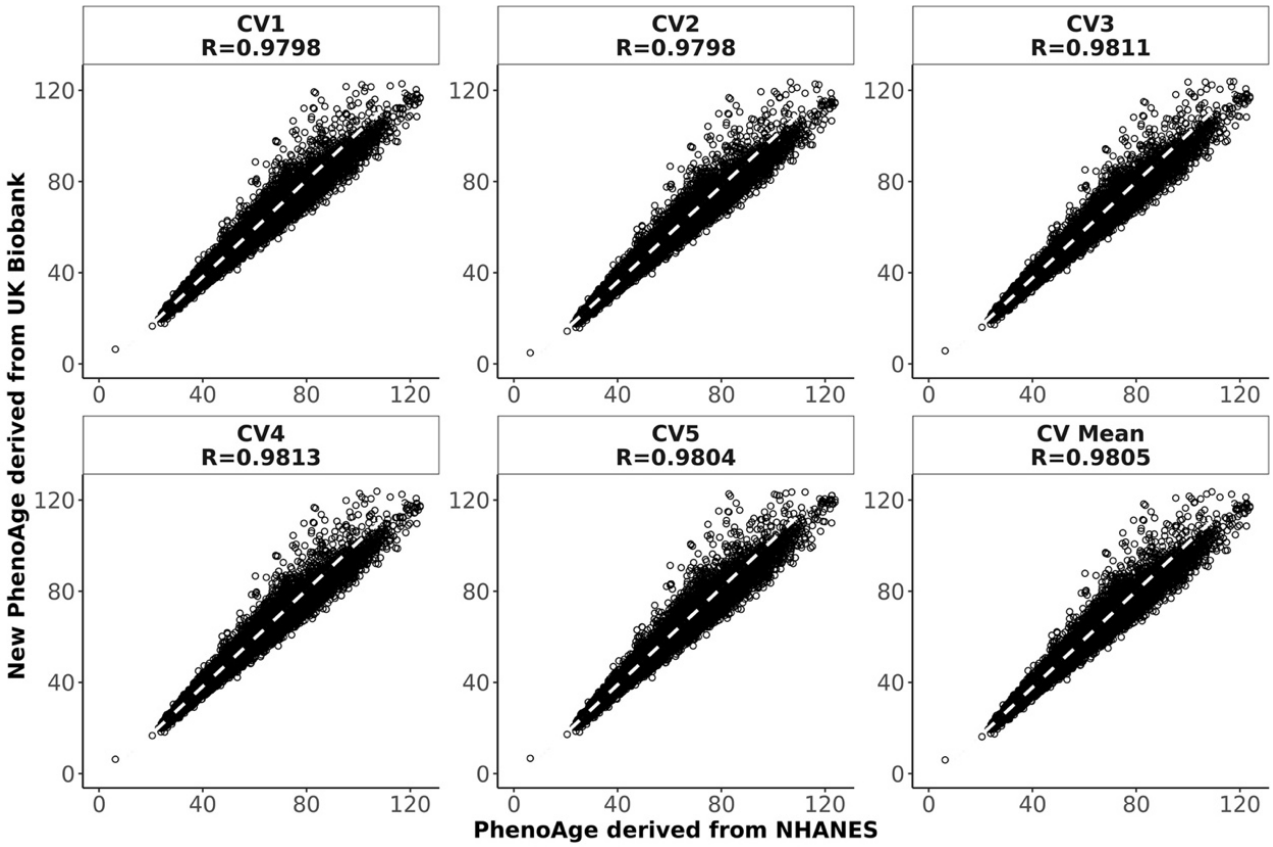

Fig. S5 The correlations of new PhenoAge retrained using the UK Biobank and the PhenoAge drived from NHANES with 5-fold cross-validation.

The UK Biobank was randomly split into five equal sets, each 4 of the 5 folds was treated as training data to calculate the new coefficients of biomarkers, using a parametric proportional hazards model based on the Gompertz distribution.

