Appendix A: Training and Construction of Algorithm-Based Biological Aging Measures

Klemera-Doubal Biological Age

Following the approach described by Levine (Levine, 2013), we calculated NHANES participants' biological ages using the Klemera-Doubal equation (Klemera and Doubal, 2006). The equation takes information from *m* number of regression lines of *m* biomarkers regressed on chronological age:

$BA_{EC} = \frac{\sum_{j=1}^{m}(x_j - q_j)\frac{k_j}{s_j^2} + \frac{CA}{s_{BA}^2}}{\sum_{j=1}^{m}\left(\frac{k_j}{s_j}\right)^2 + \frac{1}{s_{BA}^2}}$, where *x* is the value of biomarker *j* measured for an individual in the 1999-2002 NHANES. To ensure independence of the Klemera-Doubal Biological Age algorithm from the 1999-2002 NHANES database, we estimated all algorithm parameters from a reference dataset composed of the NHANES III and 2003-2014 Continuous NHANES panels. For each biomarker *j*, the parameters *q*, *k*, and *s* were estimated from a regression of the biomarker on chronological age in the reference dataset. *q*, *k*, and *s*, are the regression intercept, slope, and root mean squared error, respectively. s_{BA} is a scaling factor equal to the square root of the variance in chronological age explained by the biomarker panel in the reference database. CA is chronological age. The biomarkers used to compose the algorithm were: serum albumin, alkaline phosphatase, blood urea nitrogen, creatinine, C-reactive protein, glycated hemoglobin, total cholesterol, uric acid, white blood cell count, lymphocyte percent, mean corpuscular volume, and systolic blood pressure. Biomarkers with skewed distributions were log-transformed for analysis (alkaline phosphatase, creatinine, C-reactive protein, uric acid, and white blood cell count). Following Levine (Levine, 2013), regressions of chronological age on biomarker values included all NHANES participants aged 30-75 years and not pregnant at the time of assessment. The year of NHANES data collection was included in regressions as a panel of dummy variables to account for year-to-year variation in laboratory methods. The model intercept was set to the 2003-2004 NHANES panel. Models were estimated separately for men and women. Summary statistics

describing biomarker distributions in the training sample are reported in **Appendix Table A.1**. For each biomarker, model R-squared (R), root-mean-squared-error (S), intercept (Q), and age-coefficient (K) were saved and used to compute the S^2BA parameter. Parameters are reported in **Appendix Table A.2**. These parameters were used to form the Klemera-Doubal Biological Age algorithm in our study.

We implemented the Klemera-Doubal Biological Age Algorithm using biomarker data for NHANES 1999-2000 and 2001-2002 participants aged 20-84. To account for any differences in laboratory procedures between 1999-2000 and 2001-2002 NHANES panels used for analysis and the training sample, we re-centered analysis-sample biomarker values around the sex-specific means for the 2003-2004 NHANES panel, which formed the intercept in regressions used to develop the Klemera-Doubal Biological Age Algorithm. We then computed Klemera-Doubal-Method (KDM) Biological Ages according to the equation above. Pregnant women were excluded, as were participants with data on fewer than ten of the twelve biomarkers. Klemera-Doubal Biological Age was pro-rated to account for missing biomarkers; missing parameters were imputed as the average of the observed parameters.

Appendix Table A.1: Biomarker descriptive statistics for the reference population used to train the Klemera-Doubal Biological Age Algorithm. The reference population consisted of men and women aged 30-75 years participating in NHANES III and continuous NHANES panels collected during 2003-2016 (N=38,028, 49% male). Pregnant women were excluded.

		Women			Men		
Biomarker	**Units of Measure**	**M**	**SD**	**N**	**M**	**SD**	**N**
Albumin	g/dL	4.13	(0.33)	18,456	4.29	(0.33)	17,506
Alkaline Phosphatase	log U/L	4.28	(0.33)	18,446	4.28	(0.30)	17,503
Blood Urea Nitrogen	mg/dL	12.74	(4.70)	18,373	14.17	(4.81)	17,443
Creatinine	log mg/dL	0.60	(0.11)	18,389	0.71	(0.11)	17,450
C-Reactive Protein	log mg/dL	-1.24	(1.10)	12,714	-1.50	(1.03)	12,071
Glycated Hemoglobin	%	5.70	(0.97)	18,636	5.75	(1.01)	17,624
Uric Acid	log mg/dL	1.74	(0.22)	18,448	1.94	(0.19)	17,513
Lymphocyte Percent	%	32.19	(8.43)	18,712	30.82	(8.53)	17,683
White Blood Cell Count	log SI	2.07	(0.25)	18,746	2.07	(0.25)	17,708
Mean Corpuscular Volume	fL	88.69	(6.11)	18,739	90.06	(5.28)	17,691
Red Cell Distribution Width	%	13.26	(1.24)	18,609	13.06	(0.95)	17,596
Systolic Blood Pressure	mm/Hg	123.99	(19.40)	18,882	127.15	(17.17)	18,012

The KDM Biological Age Algorithm Training Sample included men and women aged 30-75 participating in NHANES III and the 2003-2016 panels of the Continuous NHANES. Pregnant women were excluded. M: mean; SD: standard deviation; N: sample size

Appendix Table A.2: Klemera-Doubal Biological Age Algorithm Parameters estimated from the NHANES training sample. The table reports the K, Q, S, and R parameters of the Klemera-Doubal Algorithm. These correspond to the model slope, intercept, root mean squared error, and R-squared for the regressions of the biomarkers on chronological age in the NHANES reference sample. S_{BA}^2 corresponds to the squared variance in chronological age explained by the biomarker panel in the reference sample. The reference population consisted of men and women aged 30-75 years participating in NHANES III and continuous NHANES panels collected during 2003-2016 (N=38,028, 49% male). Pregnant women were excluded.

	Women				Men			
	K	**Q**	**S**	**R**	**K**	**Q**	**S**	**R**
Albumin	-0.001	4.169	0.316	0.001	-0.007	4.663	0.303	0.076
Alkaline Phosphatase (Log)	0.006	3.903	0.307	0.059	0.002	4.160	0.284	0.005
Blood Urea Nitrogen	0.144	4.327	4.252	0.159	0.096	8.255	4.526	0.070
Creatinine (Log)	0.002	0.471	0.096	0.056	0.001	0.617	0.101	0.031
C-Reactive Protein (Log)	0.008	-1.704	1.148	0.008	0.011	-2.228	1.067	0.016
Glycated Hemoglobin	0.021	4.560	0.909	0.080	0.018	4.744	0.980	0.055
Uric Acid (Log)	0.004	1.518	0.209	0.065	0.000	1.935	0.187	0.000
Lymphocyte Percent	0.001	30.824	8.266	0.000	-0.101	34.786	8.291	0.024
White Blood Cell Count (Log)	-0.002	2.173	0.252	0.008	-0.001	2.105	0.247	0.001
Mean Corpuscular Volume	0.068	86.272	6.038	0.021	0.062	87.974	5.170	0.023
Red Cell Distribution Width	0.004	12.658	1.192	0.002	0.017	11.808	0.864	0.056
Systolic Blood Pressure	0.685	91.050	16.940	0.213	0.400	106.016	16.040	0.095
SBA2		176.08				212.27		

Homeostatic Dysregulation

We calculated NHANES participants' homeostatic dysregulation using the approach described by Cohen and colleagues (Cohen et al., 2014; Li et al., 2015). Homeostatic dysregulation quantifies deviation of a person's physiology from a reference norm based on biomarker Mahalanobis distance (Mahalanobis, 1936). We computed parameters for the homeostatic dysregulation algorithm based on the same twelve biomarkers used to calculate the Klemera-Doubal Biological Age algorithm. We formed the reference norm from young, healthy participants in NHANES III and Continuous NHANES panels spanning 2003-2014. From these NHANES panels, we selected participants aged 20-30 years who were not obese and whose biomarker values fell within the age- and sex-specific normal range (**Appendix Table A.3**). Distributions of biomarkers in this young, healthy reference sample are reported in **Appendix Table A.4**. We standardized all biomarkers to have mean=0, SD=1 within sex and computed the biomarker variance-covariance matrix (**Appendix Table A.5**). Biomarker means and standard deviations in the reference sample and the standardized-biomarker variance-covariance matrix, together with the Mahalanobis distance equation (Mahalanobis, 1936) formed the homeostatic dysregulation algorithm.

Appendix Table A.3: Ranges of biomarker values used to restrict reference population for training the Homeostatic Dysregulation Algorithm.

