

Additional file 1

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sMethod 1. Detailed information on KoGES

Korean Genome and Epidemiology Study (KoGES) consists of large-scale six prospective cohort studies employed by the Korean government (National Research Institute of Health (NIH), Centers for Disease Control and Prevention, and the Ministry of Health and Welfare, Korea). The cohort studies are categorized into population-based and gene-environment model studies. The population-based cohorts include the *Health Examinee* (HEXA) study and the *Ansan and Ansung* study. Under the supervision of trained staff, eligible participants were invited to visit the survey sites and provided data through questionnaires assessing health status and lifestyle habits, as well as physical examinations. After enrollment, they underwent periodic follow-up assessments and telephone/email surveys.

HEXA is composed of individuals recruited from the national health examinee registry, which is part of the National Health Insurance Program. The study recruited volunteers aged ≥ 40 years who visited medical institutions, primarily general hospitals, in metropolitan areas and major cities in Korea (e.g., Seoul, Busan, Changwon, Daegu, and Gwangju). The initial survey was conducted between 2004 and 2013, starting with 173,195 participants. At baseline, the mean chronological age of participants was 53.1 years (SD: 8.4), and the cohort consisted of 59,294 males and 114,063 females. The prevalence of hypertension was 30.9%, type 2 diabetes was 9.3%, and obesity was 34.8%. The first follow-up exam, conducted between 2007 and 2016, included 70,214 participants, with an approximate retention rate of 40.5% (a total of 2 waves so far).

Ansan and Ansung involved residents from two areas in Gyeonggi Province: Ansan (a suburban area) and Ansung (a rural area). To collect representative samples, registered inhabitants were randomly selected and contacted. Among them, a total of 10,030 participants aged 40–69 years were voluntarily enrolled at baseline between 2001 and 2002 (5,012 from Ansan and 5,018 from Ansung). The recruited individuals had a mean chronological age of 52.3 years (SD: 8.9) and consisted of 4,758 males and 5,272 females. This distribution was comparable to that of non-recruited individuals. The prevalence of hypertension was 33.8%, type 2 diabetes was 8.7%, and obesity was 43.0%. The *Ansan and Ansung* study conducted nine biennial follow-up surveys, resulting in a total of 10 waves by 2020. The follow-up rates for the 2nd to 10th follow-ups were 80.7%, 71.3%, 65.0%, 67.2%, 63.4%, 63.3%, 66.5%, 64.2%, and 61.9%, respectively.

sMethod 2. Assessing healthy diet for CVH score

To assess dietary quality, we used the Healthy Lifestyle Score. A score of 1 was assigned if the individual complied with the recommended intake levels (servings/day or week) for each of the nine food groups—fruits, nuts, vegetables, refined grains, fish, dairy products, processed meats, unprocessed red meats, and sugar-sweetened beverages; Otherwise, a score of 0 was given (total score ranging from 0 to 9). In the next step, individuals in the top percentile (95%) of the aggregated score were assigned a score of 100, and the remaining were assigned scores corresponding to their percentiles (zero points for the 1–24th percentile, 25 points for the 25–49th percentile, 50 points for the 50–74th percentile, and 80 points for the 75–94th percentile).

Table S1. Assessment of CVH components

Domain	CVH components	Metric	Points	Criteria
Health behaviours	Healthy diet	HLS diet scores	100	≥ 95 th percentile (ideal quantile)
			80	75–94 th percentile
			50	50–74 th percentile
			25	25–49 th percentile
			0	1–24 th percentile (least ideal quantile)
	Healthy sleep	Average hours of sleep per night	100	7-8 hours
			90	9 hours
			70	6 hours
			40	5 or ≥10 hours
			20	4 hours
			0	< 4 hours
	Nicotine avoidance	Current smoking, smoking cessation period, and secondhand smoke exposure at home	100	Never smoker
			75	Former smoker, quit ≥ 5 years
			50	Former smoker, quit 1-4 years
			25	Former smoker, quit <1 year
			0	Current smoker
			*Subtract 20 points (unless score is 0) for living with indoor smoker in home †	
	Physical activity	Minutes of exercise of intensity to induce sweating (per week)	100	≥ 150 minutes
			90	120-149 minutes
			80	90-119 minutes
			60	60-89 minutes
			40	30-59 minutes
			20	1-29 minutes
			0	0
Clinical indicators	BMI (kg/m ²)	Body weight (kilograms) divided by height squared (meters squared)	100	< 25 kg/m ²
			70	25-29.9 kg/m ²
			30	30-34.9 kg/m ²
			15	35-39.9 kg/m ²
			0	≥ 40 kg/m ²
	Blood lipids (mg/dL)	Non-HDL cholesterol	100	< 130 mg/dL
			60	130-159 mg/dL
			40	160-189 mg/dL
			20	190-219 mg/dL
			0	≥ 220 mg/dL
			*Subtract 20 points (unless score is 0), if drug-treated level	
	Blood glucose (mg/dL or %)	Diabetes diagnosis, HbA1c (%) or Fasting blood glucose (FBG, mg/dL)	100	No history of diabetes diagnosis and HbA1c < 5.7 (or FBG <100)
			60	No history of diabetes diagnosis and HbA1c 5.7-6.4 (or FBG 100-125)
			40	Diabetes diagnosis with HbA1c <7.0 or no history of diabetes diagnosis with HbA1c 6.5-6.9
			30	Diabetes diagnosis with HbA1c 7.0-7.9 or no history of diabetes diagnosis with HbA1c 7.0-7.9
			20	Diabetes diagnosis with HbA1c 8.0-8.9 or no history of diabetes diagnosis with HbA1c 8.0-8.9

