SUPPLEMENTAL METHODS TO QUANTIFICATION OF BIOLOGICAL AGING IN YOUNG ADULTS

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Sample.

Participants are members of the Dunedin Study, a longitudinal investigation of health and behavior in a complete birth cohort. Study members (N=1,037; 91% of eligible births; 52% male) were all individuals born between April 1972 and March 1973 in Dunedin, New Zealand (NZ), who were eligible based on residence in the province and who participated in the first assessment at age 3. The cohort represents the full range of socioeconomic status on NZ's South Island and as adults matches the NZ National Health and Nutrition Survey on key health indicators (e.g., BMI, smoking, GP visits) (44). Cohort members are primarily white; fewer than 7% self-identify as having partial non-Caucasian ancestry, matching the South Island (45). Assessments were carried out at birth and ages 3, 5, 7, 9, 11, 13, 15, 18, 21, 26, 32, and, most recently, 38 years, when 95% of the 1,007 study members still alive took part. At each assessment, each study member is brought to the research unit for a full day of interviews and examinations. The Otago Ethics Committee approved each phase of the study and informed consent was obtained from all study members.

Measuring aging.

By age 38 years, only 11 Study members had developed an age-related chronic disease (diagnosed type-2 diabetes, myocardial infarction, or stroke).

We measured aging in two ways.

Biological Age Algorithm. Calculating human biological age is a relatively recent enterprise(46) and there is disagreement about methods (47, 48). Our goal was to borrow and implement the best-validated methods. Recently, data from NHANES-III participants aged 30 to 75 years were used to compare the ability of five Biological Age algorithms to predict mortality

when participants were followed-up 20 years later (26). Results showed that the Klemera-Doubal method (23) performed the best in NHANES-III (i.e., it predicted mortality, did so better than chronological age, and accounted for the association between chronological age and mortality), consistent with results from other samples (23, 49). Receiver operating characteristic curve analysis in the NHANES sample showed Biological Age to be a modestly sensitive and specific predictor of mortality (Area Under the Curve=0.85, SE=0.01) (26). We calculated each Dunedin study member's Biological Age at age 38 years using the Klemera-Doubal equation (23) and parameters estimated from the NHANES-III dataset (26). The equation takes information from *m* number of regression lines of chronological age regressed on *m* number of biomarkers:

$BA_{EC} = \frac{\sum_{j=1}^{m}(x_j - q_j)\frac{k_j}{s_j^2} + \frac{CA}{s_{BA}^2}}{\sum_{j=1}^{m}\left(\frac{k_j}{s_j}\right)^2 + \frac{1}{s_{BA}^2}}$, where *x* is the value of biomarker *j* measured for an individual in the Dunedin cohort. For each biomarker *j*, the parameters *k*, *q*, and *s* are estimated from a regression of chronological age on the biomarker in data from NHANES-III. *k*, *q*, 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 NHANES database. CA is chronological age (38 for all Dunedin cohort members). Biomarkers used to calculate biological age in the Dunedin cohort at age 38 years are the same as those used in the NHANES analysis. (These ten biomarkers were selected for inclusion in the algorithm on the basis of their association with chronological age in NHANES-III.) The biomarkers are: Glycated hemoglobin, Forced expiratory volume in one second (FEV_1), Blood pressure (systolic), Total cholesterol, C-reactive protein, Creatinine, Urea nitrate, Albumin, Alkaline phosphatase, and Cytomegalovirus IgG. Details on biomarker measurements are provided in **Supplemental Table 1**. Biological Age took on a normal distribution, ranging from 28-61 years (M=38 years, SD=3.23).

Pace of Aging. We measured Pace of Aging from repeated assessments of a panel of 18 biomarkers. Seven biomarkers overlapped with the Biological Age algorithm: Glycated hemoglobin, Forced expiratory volume in one second (FEV_1), Blood pressure (mean arterial

pressure), Total cholesterol, C-reactive protein, Creatinine clearance, and Urea nitrate. In addition, Pace of Aging included the following 11 additional biomarkers: Cardiorespiratory fitness (VO_2Max), Waist-hip ratio, Forced vital capacity ratio (FEV_1/FVC), Body mass index (BMI), Leukocyte telomere length (LTL), Lipoprotein(a), Triglycerides, Periodontal disease, White blood cell count, High density lipoprotein (HDL), and Apolipoprotein B100/A1 ratio. Biomarkers were assayed at the age-26, -32, and -38 assessments. (Albumin, Alkaline phosphatase, and Cytomegalovirus IgG could not be included in the Pace of Aging because they were measured only at the age-38 assessment.) Details on biomarker measurements are provided in **Supplemental Table 1**.