	Units of Measure	Women	Men
Albumin	g/dL	3.5-5.0	
Alkaline Phosphatase	U/L	37-98	45-115
Blood Urea Nitrogen	mg/dL	6-21	8-24
Creatinine	mg/dL	0.6-1.1	0.8-1.3
C-Reactive Protein	mg/dL	<2	
Glycated Hemoglobin	%	4.0-5.6	
Total Cholesterol	mg/dL	<200	
Uric Acid	mg/dL	2.7-6.1	3.7-8.0
Lymphocyte Percent	%	28-55	
White Blood Cell Count	SI	<11	
Mean Corpuscular Volume	fL	77-93	
Systolic Blood Pressure	mm/Hg	<120	

* From http://www.mayomedicallaboratories.com/

Appendix Table A.4: Biomarker descriptive statistics for the reference population used to define the Homeostatic Dysregulation Algorithm.

		Women			Men		
Biomarker	**Units of Measure**	**M**	**SD**	**N**	**M**	**SD**	**N**
Albumin	g/dL	4.21	(0.30)	643	4.46	(0.25)	495
Alkaline Phosphatase	log U/L	4.13	(0.23)		4.32	(0.22)	
Blood Urea Nitrogen	mg/dL	10.99	(2.90)		13.46	(3.38)	
Creatinine	log mg/dL	0.60	(0.07)		0.71	(0.07)	
C-Reactive Protein	log mg/dL	-1.86	(1.05)		-1.98	(1.01)	
Glycated Hemoglobin	%	5.03	(0.29)		5.12	(0.32)	
Uric Acid	log mg/dL	1.62	(0.14)		1.88	(0.14)	
Lymphocyte Percent	%	36.45	(6.13)		36.19	(5.83)	
White Blood Cell Count	log SI	1.99	(0.21)		1.98	(0.21)	
Mean Corpuscular Volume	fL	88.17	(3.32)		88.57	(2.91)	
Red Cell Distribution Width	%	12.65	(0.89)		12.49	(0.57)	
Systolic Blood Pressure	mm/Hg	105.14	(7.44)		111.03	(5.61)	

The Homeostatic Dysregulation Algorithm Reference Sample included men and women aged 20-30 in the NHANES III and in Continuous NHANES Panels from 2003-2016 with BMI < 30. Pregnant women were excluded. M: mean; SD: standard deviation; N: sample size

Appendix Table A.5: Biomarker Variance Covariance Matrix for the reference population used to define the Homeostatic Dysregulation Algorithm. Biomarkers were standardized to Mean=0, Stand Deviation=1 by sex prior to computing the variance covariance matrix.

	Albumin	Alkaline Phosphatase	Blood Urea Nitrogen	Creatinine	C-Reactive Protein	Glycated Hemoglobin	Uric Acid	Lymphocyte Percent	White Blood Cell Count	Mean Corpuscular Volume	Red Cell Distribution Width	Systolic Blood Pressure
Women												
Albumin	1.39	0.08	0.11	0.08	-0.66	-0.28	0.01	0.35	-0.21	0.00	-0.28	-0.31
Alkaline Phosphatase (Log)	0.08	3.11	-0.20	-0.50	-0.20	0.32	0.22	0.24	0.12	-0.49	0.06	-0.28
Blood Urea Nitrogen	0.11	-0.20	2.54	1.35	0.20	1.01	0.84	0.02	-0.16	0.36	0.11	1.71
Creatinine (Log)	0.08	-0.50	1.35	2.35	0.15	0.75	1.00	0.14	-0.29	0.27	0.16	1.47
C-Reactive Protein (Log)	-0.66	-0.20	0.20	0.15	1.58	0.75	0.48	-0.44	0.41	-0.01	0.27	1.04
Glycated Hemoglobin	-0.28	0.32	1.01	0.75	0.75	6.89	0.83	0.28	0.09	-0.27	0.40	2.63
Uric Acid (Log)	0.01	0.22	0.84	1.00	0.48	0.83	2.38	0.08	0.03	-0.03	0.16	1.25
Lymphocyte Percent	0.35	0.24	0.02	0.14	-0.44	0.28	0.08	1.98	-0.80	-0.15	-0.06	-0.04
White Blood Cell Count (Log)	-0.21	0.12	-0.16	-0.29	0.41	0.09	0.03	-0.80	1.52	-0.06	0.04	-0.16
Mean Corpuscular Volume	0.00	-0.49	0.36	0.27	-0.01	-0.27	-0.03	-0.15	-0.06	2.74	-0.90	0.47
Red Cell Distribution Width	-0.28	0.06	0.11	0.16	0.27	0.40	0.16	-0.06	0.04	-0.90	1.37	0.42
Systolic Blood Pressure	-0.31	-0.28	1.71	1.47	1.04	2.63	1.25	-0.04	-0.16	0.47	0.42	8.49
Men												
Albumin	1.48	0.26	-0.31	-0.35	-0.53	-0.92	-0.02	0.07	0.03	-0.13	-0.47	-0.92
Alkaline Phosphatase (Log)	0.26	4.25	-0.66	-1.49	-0.45	-0.49	-0.40	0.45	0.02	-0.98	-0.03	-1.63
Blood Urea Nitrogen	-0.31	-0.66	1.76	1.02	0.28	0.69	0.27	-0.32	0.09	0.31	0.20	0.81
Creatinine (Log)	-0.35	-1.49	1.02	2.77	0.32	0.54	0.72	-0.33	-0.02	0.52	0.32	1.31
C-Reactive Protein (Log)	-0.53	-0.45	0.28	0.32	1.48	0.81	0.35	-0.49	0.41	0.11	0.39	1.07
Glycated Hemoglobin	-0.92	-0.49	0.69	0.54	0.81	6.96	-0.15	-0.20	0.29	-0.09	0.57	1.82
Uric Acid (Log)	-0.02	-0.40	0.27	0.72	0.35	-0.15	1.74	-0.14	0.16	-0.03	0.09	0.55
Lymphocyte Percent	0.07	0.45	-0.32	-0.33	-0.49	-0.20	-0.14	2.08	-0.66	-0.26	-0.13	-0.66
White Blood Cell Count (Log)	0.03	0.02	0.09	-0.02	0.41	0.29	0.16	-0.66	1.44	0.02	0.06	0.23
Mean Corpuscular Volume	-0.13	-0.98	0.31	0.52	0.11	-0.09	-0.03	-0.26	0.02	3.01	-0.45	0.78
Red Cell Distribution Width	-0.47	-0.03	0.20	0.32	0.39	0.57	0.09	-0.13	0.06	-0.45	1.68	0.79
Systolic Blood Pressure	-0.92	-1.63	0.81	1.31	1.07	1.82	0.55	-0.66	0.23	0.78	0.79	9.42

Appendix Table A.6: Biomarker summary statistics for the NHANES analysis sample. The NHANES analysis sample included women and men aged 20-84 participating in the 1999-2000 and 2001-2002 panels of the Continuous NHANES for whom Klemera-Doubal Biological Age, Homeostatic Dysregulation, and Telomere Length measures were available.

		Women (N=3,250)		Men (N=3,481)	
Biomarker	**Units of Measure**	**M**	**SD**	**M**	**SD**
Albumin	g/dL	4.27	(0.29)	4.44	(0.31)
Alkaline Phosphatase	U/L	74.52	(26.05)	77.23	(24.15)
Blood Urea Nitrogen	mg/dL	13.30	(4.61)	14.97	(4.71)
Creatinine	mg/dL	0.70	(0.20)	0.93	(0.23)
C-Reactive Protein	mg/dL	0.51	(0.68)	0.36	(0.67)
Glycated Hemoglobin	%	5.52	(0.87)	5.59	(0.93)
Uric Acid	mg/dL	4.77	(1.31)	6.07	(1.32)
Lymphocyte Percent	%	30.95	(8.08)	29.64	(8.35)
White Blood Cell Count	SI	7.22	(2.00)	7.02	(1.97)
Mean Corpuscular Volume	fL	89.68	(5.37)	90.74	(4.91)
Red Cell Distribution Width	%	12.74	(1.07)	12.61	(0.81)
Systolic Blood Pressure	mm/Hg	126.30	(22.76)	126.95	(17.92)
Logged Biomarker Values					
Alkaline Phosphatase		4.27	(0.32)	4.32	(0.29)
Creatinine		0.53	(0.11)	0.65	(0.11)
C-Reactive Protein		-1.35	(1.25)	-1.76	(1.20)
Uric Acid		1.73	(0.22)	1.94	(0.19)
White Blood Cell Count		2.08	(0.24)	2.05	(0.24)

Values summarized for n=6,754 individuals aged 20-85 with biomarker and telomere data.
M: mean; SD: standard deviation

Appendix B: Construction of Healthspan-related Characteristics and Life-course Risk Factors

Construction of Measures for Healthspan-related Characteristics

To conduct validation testing of our biological age measures, we selected a panel of NHANES functional assessments of capacities known to decline with advancing chronological age. These outcomes encompassed three domains: physical functioning, perceptual and cognitive functioning, and subjective functioning and pain.

