

SUPPLEMENTAL MATERIAL

Title: Circadian Rhythm Analysis Using Wearable-Based Accelerometry as a Digital Biomarker of Aging and Healthspan

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Supplementary Fig. 1 Circadian rhythm parameters with chronological age.

Supplementary Table 1. Gompertz proportional hazards regression models for CosinorAge using the training dataset.

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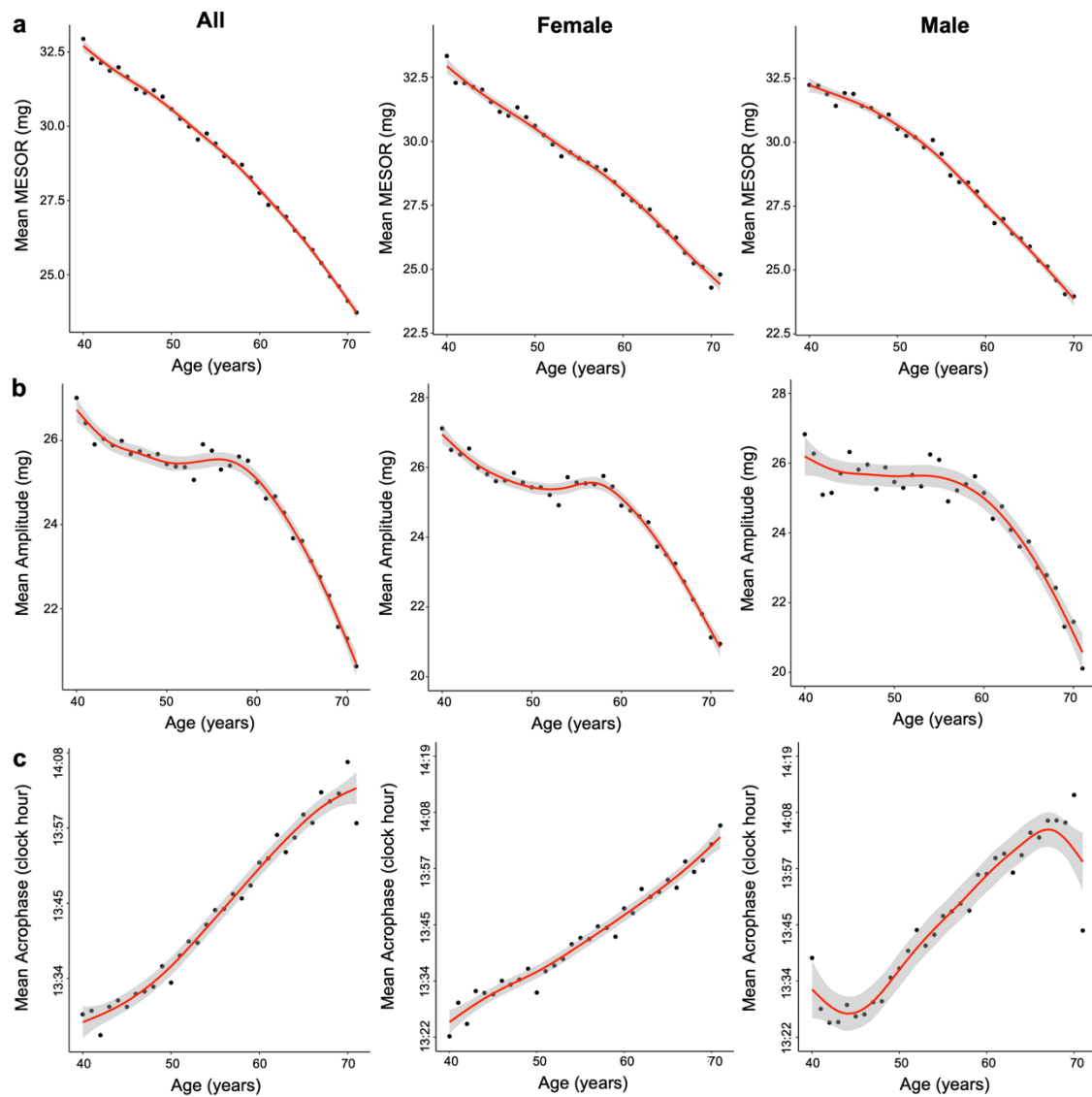
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Supplementary Methods. Derivation of CosinorAge

Supplementary Fig. 1 Circadian rhythm parameters with chronological age. **a** Midline Estimating Statistic of Rhythm (MESOR). **b** Amplitude. **c** Acrophase. Mean values are shown for individuals categorized by chronological age.