We calculated each Study member's Pace of Aging in three steps. In the first step, we transformed the biomarker values to a standardized scale. For each biomarker, we standardized values according to the age-26 distribution, setting the mean to zero and the corresponding standard deviation to one. Standardization was conducted separately for men and women. Scores were reversed for VO_2Max, FEV_1/FVC, FEV_1, LTL, creatinine clearance, and HDL cholesterol, which are known to decline with age. Thus, standardized biomarker values greater than zero indicated levels that were "older" and values less than zero indicated levels "younger" as compared to the average 26-year-old. Over the 12 years of follow-up, the biomarker panel indicated a progressive deterioration of physiological integrity with advancing chronological age; i.e. values tended to increase from the age-26 assessment to the age-38 assessment.

In the second step, we calculated each Study member's personal slope for each of the 18 biomarkers—the average year-on-year change observed over the 12-year period. Slopes were estimated using a mixed effects growth model(50) that regressed the biomarker level on age. The models took the form $B_{it} = \gamma_0 + \gamma_1 Age_{it} + \boldsymbol{\mu_{0i}} + \boldsymbol{\mu_{1i}} Age_{it} + \epsilon_{it}$, where B_{it} is a biomarker measured for individual 'i' at time 't', γ_0 and γ_1 are the fixed intercept and slope estimated for the cohort, and μ_{0i} and μ_{1i} are the "random" intercepts and slopes estimated for each individual 'i'. (Only two measurement waves were available for LTL, high sensitivity CRP (hsCRP), and creatinine clearance. Slopes for these biomarkers were calculated as difference scores; between ages 32 and 38 for hsCRP and creatinine clearance and between ages 26 and

38 for LTL.) Within individuals, levels and slopes of the 18 biomarkers were positively correlated (averaged across all pairs of biomarkers, r=0.10 for intercepts and r=0.07 for slopes). A complete list of average biomarker slopes and pairwise correlations among biomarker slopes is presented in **Supplemental Table 2**. For four of the biomarkers we examined, levels either did not change or changed in a direction counter to published associations with age-related chronic disease: White blood cell count and CRP levels did not change, HDL cholesterol increased modestly, and apolipoprotein B100/A1 ratio declined. However, slopes for these biomarkers did show the expected pattern of correlation with other biomarkers. For example, Study members whose apolipoprotein B100/A1 ratio increased during the follow-up period also showed increasing adiposity, declining lung function, and increasing systemic inflammation.

In the third step, we combined information from the slopes of the 18 biomarkers to calculate each Study member's personal "pace of aging." Because we did not have a priori basis for weighting differential contributions of the biomarkers to an overall pace of aging measure, we combined information using a unit-weighting scheme. (All biomarkers were standardized to have mean=0, SD=1 based on their age-26 distributions, so slopes were denominated in comparable units). We calculated each study member's Pace of Aging as the sum of age-dependent annual changes in biomarker Z-scores: $Pace\ of\ aging_i = \sum_{B=1}^{18} \mu_{1iB}$, where μ_{1iB} is the slope of biomarker 'B' for individual 'i'. Pace of Aging was normally distributed in the cohort (M=0.70 age-26 SD units, SD=0.29).[a]

Because the Dunedin birth cohort represents its population, its mean and distribution represent population norms. We used these norms to scale the Pace of Aging to reflect physiological change relative to the passage of time. We set the cohort mean Pace of Aging as a reference value equivalent to the physiological change expected during a single chronological year. Using this reference value, we rescaled Pace of Aging in terms of years of physiological

[a] We do not use this variance to estimate a confidence interval around a person's Pace of Aging because it does not take into account correlations among biomarker slopes and would yield an underestimate of the standard error. Taking account of correlations among biomarker slopes ideally would involve joint estimation of the 18 biomarker models. However, this is not possible with currently available tools (51). Datasets with repeated measures of multiple biomarkers are becoming available. We expect that analyses of aging will soon incorporate longitudinal repeated measures of biomarkers to track change. We also expect that analyses of aging will seek to incorporate multiple biomarkers to track change across different organ systems. New statistical methods will be needed to estimate asymptotically correct standard errors for the purposes of developing confidence intervals around a person's Pace of Aging score.

change per chronological year. On this scale, cohort members ranged in their Pace of Aging from near zero years of physiological change per chronological year to nearly three years of physiological change per chronological year (**Supplemental Figure 1**).