Physical functioning was assessed using tests of balance, muscle strength (knee extensor peak force), gait speed, and cardiorespiratory fitness (VO_2 Max). We assessed balance using a composite variable which captured variability in participants performance on the Romberg Test of Standing Firm and Compliant Support Surfaces (Weber). Briefly, this test assesses participants ability to stand unassisted under four increasingly difficult conditions. Test Condition 1 requires participants stand with both feet together on a firm surface for 15 seconds with eyes open. Test Condition 2 requires participants stand with both feet together on a firm surface for 15 seconds with eyes closed. Test Condition 3 requires participants stand with both feet together on a compliant surface (foam pad) for 30 seconds with eyes open. Test Condition 4 requires participants stand with both feet together on a compliant surface (foam pad) for 30 seconds with eyes closed. Participants are allowed a maximum of two attempts per conditions. Those who fail both attempts of earlier conditions do not continue to more difficult trials. Less than 5% of the eligible sample failed to progress to Test Condition 4. Our composite variable emphasized performance in Test Condition 4 (NHANES items BAXPFC41 & BAXPFC42). Specifically, our final analytical construct for balance was a dichotomous variable which distinguished between participants who passed Test Condition 4 and those who failed Test Condition 4 or failed both attempts at an earlier trial (Test Conditions 1-3).

Participants' muscle strength was assessed using a Kin Com MP dynamometer to evaluate isokinetic knee extensor strength, and recorded as peak torque (N/m) of the quadriceps at 60°/s. Our final analytical construct was the maximum peak force recorded for each participant (NHANES item MSDAPF). Our final analytical construct for gait speed was participants' time in seconds to complete a 20ft walk (NHANES item MSXWTIME). Cardiovascular fitness was assessed during a submaximal exercise test. Participants' were assigned one of eight treadmill test protocols based on their gender, age, body mass index, and self-reported physical activity. Each protocol includes a 2-minute warm-up, two 3-minute exercise stages, and a 2-minute cool down designed to elicit a heart rate response of 75% their age-predicted maximum. Our final analytical construct for cardiovascular fitness is estimated maximal oxygen update (VO_2 Max; NHANES item CVDESVO2).

Perceptual and cognitive functioning was assessed using tests of visual acuity, audiometry, and the digit symbol coding task from the Wechsler Adult Intelligence Scale (WAIS III). Participants' visual acuity was assessed as presenting distance visual acuity using their usual correction, if any (e.g. glass/contacts or none). Visual acuity for each eye is recorded in units of Snellen visual acuity (e.g. 20/20; NHANES items VIDRVA & VIDLVA). Participants' Snellen visual acuity was converted to LogMAR units (log of the minimum angle of resolution) to provide a robust measure of visual acuity (Holladay, 1997). Our final analytical construct for visual acuity was the average visual acuity across both eyes in LogMAR units. Audiometry testing was conducted using an Interacoustics Model AD226 audiometer with standard TDH-39 headphones and Etymotic EarTone 3A insert headphones. Hearing threshold testing was conducted on both ears at seven frequencies across the range of human hearing (500, 1000, 2000, 3000, 4000, 6000, and 8000 Hz). Signal intensity varied from -10 to as high as 120 decibels as was recorded as the lowest decibel participants could hear a given frequency (NHANES items AUXU500(L/R), AUXU1K2(L/R), AUXU2K(L/R), AUXU3K(L/R), AUXU4K(L/R),

AUXU6K(L/R), & AUXU8K(L/R)). To reduce audiometry performance to a single measure we conducted principal component analysis across all 16 items within the sample which also had all 3 biological age measures (N=2821). The item mapped to a single component with eigenvalue greater than 1 and which explained 62% of the variance across all 16 items. We extracted regression factor scores for the full sample as well as for men and women independently to use as our final analytical contrast for audiometry. Participants' cognitive functioning was assessed using the digit symbol coding task from the WAIS III. In this task participants must copy symbols that are paired with numbers using a provided key. Our final analytical construct for cognitive functioning was the number of items drawn correctly in 120 seconds (NHANES item CFDRIGHT).

Subjective functioning was assessed using measures of self-reported disability (activities of daily living, ADLs; instrumental activities of daily living, IADLs), self-rated general health, and self-reported pain. Self-reported disability was assessed using participants' responses to the Physical Functioning Questionnaire in which participants report experiencing "no difficulty", "some difficulty", "much difficulty", or "unable to do so" for various activities. The questionnaire was assessed for all participants aged 60 or older and those who were aged 20-59 who reported experiencing limitations that kept them from work. For the current analyses, we restricted our sample to only those aged 60 -84. ADLs emphasize day to day actions necessary for personal care such as getting out of bed and dressing oneself. The full list of items included in the ADL domain are reported difficulty walking a quarter mile (NHANES item PFQ060b), walking up ten steps (NHANES item PFQ060c), stooping, crouching, or kneeling (NHANES item PFQ060d), lifting or carrying 10 pounds (NHANES item PFQ060e), walking between rooms on the same floor (NHANES item PFQ060h), standing up from an armless chair (NHANES item PFQ060i), getting in and out of bed (NHANES item PFQ060j), dressing oneself (NHANES item PFQ060l), standing for long periods (NHANES item PFQ060m), sitting for long

periods (NHANES item PFQ060n), and difficulty reaching up over your head (NHANES item PFQ060o). IADLs are similar activities considered to be important for normal functioning, but which are not necessarily related to personal care such as managing money and performing house chores. The full list of items included in the IADL domain are difficulty managing money (NHANES item PFQ060a), performing household chores (NHANES item PFQ060f), preparing meals (NHANES item PFQ060g), using utensils (NHANES item PFQ060k), and grasping or holding small objects (NHANES item PFQ060p). Coding for individual items was performed as previously described (Cook et al 2006 J Disability & Rehab). Specifically, individuals reporting "much difficulty" or "unable to do so" for a given task were coded as being limited for that task. Our final analytical constructs for ADLs and IADLs were three-level variables which distinguished between those with 0 limitations, 1 limitation, or 2+ limitations within the ADL and IADL domains respectively. Participants' self-rated health was assessed based on participant responses when asked to describe their general health (NHANES item HUQ010). Our final analytical construct was incrementally coded to distinguish between those who reported "excellent", "very good", "good", "fair", or "poor" general health.

Self-reported pain was assessed using responses from the NHANES miscellaneous pain questionnaire (MPQ) which collected information on the location and duration of self-reported pain. Participants were asked to distinguish between joint pain and general, miscellaneous pain. We assessed joint pain using a composite variable which combined participants' responses when asked about pain at 16 joint sites across the body (NHANES items MPD050a-q). Our final analytical construct for joint pain distinguished between those with and those without joint pain. Joint pain was defined as reporting pain at any of the 16 sites assessed. A lack of joint pain was defined as reporting no pain across all 16 sites. Chronic pain was defined as previously described (Hardt et al., 2008) using participants' self-reported general pain. Participants were first asked if they had a problem with pain in the last month (NHANES

item MPQ100). Those responding yes were then asked about the duration of pain (NHANES item MPQ110) and to indicate which of 32 body regions were affected using a visual aide (NHANES items MPQ120a-af). Here we defined chronic pain according to College of Rheumatology criteria as pain lasting 3 or more months (Wolfe et al., 1990). For those participants reporting chronic pain we distinguished between widespread and localized chronic pain according to American College of Rheumatology criteria. Specifically, pain was widespread if it was experienced above and below the waist, on both sides of the body, and at one or more axial locations (spine, chest, upper or lower back). Our final analytical construct for chronic pain was a dichotomous variable which distinguished between those with no chronic pain and those with widespread chronic pain.

Appendix Table B.1: Healthspan-related characteristics. For continuous measures, mean and standard deviation are provided. For dichotomous measures, the % with a value of 1 is indicated. For categorical measures, the % with each value of the category is indicated.

	Mean/%	(SD)	% Male	N	Age Range	Correlation with Chronological Age
Phyical Functioning						
Cardiorespiratory Fitness (VO2max)	40.49	(10.24)	52%	1,845	20-49	-0.10
Poor Balance	39%		52%	2,746	40-84	0.43
Gait Speed	6.76	(2.87)	52%	3,046	50-84	0.29
Strength	278	(98)	52%	2,412	50-84	-0.38
Cognitive & Perceptual Functioning						
Cognitive Function	43.33	(18.53)	51%	2,035	60-84	-0.22
Hearing	0.05	(1.01)	52%	2,613	20-69	0.58
Vision	0.14	(0.19)	52%	6,474	20-84	0.24
Subjective Functioning/ Disability						
Self-rated Health			52%	6,748	20-84	0.19
Excellent	31%					
Very Good	18%					
Good	4%					
Fair	15%					
Poor	23%					
Activities of Daily Living (ADLs)			51%	2,297	60-84	0.10
0	69%					
1	10%					
2+	21%					
Instrumental Activities of Daily Living (IADLs)			51%	2,297	60-84	0.11
0	87%					
1	8%					
2+	5%					
Pain						
Joint Pain	44%		52%	6,722	20-84	0.18
Chronic Pain	3%		52%	6,747	20-84	0.04

Construction of Measures for Life-course Risk Factors

To test the hypothesis that accumulating life-course risk would be associated with accelerated biological aging, we selected a panel of NHANES survey assessments of factors known to influence life expectancy and healthspan. Specifically, we assessed educational attainment, material and social resource deficits, and mental health problems.