Supplementary Table 1. Gompertz proportional hazards regression models for CosinorAge using the training dataset.

Variable	All	Female	Male
MESOR (mg)	-0.032	-0.026	-0.024
Amplitude (mg)	-0.020	-0.022	-0.031
Acrophase (radian)	-0.017	-0.132	0.009
Chronological age (years)	0.100	0.088	0.102
Shape	0.015	0.013	0.014
Rate	-13.367	-13.285	-13.017

$$\text{CosinorAge}_{\text{all}} = 133.599 + \frac{\ln[-0.015 * \ln(1 - \text{mortality risk})]}{0.112}$$

$$\text{mortality score (MS)} = 1 - e^{\frac{-(e^{60\gamma} - 1)(e^{bx})}{\gamma}}$$

$$\gamma = 0.015$$

$$bx = -13.367 - 0.032 * \text{MESOR} - 0.02 * \text{amplitude} - 0.017 * \text{acrophase} \\ + 0.1 * \text{chronological age}$$

Supplementary Table 2. Sex-stratified associations between CosinorAge advancement and mortality risks.

Mortality	Male		Female	
	Events/ Participants	HR (95% CI)	Events/ Participants	HR (95% CI)
Internal Validation (UKB)				
All-cause	473/9045	1.07 (1.04, 1.10)*	395/13760	1.11 (1.07, 1.14)*
Aging-related	403/8975	1.07 (1.03, 1.10)*	345/13710	1.11 (1.06, 1.15)*
CVD	87/8630	1.13 (1.05, 1.22)*	55/13393	1.03 (0.94, 1.13)
Cancer	197/7713	1.06 (1.01, 1.11)*	165/11569	1.08 (1.03, 1.14)*
Diabetes	14/8212	1.37 (1.11, 1.68)*	3/13029	1.27 (0.84, 1.93)
Neurodegenerative	34/8599	1.25 (1.10, 1.42)*	27/13371	1.33 (1.13, 1.55)*
Respiratory	14/8474	1.17 (0.97, 1.40)	8/13209	1.29 (0.99, 1.69)
External Validation (NHANES)				
All-cause	113/1528	1.14 (1.06, 1.23)*	86/1842	1.15 (1.06, 1.25)*
Aging-related	75/1490	1.13 (1.02, 1.25)*	61/1817	1.11 (1.01, 1.22)*

Cox proportional hazard regression models were adjusted for age, ethnicity/race, Townsend deprivation index (UKB only), baseline assessment center (UKB only), education, employment, body mass index, smoking status, alcohol consumption, and comorbidities. Diabetes- and chronic respiratory disease-specific mortalities were adjusted for age to achieve model convergence. We account for complex survey design in NHANES. Participants with prevalent diseases corresponding to the related disease-specific mortalities were excluded from the relevant analyses. Aging-related mortality is defined as death resulting from any of the following diseases: CVD, cancer, diabetes, neurodegenerative (UKB only), and chronic respiratory diseases. * $p < 0.05$.

Supplementary Table 3. Sex-stratified associations between CosinorAge advancement and disease incidences.