Measuring diminished physical capacity at age 38 years.

Physical Functioning. We employed three measures. First, we measured balance as the maximum time achieved across three trials of the Unipedal Stance Test (with eyes closed) (52–54). Second, we measured grip strength with dominant hand (elbow held at 90°, upper arm held tight against the trunk) as the maximum value achieved across three trials using a Jamar digital dynamometer (55, 56). Third, we measured motor functioning as the time to completion of the Grooved Pegboard Test with the non-dominant hand (57).

Physical Limitations. Study member responses ("limited a lot," "limited a little," "not limited at all") to the 10-item SF-36 physical functioning scale (58) assessed their difficulty with completing various activities, e.g., climbing several flights of stairs, walking more than 1 km, participating in strenuous sports.

Measuring cognitive functioning in childhood and at age 38 years.

Cognitive Testing. IQ is a highly reliable measure of general intellectual functioning that captures overall ability across differentiable cognitive functions. We measured IQ from the individually administered Wechsler Intelligence Scale for Children-Revised (WISC-R; averaged across ages 7, 9, 11, and 13)(59) and the Wechsler Adult Intelligence Scale-IV (WAIS-IV; age 38) (60), both with M=100 and SD=15. We measured IQ decline by comparing scores from the WISC-R and the WAIS-IV.

Retinal Imaging. Digital fundus photographs were taken at the Dunedin Research Unit after 5 min of dark adaptation. The same camera (Canon NMR-45 with a 20D single-lens reflex backing; Canon, Tokyo, Japan) was used for all photographs, to avoid artifactual variation from different cameras. Both the left and the right eyes were photographed, and we report analyses of the average for the two eyes. Retinal photographs were graded at the Singapore Eye Research Institute, National University of Singapore, using semi-automated computer software, Singapore I Vessel Assessment (SIVA) Version 3.0. Trained graders, blind to participants'

characteristics, used the SIVA program to measure the retinal vessel diameters according to a standardized protocol with high inter-grader reliability (61). Diameter (or caliber) denotes the size of the lumen, which is the internal space of the vessel. Measurements were made for arterioles and venules where they passed through a region located 0.50 to 2.00 disk diameters from the optic disk margin (62). Vessel calibers were based on the six largest arterioles and venules passing though this region and were summarized as central retinal artery equivalent (CRAE) and central retinal vein equivalent (CRVE) using the revised Knudtson-Parr-Hubbard formula (61, 63).

Arteriolar and venular calibers were normally distributed within our population-representative cohort. The mean arteriolar caliber was 137.33 measuring units (SD=10.86, median=137.30, range=105.66–179.47), and the mean venular caliber was 196.20 measuring units (SD=14.83, median=195.51, range=141.07–245.68). Before all analyses, arteriolar and venular caliber were each adjusted for the effect of the other vessel, as recommended (64, 65), in order to isolate the unique effects for each vessel and adjust for any potential effects of refractive errors (66).

Measuring self-perceptions of health and others' perceptions of aging at age 38 years.

Self Rated Health. Study members rated their health on a scale of 1-5 (poor, fair, good, very good, or excellent).

Facial Aging. We took two measurements of perceived age based on facial photographs. First, Age Range was assessed by an independent panel of 4 Duke University undergraduate raters. Raters were presented with standardized (non-smiling) facial photographs of Study members (taken with a Canon PowerShot G11 camera with an optical zoom, Canon Inc., Tokyo, Japan) and were kept blind to their actual age. Photos were divided into sex-segregated slideshow batches containing approximately 50 photos, viewed for 10s each. Raters were randomized to viewing the slideshow batches in either forward progression or backwards progression. They used a Likert scale to categorize each Study member into a 5-year age range (i.e., from 20-24 years old up to 65-70 years). Scores for each study member were averaged across all raters (α=0.71). The second measure, Relative Age, was assessed by a different panel of 4 Duke University undergraduate raters. The raters were told that all photos were of people

aged 38 years old. Raters then used a 7-item Likert scale to assign a "relative age" to each study member (1="young looking", 7="old looking"). Scores for each study member were averaged across all raters (α=0.72). Age Range and Relative Age were highly correlated (r=0.73). To derive a measure of perceived age at 38 years, we standardized and averaged both Age Range and Relative Age scores to create Facial Age at 38 years.