			10	Diabetes diagnosis with HbA1c 9.0-9.9 or no history of diabetes diagnosis with HbA1c 9.0-9.9
			0	Diabetes diagnosis with HbA1c ≥ 10.0 or no history of diabetes diagnosis with HbA1c ≥ 10.0
	Blood pressure (mmHg)	Systolic and diastolic blood pressure (BP, mmHg)	100	SBP < 120 and DBP < 80
			75	SBP 120-129 and DBP < 80
			50	SBP 130-139 or DBP 80-89
			25	SBP 140-159 or DBP 90-99
			0	SBP ≥ 160 or DBP ≥ 100
			*Subtract 20 points (unless score is 0), if drug-treated level	

† We used secondhand smoke exposure at home as a proxy for living with an indoor smoker when the latter variable was missing.

Table S2. Distribution of CVH score and level

Variables		Total (N= 1,940)	Males (n= 1,125)	Females (n= 815)	P-value ^a
CVH score ^b , mean (SD)	Healthy diet	49.0 (36.9)	42.4 (35.9)	58.2 (36.3)	<.001
	Healthy sleep	74.8 (27.6)	76.6 (26.4)	71.7 (29.3)	0.005
	Health behaviours Nicotine avoidance	64.8 (39.5)	45.7 (40.1)	91.2 (17.3)	<.001
	Physical activity	35.5 (45.8)	34.9 (45.7)	36.3 (46.0)	0.506
	BMI	85.0 (21.7)	83.8 (23.1)	86.6 (19.3)	0.004
	Health indicators Blood lipids	61.9 (28.9)	63.2 (28.6)	60.1 (29.1)	0.024
	Blood glucose	74.9 (32.4)	75.4 (31.2)	74.3 (33.9)	0.471
	Blood pressure	69.9 (30.7)	67.6 (30.6)	73.2 (30.6)	<.001
	Total score (average)	63.9 (14.2)	60.4 (14.1)	68.8 (13.0)	<.001
	CVH level ^c , n (%)				
	Ideal	267 (13.76)	100 (8.89)	167 (20.49)	
	Intermediate	1377 (70.98)	786 (69.87)	591 (72.52)	<.001
	Poor	296 (15.26)	239 (21.24)	57 (6.99)	

^a Global P values were obtained from χ^2 tests for categorical variables and Student *t* tests for continuous variables to compare between the sexes.

^b Ranged from 0 to 100; A higher score means better health behaviours and health status.

^c Ideal (80-100 points), intermediate (50-79 points), and poor (0-49 points)

SD standard deviation

Table S3. The associations between CVH and EAA in total participants (sensitivity analyses)

		EAA	Total participants β (95% CI) ^a
CVH score ^b		IEAA	-0.25 (-0.44, -0.06) *
		EEAA	-0.05 (-0.24, 0.13)
		PhenoAA	-0.53 (-0.77, -0.28) **
		Grim2AA	-0.91 (-1.07, -0.76) **
		DunedinPACE	-2.62 (-3.06, -2.18) **
CVH level ^c	Ideal	IEAA	-0.29 (-0.83, 0.25)
	Poor		0.47 (-0.04, 0.99)
	Ideal	EEAA	-0.17 (-0.69, 0.35)
	Poor		-0.07 (-0.57, 0.43)
	Ideal	PhenoAA	-0.73 (-1.42, -0.04) *
	Poor		1.02 (0.35, 1.68) *
	Ideal	Grim2AA	-1.12 (-1.56, -0.68) **
	Poor		1.73 (1.31, 2.16) **
	Ideal	DunedinPACE	-3.54 (-4.79, -2.29) **
	Poor		5.80 (4.60, 7.00) **

^a Adjusted for sex, chronological age, marital status, education level, household income, and employment.