Disease Incidence	Male		Female	
	Events/ Participants	HR (95% CI)	Events/ Participants	HR (95% CI)
First incidence	1510/5552	1.02 (1.00, 1.03)*	1690/9106	1.04 (1.03, 1.06)*
Hypertension	632/5552	1.04 (1.01, 1.06)*	691/9106	1.04 (1.01, 1.06)*
CVD	423/5552	1.03 (1.00, 1.06)*	282/9106	1.03 (0.99, 1.07)
Cancer	746/5552	1.01 (0.99, 1.03)	867/9106	1.02 (1.00, 1.04)
Diabetes	116/5552	1.11 (1.05, 1.18)*	95/9106	1.16 (1.08, 1.25)*
Neurodegenerative	63/5552	1.14 (0.97, 1.12)	62/9106	1.29 (1.17, 1.42)*
Respiratory	105/5552	1.03 (0.97, 1.08)	134/9106	1.06 (1.00, 1.12)*

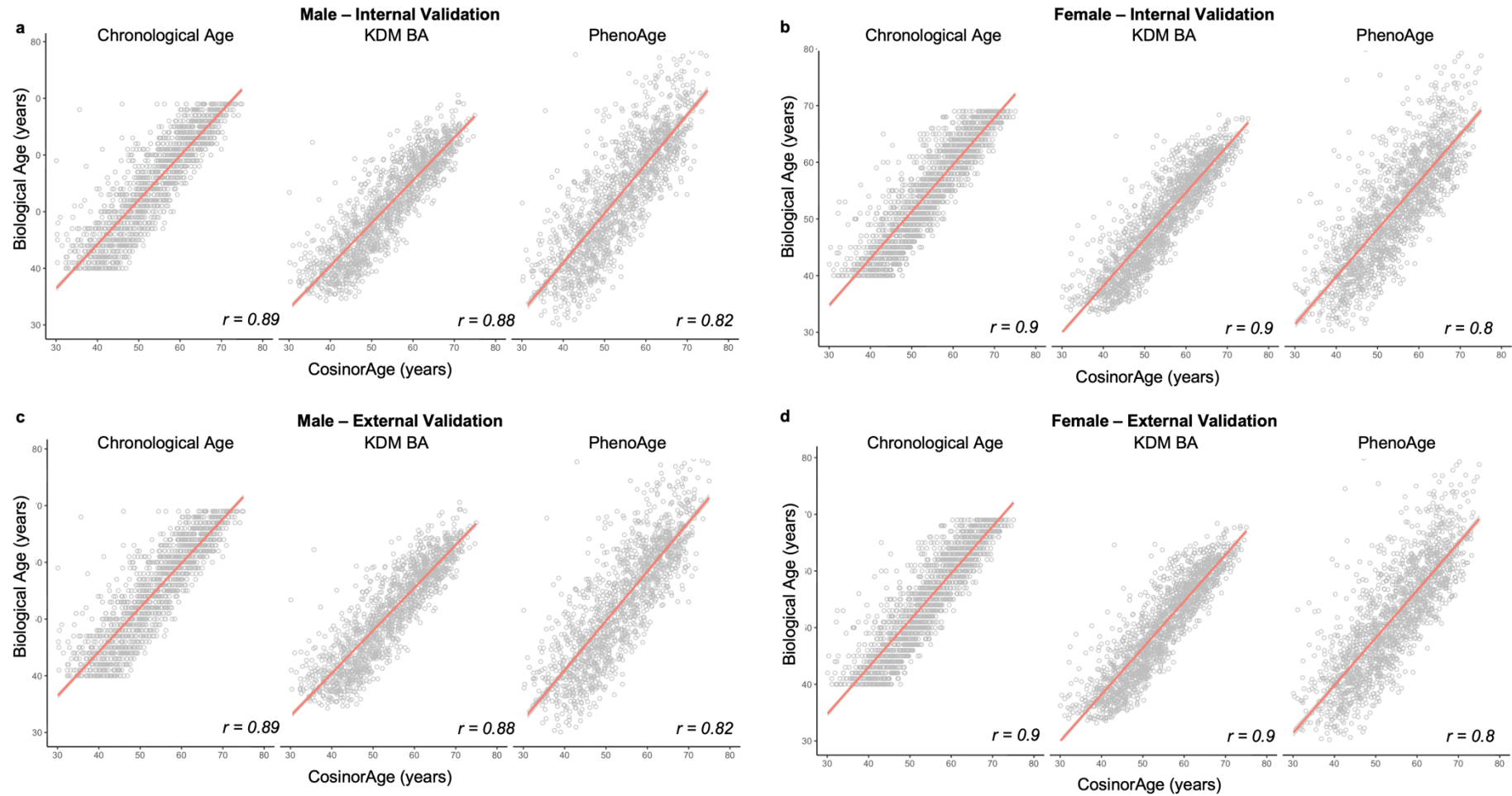
Cox proportional hazard regression models were adjusted for age, ethnicity/race, Townsend deprivation index, baseline assessment center, education, employment, body mass index, smoking status, and alcohol consumption. Diabetes- and chronic respiratory disease-specific incidences were adjusted for age to achieve model convergence. Participants with prevalent diseases were excluded from the analyses. First incidence was defined as the first occurrence of any of the aforementioned diseases. *p<0.05.