Analysis

For analysis, validation measures were standardized to have mean=0, SD=1. For measures of physical functioning, physical activity, physical limitations, retinal vessel calibers, and self-rated health, standardization was conducted separately for men and women to account for different means/SDs between the sexes. Cognitive test scores and facial ages were similarly distributed in men and women. Regression analyses were adjusted for sex. Thus, effect-sizes reported for associations between aging measures and validation measures represent population average effects independent of sex. Effect-size estimates were calculated as standardized beta-coefficients from linear regressions (equivalent to Pearson's r).

To test whether associations between Pace of Aging and the validation metrics were dependent on any single biomarker, we conducted a leave-one-out sensitivity analysis. In the leave-one-out analysis, we re-calculated Pace of Aging leaving out each biomarker in turn. Full Pace of Aging and Leave-One-Out Pace of Aging effect-sizes from models predicting Biological Age and each validation metric are reported in **Supplemental Figure 2**.

Figure S1. Distribution of Pace of Aging in the Dunedin Cohort. Pace of Aging is denominated in years of physiological change per chronological year. Pace of Aging of 1 indicates a cohort member who experienced one year of physiological change per chronological year (the cohort average). Pace of Aging of two indicates a cohort member aging at a rate of two years of physiological change per chronological year, twice as fast as the population norm. Pace of Aging equal to zero indicates a cohort member whose physiology remained unchanged between ages 26 and 38.

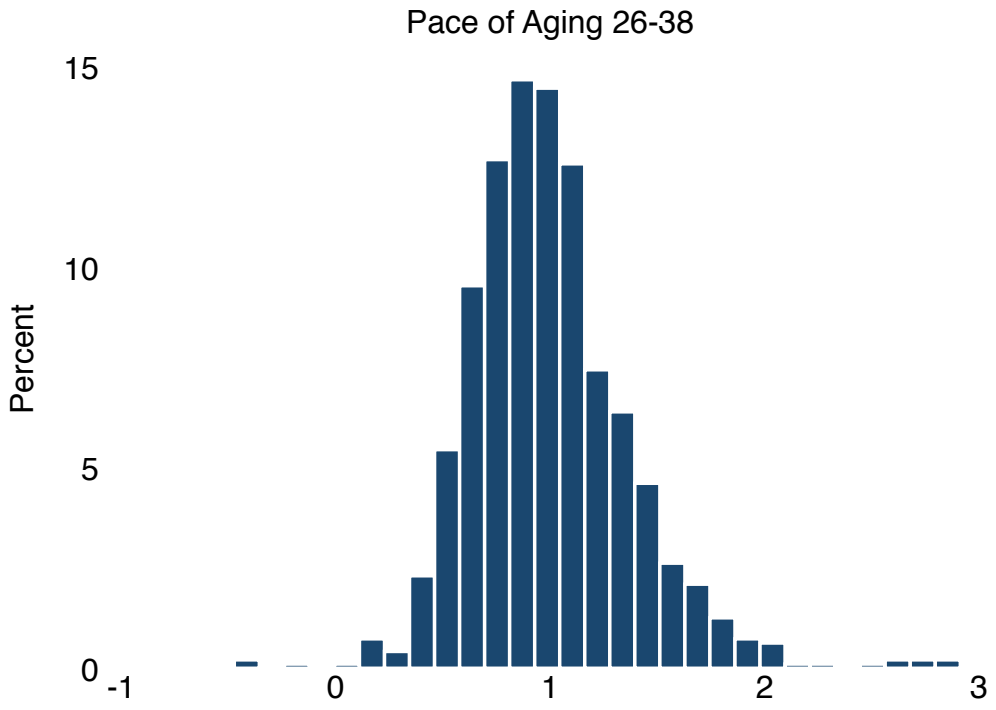

Figure S2. Pace of Aging and Leave-One-Out Pace of Aging effect sizes for models predicting Biological Age and validation metrics. The graph shows effect sizes for the full Pace of Aging (yellow bars) and for Leave-One-Out Pace of Aging measures calculated after omitting each biomarker in turn (blue bars). For example, the HbA1C Leave-One-Out Pace of Aging was calculated from the slopes of the other 17 biomarkers.