We assessed educational attainment using self-reported educational attainment for adults aged 20 or older (NHANES item DMDEDUC2). Specifically, our final analytical construct for educational attainment was a four-level variable which distinguished between those with less than a high school degree, those with a high school degree or equivalent but no college experience, those with some college experience, and those with a college degree. Material resources were assessed using poverty income ratio and food security status. Participants' PIR was calculated by dividing family income by poverty guidelines issued by the Department of Health and Human Services (NHANES item INDFMPIR). Since the PIR is top-coded at 5, we restricted our analyses to those participants with PIR 4.99 or below. Participants' food security status is determined based on responses to 10 items in the U.S. Household Food Security Module from the U.S. Department of Agriculture (NHANES item ADFDSEC)(Bickel et al., 2000). Participants' social resources were assessed using a composite variable which combined data from three items in the NHANES social support module (SSQ). Specifically, we combined data from participants' responses to questions about the availability of emotional support (NHANES item SSQ010), need for more emotional support (NHANES item SSQ030), and number of close friends (NHANES item SSQ060). Our final analytical construct for social resources was a dichotomous variable which distinguished between those with and those without social resources. A lack of social resources was defined as reporting no emotional support, reporting a need for more emotional support, or as residing in the lowest quartile for the number of close friends (SSQ060 <= 3). Availability of social resources was coded as reporting available emotional support, reporting no need for more emotional support, and residing in the top three quartiles for the number of close friends (SSQ060 > 3).

Participants' mental health was assessed as previously described (Needham et al., 2015) using a composite variable derived from participants' responses to the NHANES CIDI, an adapted version of three modules from the World Health Organization Composite International Diagnostic Interview, Version 2.1 (CIDI-Auto 2.1) which includes modules for major depression (CIQDEP), generalized anxiety disorder (CIQGAD), and panic disorder (CIQPAN). Our final analytical construct for mental health was a three-level variable which distinguished between those meeting DSM-IV criteria for one or more of major depression (NHANES item CIDDSCOR), generalized anxiety disorder (NHANES item CIDGSCOR), or panic disorder (NHANES item CIDPSCOR), those with depressive or anxious affect, and those with no depressive or anxiety symptoms. Depressive affect was defined as reporting a period of feeling sad, depressed, or empty for two weeks or longer (NHANES item CIQD001). Anxious affect was defined as reporting a period of a month or more in which participants felt worried, tense, or anxious about everyday problems such as work or family (NHANES item CIQG01).

Appendix Table B.2: Life-course Risk Factors. For continuous measures, mean and standard deviation are provided. For dichotomous measures, the % with a value of 1 is indicated. For categorical measures, the % with each value of the category is indicated. SD= standard deviation. N= sample size.

	Mean/%	(SD)	% Male	N	Age Range
Education			52%	6,747	20-84
< High School	33%				
High School Graduate	23%				
Some College	25%				
College Degree	19%				
Poverty	2.71	(1.62)	52%	6,158	20-84
Food Insecurity			52%	6,486	20-84
Secure	81%				
Marginally Insecure	7%				
Insecure without Hunger	8%				
Insecure with Hunger	4%				
Low Social Support	42%		51%	2,295	60-84
Mental Health			51%	1,060	20-39
No anxiety, depression, or panic disorder	72%				
Anxious or Depressed Affect	18%				
Diagnosis of Depression, Anxiety, or Panic Disorder	10%				

Appendix C: Supplementary Tables and Figures

Appendix Table C.1: Descriptive statistics and correlations among chronological age and biological aging measures in the pooled NHANES 1999-2000 and 2001-2002 samples. All correlations were significant at $p < 0.001$. M: mean; SD: standard deviation. Panel A shows correlations the measures described in the main text prior to adjustment for chronological age. Panel B shows unadjusted correlations for versions of the KDM Biological Age and homeostatic dysregulation algorithms computed using the same biomarkers as the LM Biological Age.

Panel A.

	M	SD	Chronological Age	KDM Biological Age	Homeostatic Dysregulation	LM Biological Age
Chronologial Age (years)	49.56	(17.77)				
KDM Biological Age (years)	50.14	(18.84)	0.91			
Homeostatic Dysregulation (log units)	3.53	(0.89)	0.56	0.73		
LM Biological Age	34.46	(18.49)	0.96	0.94	0.62	
Telomere Length (log T/S ratio)	0.00	(0.11)	-0.42	-0.39	-0.24	-0.42

Panel B.

	M	SD	Chronological Age	KDM Biological Age	Homeostatic Dysregulation	LM Biological Age
Chronologial Age (years)	49.56	(17.77)				
KDM Biological Age (years)	49.05	(19.08)	0.87			
Homeostatic Dysregulation (log units)	2.80	(0.83)	0.30	0.52		
LM Biological Age	34.46	(18.49)	0.96	0.92	0.42	
Telomere Length (log T/S ratio)	0.00	(0.11)	-0.42	-0.40	-0.16	-0.42

Appendix Table C.2: Associations between biological aging measures and healthspan-related characteristics.

		KDM Biological Age*			Homeostatic Dysregulation*			LM Biological Age			Telomere Length		
	Effect Size	Effect-size (r/OR)	95% CI	p-value	Effect-size (r/OR)	95% CI	p-value	Effect-size (r/OR)	95% CI	p-value	Effect-size (r/OR)	95% CI	p-value
Phyical Functioning													
Cardiorespiratory Fitness (VO2max)	r	-0.03	[-0.09, 0.03]	0.288	-0.05	[-0.11, 0.00]	0.057	-0.11	[-0.17, -0.05]	0.001	0.05	[0.00, 0.11]	0.039
Poor Balance	OR	1.21	[1.11, 1.32]	1.46E-05	1.23	[1.13, 1.34]	2.03E-06	1.25	[1.15, 1.37]	3.07E-07	0.91	[0.83, 1.00]	0.050
Strength	r	-0.08	[-0.12, -0.05]	5.28E-06	-0.10	[-0.13, -0.06]	0.000	-0.07	[-0.10, -0.03]	1.24E-04	0.02	[-0.02, 0.06]	0.258
Gait Speed	r	-0.15	[-0.19, -0.12]	1.04E-18	-0.16	[-0.19, -0.12]	1.19E-21	-0.15	[-0.18, -0.12]	1.11E-20	0.03	[-0.01, 0.07]	0.100
Cognitive & Perceptual Functioning													
Cognitive Function	r	-0.13	[-0.17, -0.10]	8.63E-13	-0.14	[-0.18, -0.10]	7.25E-12	-0.13	[-0.16, -0.09]	8.42E-11	0.04	[-0.01, 0.08]	0.124
Hearing	r	-0.07	[-0.09, -0.04]	1.64E-07	-0.10	[-0.12, -0.07]	8.38E-12	-0.10	[-0.13, -0.07]	5.68E-12	0.03	[0.00, 0.05]	0.037
Vision	r	-0.11	[-0.15, -0.08]	1.69E-11	-0.07	[-0.10, -0.03]	1.20E-04	-0.11	[-0.15, -0.07]	2.00E-09	0.02	[-0.01, 0.05]	0.209
Subjective Functioning/ Disability													
Self-rated Health	r	-0.20	[-0.22, -0.18]	9.96E-61	-0.19	[-0.22, -0.17]	8.04E-56	-0.21	[-0.24, -0.19]	2.56E-68	0.04	[0.02, 0.07]	0.002
ADL	IRR	1.28	[1.22, 1.35]	3.10E-21	1.28	[1.22, 1.35]	3.39E-20	1.26	[1.21, 1.32]	8.94E-23	0.95	[0.89, 1.02]	0.180
IADL	IRR	1.45	[1.32, 1.58]	1.79E-16	1.43	[1.30, 1.58]	3.49E-13	1.36	[1.25, 1.47]	1.89E-13	0.97	[0.86, 1.11]	0.694
Pain													
Joint Pain	OR	1.09	[1.04, 1.15]	0.001	1.04	[0.99, 1.09]	0.146	1.14	[1.08, 1.20]	4.62E-07	0.97	[0.92, 1.03]	0.351
Chronic Pain	OR	1.29	[1.17, 1.43]	0.000	1.22	[1.09, 1.37]	0.001	1.35	[1.23, 1.49]	4.11E-10	0.94	[0.82, 1.08]	0.405

For this analysis, KDM Biological Age and Homeostatic Dysregulation measures were computed using the same 9 biomarkers used to compute the LM Biological Age. Results for LM Biological age. All models included covariates for main effects of sex and chronological age. Biological aging measures were standardized within sex; coefficients reflect difference in outcome associated with a 1 SD difference in the biological aging measure. Continuous healthspan-related characteristics were standardized within sex to have M=0, SD=1 for analysis and analyzed with linear regression. Dichotomous healthspan-related characteristics were analyzed with logistic regression. Reported effect-sizes are odds ratios (OR). Count healthspan-related characteristics were analyzed with negative binomial regression. Reported coefficients are incidence rate ratios (IRR).