Supplementary Table 4. Sex-stratified associations between CosinorAge advancement and age-related functional performances.

Male - Internal Validation (UKB)							Female - Internal Validation (UKB)					
CosinorAge	Self-Rated Health (higher = poorer health)		Grip Strength (lower = poorer strength)		EQ-5D (lower = poorer HRQoL)		Self-Rated Health (higher = poorer health)		Grip Strength (lower = poorer strength)		EQ-5D (lower = poorer HRQoL)	
	Coefficients (SE)	p-value	Coefficients (SE)	p-value	Coefficients (SE)	p-value	Coefficients (SE)	p-value	Coefficients (SE)	p-value	Coefficients (SE)	p-value
CAA (Continuous)	0.09 (0.009)	<0.001*	0.002 (0.008)	0.746	-0.02 (0.011)	<0.03*	0.10 (0.008)	<0.001*	-0.03 (0.005)	<0.001*	-0.07 (0.011)	<0.001*
CAA (Quartiles) (Q1: Reference)												
Q2	0.09 (0.027)	<0.001*	0.02 (0.023)	0.778	-0.03 (0.033)	0.349	0.08 (0.021)	<0.001*	-0.04 (0.013)	0.003*	-0.06 (0.027)	0.04*
Q3	0.13 (0.027)	<0.001*	0.03 (0.022)	0.175	-0.04 (0.033)	0.203	0.12 (0.022)	<0.001*	-0.04 (0.013)	0.006*	-0.12 (0.028)	<0.001*
Q4	0.23 (0.027)	<0.001*	0.01 (0.022)	0.789	-0.06 (0.033)	0.064	0.28 (0.023)	<0.001*	-0.06 (0.013)	<0.001*	-0.17 (0.029)	<0.001*
Male - External Validation (NHANES)							Female - External Validation (NHANES)					
CosinorAge	Self-Rated Health		Grip Strength		ADL (higher = poorer HRQoL)		Self-Rated Health		Grip Strength		ADL (higher = poorer HRQoL)	
	Coefficients (SE)	p-value	Coefficients (SE)	p-value	Coefficients (SE)	p-value	Coefficients (SE)	p-value	Coefficients (SE)	p-value	Coefficients (SE)	p-value
CAA (Continuous)	0.08 (0.037)	0.052	0.02 (0.036)	0.628	0.07 (0.017)	<0.001*	0.13 (0.034)	<0.001*	0.02 (0.020)	0.294	0.12 (0.028)	<0.001*
CAA (Quartiles) (Q1: Reference)												
Q2	0.03 (0.067)	0.670	-0.01 (0.063)	0.838	-0.03 (0.062)	0.632	0.13 (0.104)	0.235	-0.01 (0.055)	0.795	0.08 (0.065)	0.242
Q3	0.08 (0.097)	0.421	0.08 (0.058)	0.199	0.11 (0.074)	0.140	0.12 (0.090)	0.211	0.09 (0.046)	0.053	0.05 (0.061)	0.391
Q4	0.34 (0.111)	0.006*	0.01 (0.097)	0.915	0.18 (0.055)	0.004*	0.32 (0.101)	0.005*	0.04 (0.059)	0.519	0.27 (0.072)	0.001*

Generalized linear models were adjusted for age, ethnicity/race, Townsend deprivation index (UKB only), baseline assessment center (UKB only), education, employment, body mass index, smoking status, alcohol consumption, and comorbidities. We account for complex survey design in NHANES. CAA CosinorAgeAdvance, *SE* standard errors, *EQ-5D* European Quality of Life-5 Dimensions 5-levels, *ADL* Activities of Daily Living, *HRQoL* Health-related quality of life. **p* values < 0.05. We standardized the CAAs and outcomes to have a mean value of 0 and a standard deviation of 1.