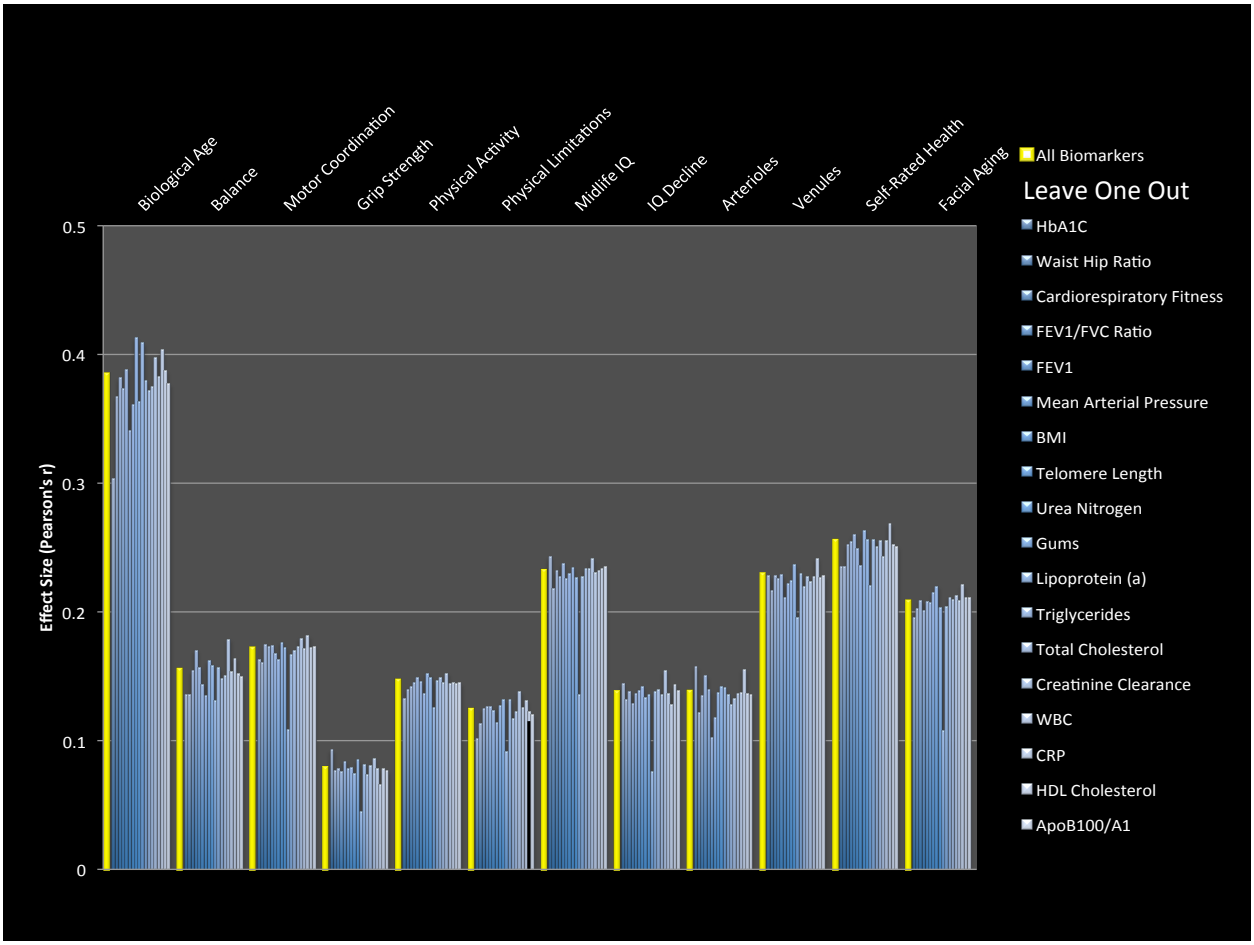

Table S1. Measurement of biomarkers used to calculate Biological Age and Pace of Aging measures. Measures were taken in counterbalanced order across Study members with the exception of blood, which was drawn at the same time of day for all Study members at all three ages. Women who were pregnant at the time of a given assessment were excluded from that wave of data collection.