^b β represents the change in EAA for each 1-SD (standard deviation; 14.2) increase in CVH score

^c Reference = Intermediate

Stratum-specific P-values: * P< 0.05; ** P< .001

Table S4. Associations between overall CVH and EAA from regression analysis (adjusted for cell type composition)

		EAA	Total (N= 1,940) β (95% CI)	Males (n= 1,125) β (95% CI)	Females (n= 815) β (95% CI)	Interaction P-value
CVH score †		IEAA	-0.26 (-0.45, -0.07)*	-0.28 (-0.53, -0.03)*	-0.35 (-0.63, -0.07)*	0.679
		EEAA	-0.17 (-0.35, 0.01)	-0.20 (-0.43, 0.03)	-0.19 (-0.45, 0.07)	0.984
		PhenoAA	-0.65 (-0.88, -0.42)**	-0.59 (-0.89, -0.29)**	-0.69 (-1.03, -0.35)**	0.713
		Grim2AA	-0.92 (-1.06, -0.78)**	-1.03 (-1.22, -0.83)**	-0.70 (-0.89, -0.51)**	0.010*
		DunedinPACE	-2.49 (-2.91, -2.06)**	-2.86 (-3.41, -2.31)**	-1.71 (-2.36, -1.06)**	0.010*
CVH level ‡	Ideal	IEAA	-0.27 (-0.82, 0.27)	-0.04 (-0.91, 0.83)	-0.66 (-1.35, 0.02)	0.541
	Poor		0.50 (-0.02, 1.02)	0.59 (-0.02, 1.20)	0.42 (-0.65, 1.49)	
	Ideal	IEAA	-0.38 (-0.88, 0.12)	-0.37 (-1.18, 0.44)	-0.51 (-1.15, 0.12)	0.252
	Poor		0.12 (-0.36, 0.60)	0.36 (-0.21, 0.92)	-0.59 (-1.58, 0.40)	
	Ideal	PhenoAA	-0.98 (-1.63, -0.33)*	-0.75 (-1.79, 0.30)	-1.26 (-2.08, -0.44)*	0.847
	Poor		1.16 (0.54, 1.78)**	1.20 (0.47, 1.94)*	0.89 (-0.39, 2.17)	
	Ideal	Grim2AA	-0.95 (-1.35, -0.55)**	-1.25 (-1.92, -0.57)**	-0.86 (-1.33, -0.39)**	0.100
	Poor		1.81 (1.43, 2.20)**	1.90 (1.43, 2.37)**	1.40 (0.68, 2.13)**	
	Ideal	DunedinPACE	-3.15 (-4.36, -1.95)**	-3.37 (-5.28, -1.45)**	-3.21 (-4.78, -1.64)**	0.309
	Poor		5.62 (4.46, 6.78)**	6.00 (4.66, 7.35)**	4.27 (1.83, 6.70)**	

Adjusted for chronological age, marital status, education level, household income, employment, current drinking, no. of comorbidities, and cell type composition (sex was additionally adjusted in total participants; menopause status was additionally adjusted in females).

[†] β represents the change in EAA for each 1-SD (standard deviation) increase in CVH score; Participants (SD): total (14.2); males (14.1); females (13.0)

[‡] Reference = Intermediate

Interaction P-values derived from interaction analysis between CVH and sex.

Stratum-specific P-values: * P< .05; ** P< .001

Table S5. The sex-stratified associations between CVH and EAA from regression analysis (The first-generation clocks)

		EAA	Total (N= 1,940) β (95% CI)	Males (n= 1,125) β (95% CI)	Females (n= 815) β (95% CI)	Interaction P-value
CVH score ^a		IEAA	-0.27 (-0.46, -0.08)*	-0.29 (-0.54, -0.04)*	-0.34 (-0.62, -0.06)*	0.765
		EEAA	-0.06 (-0.24, 0.13)	-0.07 (-0.31, 0.18)	-0.16 (-0.44, 0.11)	0.769
CVH level ^b	Ideal	IEAA	-0.30 (-0.84, 0.23)	-0.05 (-0.91, 0.82)	-0.68 (-1.36, -0.01)*	0.511
	Poor		0.53 (0.01, 1.05)*	0.63 (0.03, 1.24)*	0.38 (-0.68, 1.45)	
	Ideal	EEAA	-0.18 (-0.70, 0.34)	-0.04 (-0.88, 0.80)	-0.44 (-1.11, 0.23)	0.538
	Poor		-0.06 (-0.56, 0.45)	0.12 (-0.47, 0.71)	-0.39 (-1.43, 0.66)	

Adjusted for chronological age, marital status, education level, household income, job, current drinking, and the no. of comorbidities

(sex was additionally adjusted in total participants; menopause status was additionally adjusted in females).