Supplementary Fig. 2 Associations between CosinorAge and established biological aging measures in validation cohorts stratified by sex. **a,b** Correlations with chronological age, Klemmler-Douglas biological age (KDM BA), and phenotypic age (PhenoAge) in the UKB internal validation cohort stratified by sex. **c,d** Correlations with chronological age, KDM BA, and PhenoAge among females in the NHANES external validation cohort stratified by sex. r Pearson's correlation coefficient.



Supplementary Table 5. Sex-stratified Age-dependent variations in circadian rhythm metrics by CosinorAge advancement.

Male - Internal Validation (UKB)												
	MESOR (mg)				Amplitude (mg)				Acrophase (clock hour)			
Age groups (years)	<45	46-55	56-65	>65	<45	46-55	56-65	>65	<45	46-55	56-65	>65
Fast agers	24.1	21.9	19.2	17.9	17.1	16.2	15.5	14.4	14:24	14:15	13:52	13:36
Slow agers	42.1	39.8	35.5	33.5	38.9	36.8	34.6	32.6	13:57	13:50	13:38	13:31
Difference (Fast-Slow)	-18.0	-17.9	-16.3	-15.6	-21.8	-20.6	-19.1	-18.2	+27 minutes	+25 minutes	+14 minutes	+5 minutes
Female - Internal Validation (UKB)												
	MESOR (mg)				Amplitude (mg)				Acrophase (clock hour)			
Age groups (years)	<45	46-55	56-65	>65	<45	46-55	56-65	>65	<45	46-55	56-65	>65
Fast agers	23.7	22.2	19.5	17.8	18.0	16.9	15.5	14.5	14:15	14:10	14:01	13:54
Slow agers	41.7	39.0	35.5	33.6	37.1	35.3	33.2	30.9	13:54	13:57	13:45	13:40
Difference (Fast-Slow)	-18.0	-16.8	-16.0	-15.8	-19.1	-18.4	-17.7	-16.4	+21 minutes	+13 minutes	+16 minutes	+14 minutes

Supplementary Table 6. Sensitivity analyses of associations between CosinorAge advancement and mortality risks.

Mortality	Model 1		Model 2		Model 3	
	Events/ Participants	HR (95% CI)	Events/ Participants	HR (95% CI)	Events/ Participants	HR (95% CI)
Internal Validation (UKB)						
All-cause	827/21084	1.09 (1.06, 1.11)*	868/22805	1.08 (1.06, 1.11)*	868/22797	1.09 (1.06, 1.12)*
Aging-related	711/20968	1.08 (1.06, 1.11)*	748/22685	1.08 (1.06, 1.11)*	748/22677	1.09 (1.06, 1.12)*
CVD	135/10342	1.10 (1.04, 1.17)*	142/22023	1.09 (1.03, 1.16)*	142/22015	1.08 (1.02, 1.15)*
Cancer	340/17745	1.07 (1.03, 1.11)*	362/19282	1.07 (1.04, 1.11)*	362/19274	1.07 (1.04, 1.11)*
Diabetes	15/19615	1.15 (0.96, 1.37)	17/21241	1.18 (0.99, 1.40)	17/21233	1.17 (0.98, 1.39)
Neurodegenerative	59/20290	1.28 (1.16, 1.42)*	61/21970	1.28 (1.16, 1.42)*	61/21962	1.36 (1.22, 1.51)*
Respiratory	22/20030	1.12 (0.96, 1.30)	22/21683	1.11 (0.96, 1.30)	22/21675	1.07 (0.92, 1.26)
External Validation (NHANES)						
All-cause	-	-	199/3370	1.11 (1.05, 1.18)*	199/3370	1.10 (1.04, 1.16)*
Aging-related	-	-	136/3307	1.11 (1.03, 1.18)*	136/3307	1.09 (1.03, 1.15)*