Glycated hemoglobin level (HbA1C)	Serum glycated hemoglobin concentration (expressed as a percentage of total hemoglobin) was measured by ion exchange high performance liquid chromatography (Variant II: BioRad, Hercultes, Calif.), a method certified by the US National Glycohemoglobin Standardization Program (http://www.ngsp.org/).
Cardiorespiratory Fitness	Cardiorespiratory fitness was assessed by measuring heart rate in response to a submaximal exercise test on a friction-braked cycle ergometer. Dependent on the extent to which heart rate increased during a 2-min 50 W warm-up, the workload was adjusted to elicit a steady heart-rate in the range 130–170 beats per minute. After a further 6-min constant power output stage, the maximum heart rate was recorded and used to calculate predicted maximum oxygen uptake adjusted for body weight in milliliters per minute per kilogram (VO_2max) according to standard protocols (67).
Anthropometry	Height was measured to the nearest millimeter using a portable stadiometer (Harpenden; Holtain, Ltd). Weight was measured to the nearest 0.1 kg using calibrated scales. Individuals were weighed in light clothing. Body mass index (BMI) was calculated. Waist girth was the perimeter at the level of the noticeable waist narrowing located between the costal border and the iliac crest. Hip girth was taken as the perimeter at the level of the greatest protuberance and at about the symphysion pubic level anteriorly. Measurements were repeated and the average used to calculate Waist:hip ratio.
Lung function	We calculated post-albuterol forced expiratory volume in one second (FEV_1) and the ratio of FEV_1 to forced vital capacity (FVC) using measurements from spirometry conducted with a Sensormedics body plethysmograph (Sensormedics Corporation, Yorba Linda, CA, USA).
Blood pressure	Systolic and diastolic blood pressure were assessed according to standard protocols with a Hawksley random-zero sphygmomanometer with a constant deflation valve. Mean arterial pressure (MAP) was calculated using the formula *Diastolic Pressure*+1/3(*Systolic Pressure* - *Diastolic Pressure*).
Leukocyte telomere length	Leukocyte DNA was extracted from blood using standard procedures (68, 69). DNA was stored at -80°C. All DNA samples were assayed for leukocyte telomere length at the same time. Leukocyte telomere length was measured using a validated quantitative PCR method (70), as previously described,(71) which determines mean telomere length across all chromosomes for all cells sampled. The method involves two quantitative PCR reactions for each subject; one for a single-copy gene (S) and the other in the telomeric repeat region (T). All DNA samples were run in triplicate for

	telomere and single-copy reactions. Measurement artifacts (e.g., differences in plate conditions) may lead to spurious results when comparing leukocyte telomere length measured on the same individual at different ages. To eliminate such artifacts, we assayed DNA triplicates from the same individual from all time points, on the same plate. CV for triplicate Ct values was 0.81% for the telomere (T) and 0.48% for the single-copy gene (S).
Creatinine clearance	Serum creatinine (mmol/L) was measured by kinetic colorimetric assay on a Hitachi 917 analyzer (age 32) and Modular P analyzer (age 38) (Roche Diagnostics, Mannheim, Germany). For Pace of Aging analysis, creatinine was measured as creatinine clearance, calculated using a modified Cockcroft-Gault equation. The original equation [(140-*age*) x (*Wt in kg*) x (0.85 if *female*) / (72 x *Creatinine*)] (72) was modified as follows: (73, 74) For individuals with BMI of 18-23, we substituted "ideal body weight" in place of weight [for men, *Ideal Body Weight* = 50+(2.3x *Ht in inches* - 60); for women *Ideal Body Weight* = 50+(2.3x *Ht in inches* - 60)]. For individuals with BMI≥23, we substituted "adjusted body weight" for weight (*Adjusted Body Weight = Ideal Body Weight* + 0.4 x *Wt in kg - Ideal Body Weight*).
Urea nitrogen	Serum urea nitrogen (mmol/L) was measured by kinetic UV assay at age 26 (Hitachi 917 analyser) and by kinetic colorimetric assay at ages 32 and 38 (Hitachi 917 analyzer at age 32, Modular P analyzer at age 38).
Lipoprotein *(a)*	Serum lipoprotein *(a)* (mg/L) was measured by immunoturbidimetric assay on a Hitachi 917 analyzer (ages 26-32) and Modular P analyzer (age 38).
Non-fasting Triglycerides, Total cholesterol, and High-density lipoprotein (HDL) cholesterol	Serum non-fasting triglyceride, total cholesterol, and high-density lipoprotein levels (mmol/L) were measured by colorimetric assay on a Hitachi 917 analyzer (ages 26-32) and Modular P analyzer (age 38).
Gum health (combined attachment loss)	Examinations were conducted using calibrated dental examiners; three sites (mesiobuccal, buccal, and distolingual) per tooth were examined, and gingival recession (the distance in millimeters from the cementoenamel junction to the gingival margin) and probing depth (the distance from the probe tip to the gingival margin) were recorded using a PCP-2 probe. The combined attachment loss for each site was computed by summing gingival recession and probing depth (third molars were not included).
White blood cell count	Whole blood white blood cell counts ($x10^9$/L) were measured by flow-cytometry with a Coulter STKS (Coulter Corporation, Miami, FL) (age 26), a Sysmex XE2100 (Sysmex Corporation, Japan) (age 32) and a Sysmex XE5000 (Sysmex Corporation, Japan) (age 38). Counts were log-transformed for analysis.
C-reactive protein (hsCRP)	Serum C-reactive protein (mg/L) was measured by high sensitivity immunoturbidimetric assay on a Hitachi 917 analyzer (age 32) and Modular