Appendix Table C.3: Sex-differences in associations between biological aging measures and healthspan-related characteristics

			KDM Biological Age			Homeostatic Dysregulation			LM Biological Age			Telomere Length		
		Effect-Size	Effect-size (b / lnOR / lnIRR)	95% CI	p-value	Effect-size (b / lnOR / lnIRR)	95% CI	p-value	Effect-size (b / lnOR / lnIRR)	95% CI	p-value	Effect-size (b / lnOR / lnIRR)	95% CI	p-value
Phyical Functioning														
Cardiorespiratory Fitness	Main Effect (women)	b	-0.07	[-0.15, 0.02]	0.110	-0.14	[-0.23, -0.04]	0.004	-0.15	[-0.23, -0.08]	7.53E-05	0.03	[-0.04, 0.10]	0.430
	Interaction (sex difference)		-0.02	[-0.15, 0.11]	0.784	0.08	[-0.05, 0.21]	0.214	0.11	[-0.02, 0.23]	0.095	0.05	[-0.05, 0.15]	0.314
Poor Balance	Main Effect (women)	ln(OR)	0.10	[-0.02, 0.22]	0.115	0.15	[0.01, 0.29]	0.030	0.14	[0.02, 0.27]	0.026	-0.11	[-0.24, 0.02]	0.100
	Interaction (sex difference)		0.08	[-0.09, 0.25]	0.358	0.11	[-0.08, 0.30]	0.253	0.16	[-0.01, 0.33]	0.071	0.03	[-0.15, 0.22]	0.720
Strength	Main Effect (women)	b	0.05	[0.00, 0.10]	0.073	-0.01	[-0.07, 0.05]	0.684	-0.03	[-0.08, 0.03]	0.337	0.02	[-0.04, 0.08]	0.468
	Interaction (sex difference)		-0.12	[-0.19, -0.05]	4.81E-04	-0.09	[-0.17, -0.01]	0.030	-0.08	[-0.15, -0.01]	0.035	0.00	[-0.07, 0.08]	0.915
Gait Speed	Main Effect (women)	b	-0.10	[-0.15, -0.06]	3.58E-05	-0.14	[-0.19, -0.08]	1.65E-07	-0.17	[-0.22, -0.12]	3.95E-13	0.02	[-0.03, 0.06]	0.485
	Interaction (sex difference)		0.02	[-0.05, 0.09]	0.601	-0.01	[-0.08, 0.06]	0.716	0.03	[-0.03, 0.10]	0.310	0.03	[-0.04, 0.10]	0.424
Cognitive & Perceptual Functioning														
Cognitive Function	Main Effect (women)	b	-0.17	[-0.21, -0.12]	1.61E-12	-0.27	[-0.34, -0.20]	3.77E-14	-0.16	[-0.22, -0.11]	3.99E-09	0.05	[-0.02, 0.11]	0.138
	Interaction (sex difference)		0.07	[0.00, 0.14]	0.054	0.06	[-0.04, 0.16]	0.218	0.07	[-0.01, 0.14]	0.081	-0.02	[-0.11, 0.07]	0.630
Hearing	Main Effect (women)	b	-0.07	[-0.11, -0.03]	7.05E-04	-0.09	[-0.13, -0.05]	8.48E-06	-0.10	[-0.14, -0.06]	1.44E-06	0.02	[-0.02, 0.05]	0.385
	Interaction (sex difference)		-0.01	[-0.07, 0.04]	0.670	-0.01	[-0.06, 0.04]	0.781	-0.01	[-0.06, 0.05]	0.836	0.02	[-0.02, 0.07]	0.359
Vision	Main Effect (women)	b	-0.11	[-0.16, -0.05]	1.09E-04	-0.09	[-0.15, -0.03]	0.002	-0.11	[-0.16, -0.06]	1.99E-05	0.01	[-0.03, 0.05]	0.655
	Interaction (sex difference)		0.01	[-0.06, 0.09]	0.716	0.01	[-0.06, 0.08]	0.785	0.00	[-0.08, 0.07]	0.902	0.02	[-0.04, 0.08]	0.504
Subjective Functioning/Disability														
Self-rated Health	Main Effect (women)	b	-0.18	[-0.22, -0.15]	3.60E-27	-0.25	[-0.29, -0.22]	5.98E-41	-0.23	[-0.26, -0.19]	1.21E-39	0.04	[0.01, 0.08]	0.013
	Interaction (sex difference)		0.01	[-0.04, 0.06]	0.642	0.00	[-0.04, 0.05]	0.876	0.03	[-0.02, 0.07]	0.276	0.00	[-0.05, 0.04]	0.850
ADL	Main Effect (women)	ln(IRR)	0.13	[0.06, 0.19]	1.04E-04	0.21	[0.11, 0.31]	2.70E-05	0.23	[0.16, 0.29]	3.02E-12	-0.09	[-0.18, 0.00]	0.060
	Interaction (sex difference)		0.09	[-0.01, 0.18]	0.066	0.08	[-0.06, 0.23]	0.276	0.02	[-0.08, 0.11]	0.734	0.09	[-0.05, 0.23]	0.216
IADL	Main Effect (women)	ln(IRR)	0.15	[0.03, 0.26]	0.012	0.36	[0.19, 0.53]	3.60E-05	0.36	[0.24, 0.47]	6.36E-10	-0.08	[-0.25, 0.08]	0.322
	Interaction (sex difference)		0.14	[-0.02, 0.31]	0.086	0.07	[-0.18, 0.32]	0.577	-0.10	[-0.26, 0.07]	0.253	0.13	[-0.12, 0.38]	0.312
Pain														
Joint Pain	Main Effect (women)	ln(OR)	0.11	[0.04, 0.18]	0.003	0.12	[0.04, 0.19]	0.004	0.17	[0.10, 0.24]	2.66E-06	-0.05	[-0.12, 0.02]	0.172
	Interaction (sex difference)		-0.04	[-0.14, 0.06]	0.409	-0.14	[-0.24, -0.04]	0.006	-0.08	[-0.18, 0.02]	0.100	0.05	[-0.05, 0.15]	0.321
Chronic Pain	Main Effect (women)	ln(OR)	0.20	[0.03, 0.37]	0.019	0.26	[0.09, 0.44]	0.003	0.34	[0.21, 0.47]	3.82E-07	-0.05	[-0.23, 0.13]	0.563
	Interaction (sex difference)		0.00	[-0.23, 0.24]	0.989	-0.08	[-0.31, 0.15]	0.500	-0.08	[-0.26, 0.10]	0.383	-0.02	[-0.26, 0.23]	0.900

All models included covariates for main effects of sex, chronological age, and the interaction between sex and chronological age. Biological aging measures were standardized within sex; coefficients reflect change in the outcome variable associated with a 1.5 SD increase in the biological aging measure. Continuous healthspan-related characteristics standardized within sex to have M=0, SD=1 for analysis and analyzed with linear regression. Dichotomous healthspan-related characteristics were analyzed with logistic regression. Reported effect-sizes are log odds ratios (lnOR). Count healthspan-related characteristics were analyzed with negative binomial regression. Reported coefficients are log incidence rate ratios (lnIRR).