Cox proportional hazard regression models were adjusted for age, ethnicity/race, Townsend deprivation index (UKB only), baseline assessment center (UKB only), education, employment, body mass index, smoking status, alcohol consumption, and comorbidities. Diabetes- and chronic respiratory disease-specific mortalities were adjusted for age to achieve model convergence. We account for complex survey design in NHANES. Participants with prevalent diseases corresponding to the related disease-specific mortalities were excluded from the relevant analyses. Aging-related mortality is defined as death resulting from any of the following diseases: CVD, cancer, diabetes, neurodegenerative (UKB only), and chronic respiratory diseases. *p<0.05. **Model 1** excluded participants with shift work history (UKB only). **Model 2** additionally adjusted for sleep disorders. **Model 3** additionally adjusted for circadian rhythm fragmentation and stability.

Supplementary Table 7. Sensitivity analyses of associations between CosinorAge advancement and disease incidences.

Disease Incidence	Model 1		Model 2		Model 3		Model 4	
	Events/ Participants	HR (95% CI)	Events/ Participants	HR (95% CI)	Events/ Participants	HR (95% CI)	Events/ Participants	HR (95% CI)
First incidence	2875/13447	1.03 (1.02, 1.04)*	3200/14658	1.02 (1.01, 1.04)*	3200/14650	1.02 (1.01, 1.04)*	3165/14618	1.02 (1.01, 1.04)*
Hypertension	1213/13447	1.04 (1.02, 1.15)*	1323/14658	1.03 (1.01, 1.05)*	1323/14650	1.03 (1.01, 1.05)*	1315/14618	1.03 (1.01, 1.05)*
CVD	649/13447	1.03 (1.00, 1.05)*	705/14658	1.02 (1.00, 1.05)*	705/14650	1.02 (1.00, 1.05)*	695/14618	1.02 (1.00, 1.05)*
Cancer	1513/13447	1.01 (0.99, 1.02)	1613/14658	1.01 (0.99, 1.03)	16113/14650	1.01 (0.99, 1.03)	1587/14618	1.01 (0.99, 1.03)
Diabetes	194/13447	1.12 (1.07, 1.18)*	211/14658	1.10 (1.05, 1.15)*	211/14650	1.09 (1.04, 1.14)*	209/14618	1.10 (1.05, 1.15)*
Neurodegenerative	119/13447	1.14 (1.07, 1.21)*	125/14658	1.14 (1.07, 1.21)*	125/14650	1.17 (1.09, 1.24)*	124/14618	1.15 (1.08, 1.22)*
Respiratory	223/13447	1.03 (0.99, 1.07)	239/14658	1.03 (0.99, 1.07)	239/14650	1.04 (0.99, 1.08)	237/14618	1.03 (0.99, 1.07)

Cox proportional hazard regression models were adjusted for age, ethnicity/race, Townsend deprivation index, baseline assessment center, education, employment, body mass index, smoking status, and alcohol consumption. Diabetes- and chronic respiratory disease-specific incidences were adjusted for age to achieve model convergence. Participants with prevalent diseases were excluded from the analyses. First incidence was defined as the first occurrence of any of the aforementioned diseases. *p<0.05. **Model 1** excluded participants with shift work history. **Model 2** additionally adjusted for sleep disorders. **Model 3** additionally adjusted for circadian rhythm stability and fragmentation. **Model 4** excluded participants with less than 2 years of follow-up time.

Supplementary Table 8. Sensitivity analyses of associations between CosinorAge advancement and age-related functional performances.