	P analyzer (age 38). Values were log transformed for analysis.
Apolipoprotein *A1*	Serum apolipoprotein *A1* (g/L) was measured by immunoturbidimetric assay on a Hitachi 917 analyzer (ages 26-32) and Modular P analyzer (age 38).
Apolipoprotein *B100*	Serum apolipoprotein *B100* (g/L) was measured by immunoturbidimetric assay on a Hitachi 917 analyzer (ages 26-32) and Modular P analyzer (age 38).
Albumin	Serum albumin (g/L) was measured by immunoturbidimetric assay on a Hitachi 917 analyzer (ages 26-32) and Modular P analyzer (age 38).
Alkaline phosphatase	Serum alkaline phosphatase, ALP (U/L) was measured by enzymatic colorimetric assay on a Hitachi 917 analyzer (ages 26-32) and Modular P analyzer (age 38).
Cytomegalovirus Optical Density	Plasma cytomegalovirus (CMV) IgG antibodies (IU/ml) were measured by EIA assay (Diamedix, FL, USA) on a Molecular Devices Spectramax384 plate reader (Molecular Devices, CA, USA).

Table S2. Pairwise correlations among Study-member specific intercepts (Panel A) and slopes (Panel B) for 18 biomarkers. Correlations with r>0.05 are highlighted in yellow. Correlations with r>0.1 are highlighted in pink.

Panel A.

Biomarker Intercept Correlations	Glycated Hemoglobin	Waist-Hip Ratio	Cardiorespiratory Fitness	FEV1/FVC ratio	FEV1	Mean Arterial Pressure	BMI	Telomere Length	Urea Nitrogen	Gums	Lipoprotein (a)	Triglycerides	Cholesterol	Creatinine Clearance	White Blood Cell Count	CRP	HDL Cholesterol	ApoB100/A1 Ratio
Glycated Hemoglobin																		
Waist-Hip Ratio	0.1																	
Cardiorespiratory Fitness	0.1	0.4																
FEV1/FVC ratio	0.0	0.1	0.1															
FEV1	0.1	0.1	0.0	0.3														
Mean Arterial Pressure	0.1	0.2	0.3	0.0	0.0													
BMI	0.1	0.5	0.8	0.1	0.1	0.2												
Telomere Length	0.1	0.0	0.1	0.0	0.1	0.1	0.0											
Urea Nitrogen	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0										
Gums	0.1	0.1	0.0	0.1	0.0	0.0	0.0	0.0	0.0									
Lipoprotein (a)	0.0	0.0	0.1	0.0	0.0	0.0	0.1	0.0	0.0	0.0								
Triglycerides	0.1	0.4	0.3	0.0	0.1	0.2	0.3	0.1	0.1	0.0	0.1							
Cholesterol	0.1	0.2	0.2	0.0	0.1	0.1	0.2	0.0	0.0	0.0	0.2	0.4						
Creatinine Clearance	0.0	-0.1	-0.3	0.0	0.1	0.0	-0.2	0.1	0.1	0.0	0.0	0.0	0.0					
White Blood Cell Count	0.2	0.2	0.2	0.1	0.1	0.1	0.1	0.0	0.0	0.3	0.0	0.2	0.1	0.0				
CRP	0.0	0.0	0.1	0.0	0.0	0.1	0.1	0.0	0.0	0.0	0.0	0.0	0.0	-0.1	0.0			
HDL Cholesterol	0.0	0.3	0.3	0.0	0.1	0.1	0.3	0.1	0.0	0.1	0.0	0.4	-0.1	-0.1	0.1	0.0		
ApoB100/A1 Ratio	0.1	0.3	0.4	0.1	0.1	0.1	0.4	0.1	0.0	0.1	0.1	0.5	0.7	0.0	0.2	0.0	0.6	

Panel B.