Appendix Table C.4: Associations between biological aging measures and healthspan-related characteristics after adjustment for BMI

		KDM Biological Age			Homeostatic Dysregulation			LM Biological Age			Telomere Length		
	Effect Size	Effect-size (r/OR)	95% CI	p-value	Effect-size (r/OR)	95% CI	p-value	Effect-size (r/OR)	95% CI	p-value	Effect-size (r/OR)	95% CI	p-value
Phyical Functioning													
Cardiorespiratory Fitness (VO2max)	r	0.01	[-0.07, 0.08]	0.890	-0.05	[-0.12, 0.01]	0.106	-0.05	[-0.12, 0.01]	0.121	0.04	[-0.01, 0.09]	0.092
Poor Balance	OR	1.21	[1.11, 1.32]	2.89E-05	1.29	[1.16, 1.42]	9.79E-07	1.32	[1.20, 1.45]	2.90E-09	0.91	[0.82, 1.00]	0.040
Strength	r	-0.05	[-0.08, 0.01]	0.006	-0.08	[-0.13, 0.04]	1.17E-04	-0.11	[-0.14, 0.07]	6.81E-09	0.03	[-0.01, 0.07]	0.167
Gait Speed	r	-0.07	[-0.10, 0.04]	1.55E-06	-0.12	[-0.16, 0.09]	1.19E-11	-0.12	[-0.15, 0.09]	2.32E-15	0.03	[-0.01, 0.07]	0.139
Cognitive & Perceptual Functioning													
Cognitive Function	r	-0.13	[-0.16, 0.09]	2.64E-11	-0.23	[-0.28, 0.18]	6.67E-19	-0.12	[-0.16, 0.08]	2.31E-08	0.04	[-0.01, 0.09]	0.121
Hearing	r	-0.08	[-0.11, 0.05]	1.91E-08	-0.10	[-0.13, 0.07]	1.75E-11	-0.10	[-0.13, 0.07]	3.80E-12	0.03	[0.00, 0.06]	0.020
Vision	r	-0.10	[-0.14, 0.05]	3.52E-06	-0.07	[-0.11, 0.03]	7.62E-04	-0.09	[-0.13, 0.06]	1.52E-06	0.02	[-0.01, 0.05]	0.265
Subjective Functioning/ Disability													
Self-rated Health	r	-0.14	[-0.17, 0.12]	3.50E-29	-0.22	[-0.25, 0.19]	1.84E-52	-0.18	[-0.20, 0.15]	4.26E-45	0.03	[0.01, 0.06]	0.008
ADL	IRR	1.12	[1.06, 1.18]	5.04E-05	1.22	[1.13, 1.32]	5.14E-07	1.20	[1.14, 1.26]	1.57E-11	0.94	[0.88, 1.02]	0.121
IADL	IRR	1.19	[1.08, 1.31]	5.06E-04	1.42	[1.24, 1.63]	5.36E-07	1.29	[1.17, 1.42]	1.19E-07	0.98	[0.85, 1.12]	0.770
Pain													
Joint Pain	OR	1.01	[0.96, 1.06]	0.719	0.99	[0.93, 1.05]	0.646	1.07	[1.01, 1.13]	0.014	0.98	[0.93, 1.04]	0.514
Chronic Pain	OR	1.08	[0.95, 1.23]	0.222	1.14	[0.98, 1.32]	0.095	1.24	[1.11, 1.38]	1.00E-04	0.96	[0.83, 1.10]	0.533

All models included covariates for main effects of body-mass index, sex and chronological age. Biological aging measures were standardized within sex; coefficients reflect difference in outcome associated with a 1 SD difference in the biological aging measure. Continuous healthspan-related characteristics were standardized within sex to have M=0, SD=1 for analysis and analyzed with linear regression. Dichotomous healthspan-related characteristics were analyzed with logistic regression. Reported effect-sizes are odds ratios (OR). Count healthspan-related characteristics were analyzed with negative binomial regression. Reported coefficients are incidence rate ratios (IRR).

Appendix Table C.5: Associations between biological aging measures and healthspan-related characteristics after adjustment for race/ethnicity

		KDM Biological Age			Homeostatic Dysregulation			LM Biological Age			Telomere Length		
	Effect Size	Effect-size (r/OR)	95% CI	p-value	Effect-size (r/OR)	95% CI	p-value	Effect-size (r/OR)	95% CI	p-value	Effect-size (r/OR)	95% CI	p-value
Phyical Functioning													
Cardiorespiratory Fitness (VO2max)	r	-0.06	[-0.13, 0.01]	0.070	-0.07	[-0.14, 0.01]	0.028	-0.10	[-0.16, 0.03]	0.002	0.07	[0.02, 0.12]	0.011
Poor Balance	OR	1.14	[1.05, 1.24]	0.003	1.21	[1.09, 1.34]	1.97E-04	1.25	[1.15, 1.37]	5.48E-07	0.91	[0.83, 1.00]	0.048
Strength	r	0.00	[-0.04, 0.03]	0.842	-0.04	[-0.08, 0.00]	0.065	-0.07	[-0.10, 0.03]	3.08E-04	0.02	[-0.02, 0.06]	0.325
Gait Speed	r	-0.08	[-0.11, 0.04]	2.03E-05	-0.10	[-0.15, 0.06]	6.13E-07	-0.14	[-0.17, 0.11]	6.95E-17	0.03	[-0.01, 0.07]	0.096
Cognitive & Perceptual Functioning													
Cognitive Function	r	-0.10	[-0.13, 0.06]	3.81E-09	-0.15	[-0.20, 0.11]	2.42E-11	-0.11	[-0.14, 0.07]	1.06E-09	0.03	[-0.01, 0.07]	0.167
Hearing	r	-0.07	[-0.09, 0.04]	1.19E-06	-0.08	[-0.11, 0.05]	1.37E-07	-0.10	[-0.13, 0.07]	5.27E-11	0.03	[0.00, 0.05]	0.057
Vision	r	-0.12	[-0.16, 0.08]	2.75E-10	-0.11	[-0.15, 0.07]	4.74E-07	-0.12	[-0.16, 0.09]	4.84E-12	0.01	[-0.02, 0.04]	0.461
Subjective Functioning/ Disability													
Self-rated Health	r	-0.17	[-0.19, 0.15]	1.66E-46	-0.22	[-0.25, 0.19]	6.22E-55	-0.21	[-0.23, 0.18]	3.63E-67	0.03	[0.00, 0.05]	0.033
ADL	IRR	1.19	[1.13, 1.25]	9.68E-12	1.27	[1.18, 1.37]	5.68E-10	1.27	[1.21, 1.33]	1.49E-23	0.96	[0.89, 1.03]	0.223
IADL	IRR	1.25	[1.14, 1.36]	5.34E-07	1.46	[1.28, 1.66]	1.64E-08	1.39	[1.28, 1.51]	1.34E-14	0.98	[0.87, 1.11]	0.802
Pain													
Joint Pain	OR	1.10	[1.04, 1.15]	3.26E-04	1.07	[1.01, 1.14]	0.027	1.14	[1.09, 1.20]	2.56E-07	0.96	[0.91, 1.01]	0.134
Chronic Pain	OR	1.22	[1.08, 1.37]	0.001	1.26	[1.09, 1.47]	0.002	1.35	[1.23, 1.49]	8.39E-10	0.92	[0.80, 1.06]	0.275

All models included covariates for main effects of race/ethnicity, sex and chronological age. Biological aging measures were standardized within sex; coefficients reflect difference in outcome associated with a 1 SD difference in the biological aging measure. Continuous healthspan-related characteristics were standardized within sex to have M=0, SD=1 for analysis and analyzed with linear regression. Dichotomous healthspan-related characteristics were analyzed with logistic regression. Reported effect-sizes are odds ratios (OR). Count healthspan-related characteristics were analyzed with negative binomial regression. Reported coefficients are incidence rate ratios (IRR).

Appendix Table C.6: Associations between biological aging measures and cognitive & perceptual functioning after adjustment for educational attainment

		KDM Biological Age			Homeostatic Dysregulation			LM Biological Age			Telomere Length		
	Effect Size	Effect-size (r/OR)	95% CI	p-value	Effect-size (r/OR)	95% CI	p-value	Effect-size (r/OR)	95% CI	p-value	Effect-size (r/OR)	95% CI	p-value
Cognitive & Perceptual Functioning													
Cognitive Function	r	-0.09	[-0.12, -0.06]	7.33E-10	-0.15	[-0.20, -0.11]	2.10E-13	-0.09	[-0.12, -0.05]	1.07E-07	0.01	[-0.03, 0.05]	0.714
Hearing	r	-0.06	[-0.09, -0.03]	1.24E-05	-0.07	[-0.10, -0.04]	1.20E-06	-0.09	[-0.11, -0.06]	3.53E-09	0.01	[-0.01, 0.04]	0.260
Vision	r	-0.09	[-0.13, -0.05]	3.62E-06	-0.05	[-0.09, -0.01]	0.010	-0.09	[-0.13, -0.06]	3.80E-07	0.01	[-0.02, 0.04]	0.585

All models included covariates for main effects of educational attainment, sex and chronological age. Biological aging measures were standardized within sex; coefficients reflect difference in outcome associated with a 1 SD difference in the biological aging measure. Continuous healthspan-related characteristics were standardized within sex to have M=0, SD=1 for analysis and analyzed with linear regression. Dichotomous healthspan-related characteristics were analyzed with logistic regression. Reported effect-sizes are odds ratios (OR). Count healthspan-related characteristics were analyzed with negative binomial regression. Reported coefficients are incidence rate ratios (IRR).