Internal Validation (UKB): Model 1						
CosinorAge	Self-Rated Health		Grip Strength		EQ-5D	
	Coefficients (SE)	p-value	Coefficients (SE)	p-value	Coefficients (SE)	p-value
CAA (Continuous)	0.09 (0.006)	<0.001*	-0.03 (0.006)	<0.001*	-0.05 (0.008)	<0.001*
CAA (Quartiles) (Q1: Reference)						
Q2	0.08 (0.017)	<0.001*	-0.08 (0.018)	<0.001*	-0.05 (0.022)	0.012*
Q3	0.12 (0.017)	<0.001*	-0.05 (0.019)	0.006*	-0.09 (0.022)	<0.001*
Q4	0.26 (0.018)	<0.001*	-0.04 (0.019)	0.059	-0.13 (0.022)	<0.001*
Internal Validation (UKB): Model 2						
CosinorAge	Self-Rated Health		Grip Strength		EQ-5D	
	Coefficients (SE)	p-value	Coefficients (SE)	p-value	Coefficients (SE)	p-value
CAA (Continuous)	0.09 (0.006)	<0.001*	-0.03 (0.06)	<0.001*	-0.05 (0.007)	<0.001*
CAA (Quartiles) (Q1: Reference)						
Q2	0.08 (0.017)	<0.001*	-0.08 (0.018)	<0.001*	-0.05 (0.021)	0.015*
Q3	0.12 (0.017)	<0.001*	-0.04 (0.018)	0.015*	-0.09 (0.021)	<0.001*
Q4	0.25 (0.017)	<0.001*	-0.03 (0.018)	0.087	-0.13 (0.022)	<0.001*
Internal Validation (UKB): Model 3						
CosinorAge	Self-Rated Health		Grip Strength		EQ-5D	
	Coefficients (SE)	p-value	Coefficients (SE)	p-value	Coefficients (SE)	p-value
CAA (Continuous)	0.09 (0.006)	<0.001*	-0.08 (0.007)	<0.001*	-0.05 (0.008)	<0.001*
CAA (Quartiles) (Q1: Reference)						
Q2	0.08 (0.017)	<0.001*	-0.12 (0.017)	<0.001*	-0.05 (0.021)	0.011*

Q3	0.12 (0.017)	<0.001*	-0.12 (0.018)	<0.001*	-0.10 (0.022)	<0.001*
Q4	0.25 (0.018)	<0.001*	-0.14 (0.019)	<0.001*	-0.14 (0.023)	<0.001*

External Validation (NHANES): Model 2						
CosinorAge	Self-Rated Health		Grip Strength		ADL	
	Coefficients (SE)	p-value	Coefficients (SE)	p-value	Coefficients (SE)	p-value
CAA (Continuous)	0.09 (0.020)	<0.001*	0.02 (0.019)	0.416	0.08 (0.019)	<0.001*
CAA (Quartiles) (Q1: Reference)						
Q2	0.07 (0.069)	0.336	-0.02 (0.042)	0.664	0.03 (0.051)	0.551
Q3	0.07 (0.057)	0.226	0.07 (0.033)	0.037*	0.06 (0.048)	0.212
Q4	0.29 (0.066)	<0.001*	0.02 (0.050)	0.736	0.21 (0.056)	0.001*
External Validation (NHANES): Model 3						
CosinorAge	Self-Rated Health		Grip Strength		ADL	
	Coefficients (SE)	p-value	Coefficients (SE)	p-value	Coefficients (SE)	p-value
CAA (Continuous)	0.10 (0.022)	<0.001*	0.02 (0.022)	0.480	0.09 (0.020)	<0.001*
CAA (Quartiles) (Q1: Reference)						
Q2	0.07 (0.070)	0.306	-0.02 (0.044)	0.681	0.03 (0.049)	0.535
Q3	0.09 (0.055)	0.126	0.08 (0.035)	0.050	0.07 (0.050)	0.185
Q4	0.32 (0.068)	<0.001*	0.02 (0.056)	0.787	0.22 (0.057)	0.001*

Generalized linear models were adjusted for age, ethnicity/race, Townsend deprivation index (UKB only), baseline assessment center (UKB only), education, employment, body mass index, smoking status, alcohol consumption, and comorbidities. We account for complex survey design in NHANES. CAA CosinorAgeAdvance, SE standard errors, EQ-5D European Quality of Life-5 Dimensions 5-levels, ADL Activities of Daily Living, HRQoL Health-related quality of life. *p values < 0.05. We standardized the CAAs and outcomes to have a mean value of 0 and a standard deviation of 1. **Model 1** excluded participants with shift work history (UKB only). **Model 2** additionally adjusted for sleep disorders. **Model 3** additionally adjusted for circadian rhythm stability and fragmentation.