Biomarker Slope Correlations	Glycated Hemoglobin	Waist-Hip Ratio	Cardiorespiratory Fitness	FEV1/FVC ratio	FEV1	Mean Arterial Pressure	BMI	Telomere Length	Urea Nitrogen	Gums	Lipoprotein (a)	Triglycerides	Cholesterol	Creatinine Clearance	White Blood Cell Count	CRP	HDL Cholesterol	ApoB100/A1 Ratio
Slope	0.13	0.10	0.10	0.07	0.06	0.06	0.04	0.03	0.03	0.04	0.03	0.02	0.02	0.03	0.00	-0.01	-0.02	-0.03
Glycated Hemoglobin																		
Waist-Hip Ratio	0.2																	
Cardiorespiratory Fitness	0.0	0.2																
FEV1/FVC ratio	0.0	-0.1	0.1															
FEV1	0.1	0.0	0.1	0.4														
Mean Arterial Pressure	0.1	0.2	0.2	-0.1	0.0													
BMI	0.1	0.4	0.6	-0.1	0.1	0.3												
Telomere Length	0.0	0.0	0.0	0.0	0.0	0.0	0.0											
Urea Nitrogen	0.0	0.0	0.0	0.0	-0.1	0.0	0.0	-0.1										
Gums	0.1	0.1	0.0	0.1	0.1	0.0	0.0	0.0	0.0									
Lipoprotein (a)	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.0								
Triglycerides	0.2	0.3	0.2	0.0	0.1	0.2	0.4	0.0	0.1	0.0	0.0							
Cholesterol	0.1	0.1	0.3	0.1	0.1	0.2	0.2	0.0	0.0	0.0	0.1	0.3						
Creatinine Clearance	0.0	0.0	-0.1	-0.1	-0.1	0.0	-0.2	0.0	0.1	0.0	0.0	-0.2	-0.1					
White Blood Cell Count	0.2	0.1	0.1	0.1	0.0	0.1	0.1	0.0	0.0	0.1	0.0	0.2	0.2	0.0				
CRP	0.0	0.0	0.1	0.0	0.0	0.0	0.1	0.0	-0.1	0.0	0.0	0.0	0.0	-0.1	0.0			
HDL Cholesterol	0.1	0.2	0.2	0.0	0.1	0.0	0.4	0.0	0.0	0.0	-0.1	0.4	-0.1	-0.1	0.1	0.1		
ApoB100/A1 Ratio	0.1	0.2	0.3	0.1	0.1	0.1	0.4	0.0	-0.1	0.0	0.0	0.3	0.4	-0.1	0.1	0.1	0.5	

Table S3. Associations between measures of biological aging and cognitive functions measured by the Wechsler Intelligence Test Subtests. Subtests are divided into tests of crystalized and fluid dimensions of intelligence. The first set of columns labeled "Age 38 Performance" present results from analysis of cognitive test performance when Study members were aged 38 years. The second set of columns labeled "Change from Childhood" present results from identical models that also include control variables measuring the Study members' performance on the same cognitive test when they children. Models in the second set of columns test if faster biological aging is associated with cognitive change since childhood. In the top set of rows, Biological Age is the predictor and cognitive test performance is the outcome. In the bottom set of rows, Pace of Aging is the predictor and cognitive test performance is the outcome.

	Age 38 Performance		Change from Childhood	
Subtest	**r**	**p**	**r**	**p**
		Biological Age Analysis		
Tests of Crystalized Intelligence				
Information	-0.07	0.046	0.00	0.912
Similarities	-0.14	<0.001	-0.06	0.045
Vocabulary	-0.13	<0.001	-0.06	0.026
Tests of Fluid Intelligence				
Digit Symbol Coding	-0.13	<0.001	-0.10	<0.001
Arithmetic	-0.11	<0.001	-0.05	0.042
Block Design	-0.16	<0.001	-0.07	0.016
Picture Completion	-0.10	0.005	-0.06	0.079
		Pace of Aging Analysis		
Tests of Crystalized Intelligence				
Information	-0.15	<0.001	-0.03	0.186
Similarities	-0.17	<0.001	-0.08	0.003
Vocabulary	-0.17	<0.001	-0.06	0.024
Tests of Fluid Intelligence				
Digit Symbol Coding	-0.20	<0.001	-0.15	<0.001
Arithmetic	-0.18	<0.001	-0.09	<0.001
Block Design	-0.16	<0.001	-0.07	0.012
Picture Completion	-0.09	0.005	-0.05	0.128