^a β represents the change in EAA for each 1-SD (standard deviation) increase in CVH score; Participants (SD): total (14.2); male (14.1); female (13.0)

Interaction P-values derived from interaction analysis between CVH and sex.

^b Reference= Intermediate

Stratum-specific P-values: * P< 0.05

Table S6. Associations between individual CVH components and EAA from regression analysis by sex

CVH components	EAA	Males (n= 1,125) β (95% CI)	Females (n= 815) β (95% CI)	Interaction P-value	
Health behaviors	Healthy diet	PhenoAA	0.30 (-0.11, 0.72)	0.04 (-0.48, 0.56)	0.217
		Grim2AA	0.05 (-0.21, 0.30)	-0.20 (-0.50, 0.11)	0.077
		DunedinPACE	-0.03 (-0.75, 0.70)	-0.16 (-1.16, 0.83)	0.576
	Healthy sleep	PhenoAA	0.06 (-0.34, 0.47)	0.23 (-0.28, 0.74)	0.834
		Grim2AA	-0.03 (-0.28, 0.22)	0.16 (-0.14, 0.46)	0.464
		DunedinPACE	0.10 (-0.61, 0.81)	0.53 (-0.46, 1.51)	0.570
	Nicotine avoidance	PhenoAA	-0.50 (-0.95, -0.06)*	-0.34 (-0.86, 0.17)	0.347
		Grim2AA	-1.74 (-2.01, -1.47)**	-0.61 (-0.91, -0.31)**	0.737
		DunedinPACE	-3.56 (-4.34, -2.78)**	-1.03 (-2.02, -0.04)*	0.543
	Physical activity	PhenoAA	-0.25 (-0.67, 0.17)	-0.32 (-0.81, 0.17)	0.858
		Grim2AA	-0.04 (-0.30, 0.23)	-0.40 (-0.69, -0.12)*	0.055
		DunedinPACE	-0.49 (-1.23, 0.25)	-1.06 (-1.99, -0.12)*	0.352
Health indicators	Better BMI	PhenoAA	0.15 (-0.18, 0.48)	-0.43 (-0.79, -0.06)*	0.036*
		Grim2AA	0.13 (-0.09, 0.35)	-0.32 (-0.53, -0.11)*	0.031*
		DunedinPACE	-0.74 (-1.34, -0.15)*	-1.30 (-1.94, -0.65)**	0.183
	Better blood lipids	PhenoAA	0.21 (-0.10, 0.52)	0.06 (-0.30, 0.42)	0.627
		Grim2AA	0.10 (-0.11, 0.31)	0.04 (-0.17, 0.25)	0.992
		DunedinPACE	0.14 (-0.43, 0.70)	0.57 (-0.07, 1.20)	0.351
	Better blood glucose	PhenoAA	-0.67 (-0.99, -0.36)**	-0.41 (-0.81, -0.02)*	0.230
		Grim2AA	-0.98 (-1.19, -0.76)**	-0.69 (-0.92, -0.46)**	0.008*
		DunedinPACE	-2.44 (-3.02, -1.87)**	-2.63 (-3.33, -1.94)**	0.572
	Better blood pressure	PhenoAA	-0.39 (-0.70, -0.07)*	-0.39 (-0.76, -0.01)*	0.833
		Grim2AA	-0.08 (-0.29, 0.13)	0.08 (-0.14, 0.30)	0.114
		DunedinPACE	-0.30 (-0.87, 0.28)	0.02 (-0.64, 0.68)	0.312

Adjusted for chronological age, marital status, education level, household income, employment, current drinking, no. of comorbidities, and four components of health behaviors or health indicators (menopause status was additionally adjusted in females).

β represents the change in EAA for each 1-SD (standard deviation) increase in CVH score.

Components (SD): healthy diet (35.9); healthy sleep (26.4); nicotine avoidance (40.1); physical activity (45.7); better BMI (23.1); better blood lipids (28.6); better blood glucose (31.2); better blood pressure (30.6) in males; healthy diet (36.3); healthy sleep (29.3); nicotine avoidance (17.3); physical activity (46.0); better BMI (19.3); better blood lipids (29.1); better blood glucose (33.9); better blood pressure (30.6) in females.