Appendix Table C.7: Associations between life-course risk factors and biological aging measures.

	KDM Biological Age			Homeostatic Dysregulation			LM Biological Age			Telomere Length		
	Effect-size (r/OR)	95% CI	p-value									
Stressors Hypothesized to Accelerate Aging												
Education	0.13	[0.11, 0.15]	6.11E-27	0.12	[0.09, 0.14]	5.99E-24	0.11	[0.09, 0.14]	2.03E-20	-0.07	[-0.09, -0.04]	1.99E-09
Poverty	0.13	[0.10, 0.15]	1.59E-24	0.12	[0.10, 0.15]	1.03E-24	0.14	[0.11, 0.16]	1.89E-27	-0.05	[-0.07, -0.03]	2.83E-05
Food Insecurity	0.08	[0.05, 0.11]	4.97E-09	0.06	[0.04, 0.09]	3.14E-07	0.07	[0.05, 0.10]	4.26E-08	-0.02	[-0.04, 0.00]	0.033
Low Social Support	0.16	[0.07, 0.25]	6.41E-04	0.22	[0.13, 0.31]	1.11E-06	0.21	[0.11, 0.30]	2.02E-05	-0.04	[-0.12, 0.03]	0.251
Poor Mental Health	0.04	[-0.04, 0.12]	0.338	0.03	[-0.04, 0.11]	0.382	0.04	[-0.04, 0.12]	0.290	0.02	[-0.06, 0.10]	0.667

For this analysis, KDM Biological Age and Homeostatic Dysregulation measures were computed using the same 9 biomarkers used to compute the LM Biological Age. Results for LM Biological age. All models included covariates for main effects of sex and chronological age. Biological aging measures were standardized within sex to have M=0, SD=1 for analysis. Coefficients reflect SD acceleration in biological aging per unit increase in the exposure. Education, poverty, and food-insecurity exposure measures were standardized to have M=0, SD=1 for analysis. Low Social Support and poor mental health are dichotomous indicators.

Appendix Table C.8: Associations between life-course risk factors and biological aging measures after adjustment for BMI.

	KDM Biological Age			Homeostatic Dysregulation			LM Biological Age			Telomere Length		
	Effect-size (r/OR)	95% CI	p-value									
Stressors Hypothesized to Accelerate Aging												
Education	0.09	[0.06, 0.11]	3.35E-13	0.12	[0.10, 0.14]	1.05E-34	0.09	[0.07, 0.11]	3.17E-14	-0.06	[-0.09, -0.04]	6.92E-09
Poverty	0.09	[0.06, 0.11]	1.06E-12	0.11	[0.09, 0.13]	7.51E-28	0.12	[0.10, 0.14]	2.60E-23	-0.05	[-0.07, -0.03]	3.66E-05
Food Insecurity	0.04	[0.01, 0.06]	0.002	0.07	[0.05, 0.09]	1.72E-10	0.06	[0.04, 0.08]	1.19E-06	-0.02	[-0.04, 0.00]	0.042
Low Social Support	0.12	[0.03, 0.22]	0.012	0.15	[0.08, 0.22]	2.77E-05	0.19	[0.10, 0.29]	3.87E-05	-0.04	[-0.11, 0.04]	0.362
Poor Mental Health	0.01	[-0.06, 0.08]	0.802	0.00	[-0.07, 0.06]	0.883	0.04	[-0.03, 0.11]	0.263	0.02	[-0.06, 0.10]	0.619

All models included covariates for main effects of body-mass index, sex and chronological age. Biological aging measures were standardized within sex to have M=0 SD=1 for analysis. Coefficients reflect SD acceleration in biological aging per unit increase in the exposure. Education, poverty, and food-insecurity exposure measures were standardized to have M=0 SD=1 for analysis. Low social support and poor mental health are dichotomous indicators.

Appendix Table C.9: Associations between life-course risk factors and biological aging measures after adjustment for race/ethnicity.

	KDM Biological Age			Homeostatic Dysregulation			LM Biological Age			Telomere Length		
	Effect-size (r/OR)	95% CI	p-value									
Stressors Hypothesized to Accelerate Aging												
Education	0.11	[0.09, 0.14]	1.46E-17	0.11	[0.09, 0.13]	1.71E-25	0.12	[0.10, 0.15]	1.36E-20	-0.05	[-0.07, -0.03]	2.38E-05
Poverty	0.09	[0.06, 0.12]	6.64E-12	0.09	[0.07, 0.11]	1.96E-17	0.14	[0.11, 0.16]	2.58E-24	-0.04	[-0.06, -0.02]	8.17E-04
Food Insecurity	0.03	[0.01, 0.06]	0.006	0.05	[0.03, 0.07]	1.69E-06	0.07	[0.04, 0.10]	2.79E-07	-0.01	[-0.03, 0.01]	0.330
Low Social Support	0.10	[0.00, 0.20]	0.051	0.11	[0.04, 0.18]	0.004	0.18	[0.08, 0.27]	3.16E-04	-0.04	[-0.12, 0.04]	0.357
Poor Mental Health	0.01	[-0.07, 0.08]	0.843	-0.01	[-0.07, 0.06]	0.846	0.04	[-0.04, 0.12]	0.311	0.02	[-0.06, 0.10]	0.670

All models included covariates for main effects of race/ethncity, sex and chronological age. Biological aging measures were standardized within sex to have M=0 SD=1 for analysis. Coefficients reflect SD acceleration in biological aging per unit increase in the exposure. Education, poverty, and food-insecurity exposure measures were standardized to have M=0 SD=1 for analysis. Low social support and poor mental health are dichotomous indicators.

Appendix Table C.10: Associations between biological aging measures and healthspan-related characteristics: Effect-sizes for biological aging measures computed without and with leukocyte telomere length. Analysis includes data only from NHANES 1999-2000 (NHANES 2001-2002 used to train telomere parameters for biological aging algorithms).

		KDM Biological Age			KDM Biological Age w/ LTL			Homeostatic Dysregulation			Homeotatic Dysregulation w/ LTL		
	Effect Size	Effect-size (r/OR)	95% CI	p-value	Effect-size (r/OR)	95% CI	p-value	Effect-size (r/OR)	95% CI	p-value	Effect-size (r/OR)	95% CI	p-value
Phyical Functioning													
Cardiorespiratory Fitness (VO2max)	r	-0.08	[-0.18, 0.02]	0.119	-0.12	[-0.21, -0.02]	0.013	-0.05	[-0.15, 0.05]	0.285	-0.06	[-0.16, 0.04]	0.214
Poor Balance	OR	1.42	[1.19, 1.70]	1.28E-04	1.46	[1.22, 1.75]	4.81E-05	1.30	[1.08, 1.56]	0.005	1.30	[1.08, 1.56]	0.006
Strength	r	0.00	[-0.05, 0.06]	0.917	-0.02	[-0.08, 0.03]	0.374	-0.06	[-0.12, 0.00]	0.062	-0.07	[-0.14, -0.01]	0.026
Gait Speed	r	-0.09	[-0.13, -0.04]	9.88E-05	-0.10	[-0.15, -0.05]	2.02E-05	-0.14	[-0.20, -0.09]	1.34E-07	-0.15	[-0.20, -0.09]	8.20E-08
Cognitive & Perceptual Functioning													
Cognitive Function	r	-0.13	[-0.18, -0.08]	1.26E-06	-0.14	[-0.20, -0.09]	3.36E-07	-0.21	[-0.28, -0.14]	1.03E-08	-0.22	[-0.30, -0.15]	1.95E-09
Hearing	r	-0.09	[-0.13, -0.05]	4.75E-05	-0.09	[-0.13, -0.05]	1.28E-05	-0.11	[-0.16, -0.06]	2.83E-06	-0.12	[-0.16, -0.07]	3.69E-07
Vision	r	-0.10	[-0.16, -0.04]	9.28E-04	-0.09	[-0.15, -0.04]	0.001	-0.09	[-0.15, -0.03]	0.004	-0.09	[-0.15, -0.03]	0.004
Subjective Functioning/ Disability													
Self-rated Health	r	-0.16	[-0.19, -0.12]	4.11E-19	-0.17	[-0.21, -0.14]	5.17E-23	-0.23	[-0.27, -0.19]	9.28E-29	-0.23	[-0.27, -0.19]	3.42E-30
ADL	IRR	1.19	[1.11, 1.27]	3.64E-07	1.20	[1.12, 1.29]	5.01E-07	1.29	[1.17, 1.43]	8.62E-07	1.30	[1.18, 1.44]	3.46E-07
IADL	IRR	1.27	[1.13, 1.44]	8.81E-05	1.29	[1.13, 1.47]	1.64E-04	1.49	[1.25, 1.77]	1.00E-05	1.49	[1.24, 1.79]	1.99E-05
Pain													
Joint Pain	OR	1.05	[0.98, 1.13]	0.140	1.07	[1.00, 1.15]	0.059	1.01	[0.93, 1.10]	0.803	1.02	[0.93, 1.11]	0.696
Chronic Pain	OR	1.26	[1.05, 1.50]	0.013	1.30	[1.08, 1.56]	0.005	1.34	[1.09, 1.66]	0.006	1.42	[1.14, 1.75]	0.001

All models included covariates for main effects of sex and chronological age. Biological aging measures were standardized within sex; coefficients reflect difference in outcome associated with a 1 SD difference in the biological aging measure. Continuous healthspan-related characteristics were standardized within sex to have M=0, SD=1 for analysis and analyzed with linear regression. Dichotomous healthspan-related characteristics were analyzed with logistic regression. Reported effect-sizes are odds ratios (OR). Count healthspan-related characteristics were analyzed with negative binomial regression. Reported coefficients are incidence rate ratios (IRR).