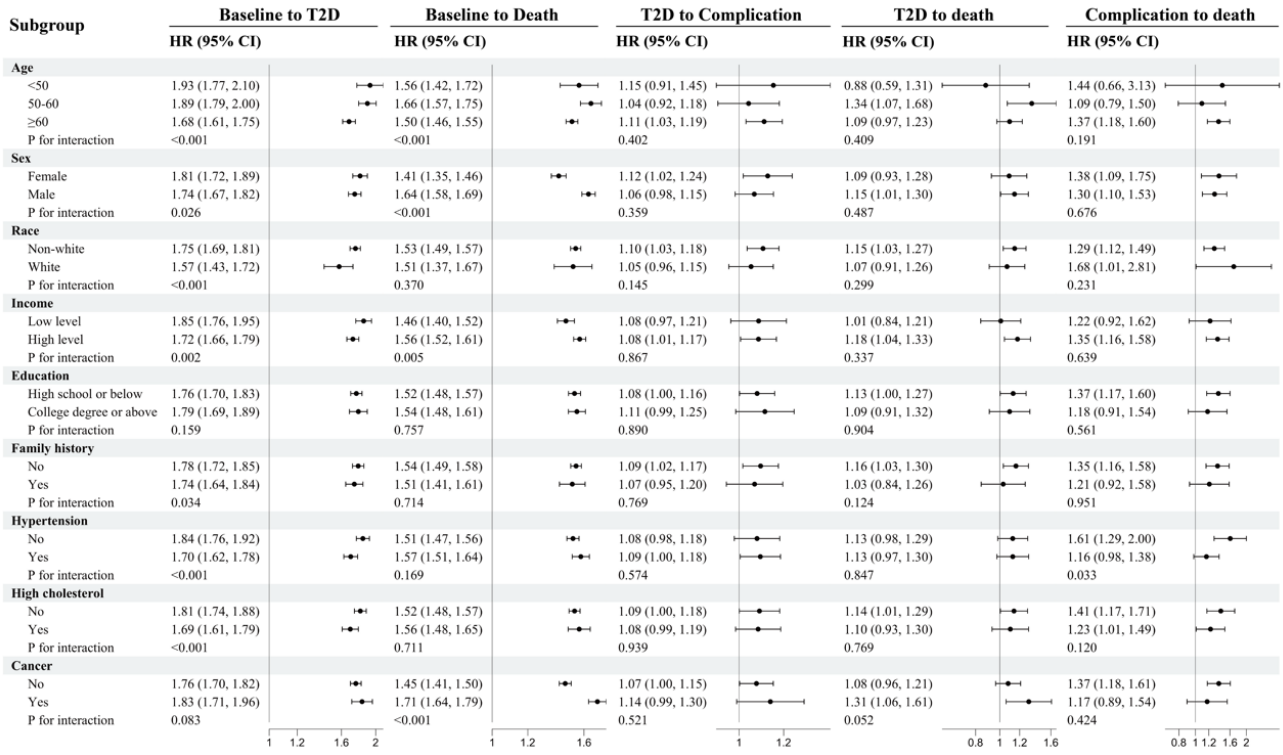

Fig. S6 Associations of PhenoAgeAccel with transitions of T2D trajectory, stratified by baseline characteristics.

Multi-state model adjusted for age, sex, race, income, education, family history, obesity, smoking status, drinking status, physical activity, healthy diet, sleep status, hypertension, high cholesterol, and cancer, except for stratification variable.

The multiplicative interaction was tested by using the likelihood ratio test comparing models with and without interaction terms.

Abbreviation: HR, hazard ratio; CI, confidence interval; T2D, type 2 diabetes.

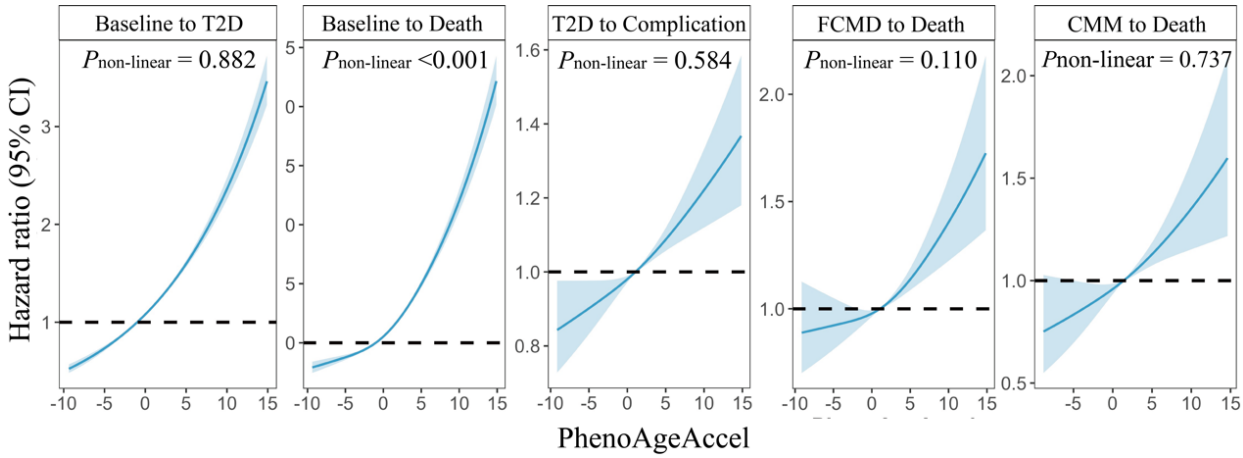

Fig. S7 Nonlinear associations between PhenoAgeAccel and five transitions of T2D trajectory.

Multi-state model adjusted for age, sex, race, income, education, family history, obesity, smoking status, drinking status, physical activity, healthy diet, sleep status, hypertension, high cholesterol, and cancer.

Three knots of restricted cubic spline were placed at the 25th, 50th, and 75th percentiles. Nonlinear associations were evaluated by likelihood ratio tests.

Abbreviation: T2D, type 2 diabetes.