Supplementary Table 9. International Classification of Diseases (ICD) codes used for identifying cause-specific mortality.

Cause of Death		ICD-10
CVD		I20-I25, I46, I50, I60-I64
Cancer		C00-C97
Diabetes		E10-E14
Neurodegenerative	F01-F03, G122, G20, G21, G231-G233, G238, G239, G30, G31	
Respiratory		J40-J44, J47

Supplementary Table 10. Codes used for identifying prevalent and incident diseases in UK Biobank.

Disease Type	Self-reported – touchscreen questionnaire	Self-reported – interview	Hospital records, Death records (ICD-10)	Cancer registry (ICD-10)
Case classification	Prevalent	Prevalent: diagnosis age < age, Incident: diagnosis age ≥ age	Prevalent: onset date of illness < start date of accelerometer use, Incident: onset date of illness ≥ start date of accelerometer use	
Hypertension	6150 (4)	20002 (1065,1072, 1073)	I10-I13, I15	-
CVD	2443	20002 (1220)	E10-E14	-
Cancer	6150 (1,2,3)	20002 (1066, 1074, 1075, 1076, 1081, 1086, 1491, 1583)	I20-I25, I46, I50, I60-I64	-
Diabetes	2453	20001	C00-C97	C00-C97
Neurodegenerative	-	20002 (1259,1262,1263)	F01-F03, G122, G20, G21, G231-G233, G238, G239, G30, G31	-
Respiratory	6152 (6)	20002 (1112,1113,1472)	J40-J44, J47	-

Supplementary Methods. Derivation of CosinorAge

1. Gompertz model

$$CDF(x, t) = 1 - e^{-\frac{(e^{\gamma t} - 1)(e^{bx})}{\gamma}}$$

$$f(x, t) = e^{\left[bx + \gamma t - \frac{(e^{\gamma t} - 1)(e^{bx})}{\gamma} \right]}$$

$$S(x, t) = e^{-\frac{(e^{\gamma t} - 1)(e^{bx})}{\gamma}} = 1 - CDF(x, t)$$

$CDF(x, t)$ is the cumulative distribution function. $f(x, t)$ is the probability density function. $S(x, t)$ is the survival function.

$bx = \sum_{i=1}^p x_i b_i + b_0$ where p is the number of predictors.

γ = a shape parameter.

2. Find parameters of Gompertz distribution

We use maximum likelihood estimation (MLE) to estimate $b_0, b_1, \dots, b_p \mid \gamma$.

$$\operatorname{argmax} L(x_1, t_1, \dots, x_n^+, t_n^+) = \prod_{i=1}^r f(x_i, t_i) \prod_{i=r+1}^n S(x_i^+, t_i^+)$$

⁺ indicates censoring.

To solve this, we can compute the derivative and solve for zero.

$$\frac{dL}{d\beta_i} = 0, i = 0, \dots, p$$

$$\frac{dL}{d\gamma} = 0$$

3. Compute mortality scores

Since we now know b_0, b_p, γ , we compute the mortality score (MS) for a set of predictors x_i for an individual i as follows:

$$MS = CDF(60, x_i)$$

This represents the 5 year (60 months) mortality risk for an individual i .

Additionally, we fit a $CDF(t, CA_i)$, where chronological age (CA) is the only predictor following steps 1-3 above. The goal is to find b_0, b_1, γ for CA. This new parametric distribution we denoted from now on CDF_{CA} .

4. Compute cosinor age

Convert the mortality score into biological age (BA), so-called "CosinorAge", by executing

$$CDF(60, x_i) \stackrel{!}{=} CDF_{CA}(60, BA)$$

The obtained BA stands for "CosinorAge"