Appendix Table C.11: Associations between life-course risk factors and biological aging composite scores. Analysis includes data only from NHANES 1999-2000 (NHANES 2001-2002 used to train telomere parameters for biological aging algorithms).

	KDM Biological Age			KDM Biological Age w/ LTL			Homeostatic Dysregulation			Homeostatic Dysregulation w/ LTL		
	Effect-size (r/OR)	95% CI	p-value	Effect-size (r/OR)	95% CI	p-value	Effect-size (r/OR)	95% CI	p-value	Effect-size (r/OR)	95% CI	p-value
Stressors Hypothesized to Accelerate Aging												
Education	0.11	[0.08, 0.13]	1.73E-18	0.13	[0.11, 0.16]	1.58E-28	0.13	[0.11, 0.15]	2.26E-39	0.13	[0.11, 0.15]	3.96E-37
Poverty	0.10	[0.08, 0.13]	3.11E-16	0.12	[0.10, 0.15]	2.40E-22	0.12	[0.10, 0.14]	7.59E-32	0.12	[0.10, 0.14]	3.25E-32
Food Insecurity	0.04	[0.02, 0.06]	8.94E-04	0.06	[0.03, 0.08]	5.79E-06	0.07	[0.05, 0.09]	1.41E-11	0.07	[0.05, 0.09]	2.39E-11
Low Social Support	0.16	[0.06, 0.26]	0.002	0.17	[0.07, 0.26]	6.63E-04	0.17	[0.10, 0.24]	2.17E-06	0.20	[0.13, 0.27]	2.40E-08
Poor Mental Health	0.01	[-0.06, 0.08]	0.796	0.00	[-0.08, 0.08]	0.995	-0.01	[-0.07, 0.06]	0.853	-0.01	[-0.08, 0.06]	0.832

All models included covariates for main effects of sex and chronological age. Biological aging measures were standardized within sex to have M=0 SD=1 for analysis. Coefficients reflect SD acceleration in biological aging per 1 unit increase in the exposure. Education, poverty, and food-insecurity exposure measures were standardized to have M=0 SD=1 for analysis. Low social support and poor mental health are dichotomous indicators.

Appendix Table C.12 Associations of KDM Biological Age, homeostatic dysregulation, and LM Biological Age measures computed from the same biomarkers with healthspan-related characteristics. For this analysis, KDM Biological Age and homeostatic dysregulation measures were computed from the same set of biomarkers included in the LM Biological Age.

		KDM Biological Age*			Homeostatic Dysregulation*			LM Biological Age		
	Effect	Effect-size (r/OR)	95% CI	p-value	Effect-size (r/OR)	95% CI	p-value	Effect-size (r/OR)	95% CI	p-value
Phyical Functioning										
Cardiorespiratory Fitness (VO2max)	r	-0.03	[-0.09, 0.03]	0.288	-0.05	[-0.11, 0.00]	0.057	-0.11	[-0.17, -0.05]	0.001
Poor Balance	OR	1.21	[1.11, 1.32]	1.46E-05	1.23	[1.13, 1.34]	2.03E-06	1.25	[1.15, 1.37]	3.07E-07
Strength	r	-0.08	[-0.12, -0.05]	5.28E-06	-0.10	[-0.13, -0.06]	1.55E-07	-0.07	[-0.10, -0.03]	1.24E-04
Gait Speed	r	-0.15	[-0.19, -0.12]	1.04E-18	-0.16	[-0.19, -0.12]	1.19E-21	-0.15	[-0.18, -0.12]	1.11E-20
Cognitive & Perceptual Functioning										
Cognitive Function	r	-0.13	[-0.17, -0.10]	8.63E-13	-0.14	[-0.18, -0.10]	7.25E-12	-0.13	[-0.16, -0.09]	8.42E-11
Hearing	r	-0.07	[-0.09, -0.04]	1.64E-07	-0.10	[-0.12, -0.07]	8.38E-12	-0.10	[-0.13, -0.07]	5.68E-12
Vision	r	-0.11	[-0.15, -0.08]	1.69E-11	-0.07	[-0.10, -0.03]	1.20E-04	-0.11	[-0.15, -0.07]	2.00E-09
Subjective Functioning/Disability										
Self-rated Health	r	-0.20	[-0.22, -0.18]	9.96E-61	-0.19	[-0.22, -0.17]	8.04E-56	-0.21	[-0.24, -0.19]	2.56E-68
ADL	IRR	1.28	[1.22, 1.35]	3.10E-21	1.28	[1.22, 1.35]	3.39E-20	1.26	[1.21, 1.32]	8.94E-23
IADL	IRR	1.45	[1.32, 1.58]	1.79E-16	1.43	[1.30, 1.58]	3.49E-13	1.36	[1.25, 1.47]	1.89E-13
Pain										
Joint Pain	OR	1.09	[1.04, 1.15]	0.001	1.04	[0.99, 1.09]	0.146	1.14	[1.08, 1.20]	4.62E-07
Chronic Pain	OR	1.29	[1.17, 1.43]	3.47E-07	1.22	[1.09, 1.37]	0.001	1.35	[1.23, 1.49]	4.11E-10

For this analysis, KDM Biological Age and Homeostatic Dysregulation measures were computed using the same 9 biomarkers used to compute the LM Biological Age. Results for LM Biological age. All models included covariates for main effects of sex and chronological age. Biological aging measures were standardized within sex; coefficients reflect difference in outcome associated with a 1 SD difference in the biological aging measure. Continuous healthspan-related characteristics were standardized within sex to have M=0, SD=1 for analysis and analyzed with linear regression. Dichotomous healthspan-related characteristics were analyzed with logistic regression. Reported effect-sizes are odds ratios (OR). Count healthspan-related characteristics were analyzed with negative binomial regression. Reported coefficients are incidence rate ratios (IRR).

Appendix Table C.13 Associations of life-course risk factors with KDM Biological Age, homeostatic dysregulation, and LM Biological Age measures computed from the same biomarkers. For this analysis, KDM Biological Age and homeostatic dysregulation measures were computed from the same set of biomarkers included in the LM Biological Age.

	KDM Biological Age			Homeostatic Dysregulation			LM Biological Age		
	Effect-size (r/OR)	95% CI	p-value						
Stressors Hypothesized to Accelerate Aging									
Education	0.13	[0.11, 0.15]	6.11E-27	0.12	[0.09, 0.14]	5.99E-24	0.11	[0.09, 0.14]	2.03E-20
Poverty	0.13	[0.10, 0.15]	1.59E-24	0.12	[0.10, 0.15]	1.03E-24	0.14	[0.11, 0.16]	1.89E-27
Food Insecurity	0.08	[0.05, 0.11]	4.97E-09	0.06	[0.04, 0.09]	3.14E-07	0.07	[0.05, 0.10]	4.26E-08
Low Social Support	0.16	[0.07, 0.25]	6.41E-04	0.22	[0.13, 0.31]	1.11E-06	0.21	[0.11, 0.30]	2.02E-05
Poor Mental Health	0.04	[-0.04, 0.12]	0.338	0.03	[-0.04, 0.11]	0.382	0.04	[-0.04, 0.12]	0.290

For this analysis, KDM Biological Age and Homeostatic Dysregulation measures were computed using the same 9 biomarkers used to compute the LM Biological Age. Results for LM Biological age. All models included covariates for main effects of sex and chronological age. Biological aging measures were standardized within sex to have M=0 SD=1 for analysis. Coefficients reflect SD acceleration in biological aging per unit increase in the exposure. Education, poverty, and food-insecurity exposure measures were standardized to have M=0 SD=1 for analysis. Low social support and poor mental health are dichotomous indicators.