Interaction P-values derived from interaction analysis between CVH and sex.

Stratum-specific P-values: * $P < .05$; ** $P < .001$

Table S7. Associations between individual CVH components and EAA from regression analysis (adjusted for cell type composition)

CVH components	EAA	Total (N= 1,940) β (95% CI)	Males (n= 1,125) β (95% CI)	Females (n= 815) β (95% CI)	Interaction P-value
Health behaviors	Healthy diet	PhenoAA	0.21 (-0.10, 0.51)	-0.15 (-0.63, 0.33)	0.143
		Grim2AA	-0.01 (-0.19, 0.18)	-0.17 (-0.45, 0.12)	0.134
		DunedinPACE	-0.29 (-0.86, 0.28)	-0.20 (-1.17, 0.77)	0.587
	Healthy sleep	PhenoAA	0.04 (-0.25, 0.33)	0.01 (-0.47, 0.48)	0.454
		Grim2AA	0.09 (-0.09, 0.26)	0.12 (-0.16, 0.40)	0.900
		DunedinPACE	0.36 (-0.19, 0.92)	0.26 (-0.69, 1.22)	0.673
	Nicotine avoidance	PhenoAA	-0.57 (-0.92, -0.23)*	-0.67 (-1.16, -0.19)*	0.149
		Grim2AA	-1.46 (-1.66, -1.25)**	-0.62 (-0.91, -0.34)**	0.877
		DunedinPACE	-3.81 (-4.46, -3.17)**	-1.16 (-2.14, -0.19)*	0.961
	Physical activity	PhenoAA	-0.20 (-0.49, 0.09)	-0.16 (-0.61, 0.29)	0.772
		Grim2AA	-0.13 (-0.30, 0.04)	-0.27 (-0.54, -0.01)*	0.249
		DunedinPACE	-0.66 (-1.21, -0.12)*	-0.78 (-1.68, 0.13)	0.846
Health indicators	Better BMI	PhenoAA	-0.11 (-0.33, 0.12)	-0.53 (-0.87, -0.20)*	0.010*
		Grim2AA	-0.11 (-0.25, 0.04)	-0.38 (-0.57, -0.20)**	0.006*
		DunedinPACE	-1.04 (-1.47, -0.60)**	-1.39 (-2.00, -0.77)**	0.080
	Better blood lipids	PhenoAA	0.02 (-0.21, 0.24)	-0.15 (-0.48, 0.18)	0.448
		Grim2AA	0.00 (-0.13, 0.14)	-0.12 (-0.30, 0.06)	0.450
		DunedinPACE	0.32 (-0.10, 0.74)	0.38 (-0.23, 0.99)	0.551
	Better blood glucose	PhenoAA	-0.54 (-0.77, -0.31)**	-0.27 (-0.64, 0.09)	0.150
		Grim2AA	-0.85 (-1.00, -0.71)**	-0.68 (-0.88, -0.48)**	0.023*
		DunedinPACE	-2.44 (-2.88, -2.00)**	-2.50 (-3.16, -1.83)**	0.651
	Better blood pressure	PhenoAA	-0.20 (-0.43, 0.02)	-0.20 (-0.54, 0.14)	0.759
		Grim2AA	-0.09 (-0.23, 0.05)	0.07 (-0.12, 0.26)	0.125
		DunedinPACE	-0.39 (-0.82, 0.04)	-0.48 (-1.03, 0.08)	0.228

Adjusted for chronological age, marital status, education level, household income, employment, current drinking, no. of comorbidities, four components of health behaviors or health indicators, and cell type composition (sex was additionally adjusted in total participants; menopause status was additionally adjusted in females).

β represents the change in EAA for each 1-SD (standard deviation) increase in CVH score.

Components (SD): healthy diet (36.9); healthy sleep (27.6); nicotine avoidance (39.5); physical activity (45.8); better BMI (21.7); better blood lipids (28.9); better blood glucose (32.4); better blood pressure (30.7) in total participants; healthy diet (35.9); healthy sleep (26.4); nicotine avoidance (40.1); physical activity (45.7); better BMI (23.1); better blood lipids (28.6); better blood glucose (31.2); better blood pressure (30.6) in males; healthy diet (36.3); healthy sleep (29.3); nicotine avoidance (17.3); physical activity (46.0); better BMI (19.3); better blood lipids (29.1); better blood glucose (33.9); better blood pressure (30.6) in females.

Interaction P-values derived from interaction analysis between CVH and sex.

Stratum-specific P-values: * P< .05; ** P< .001

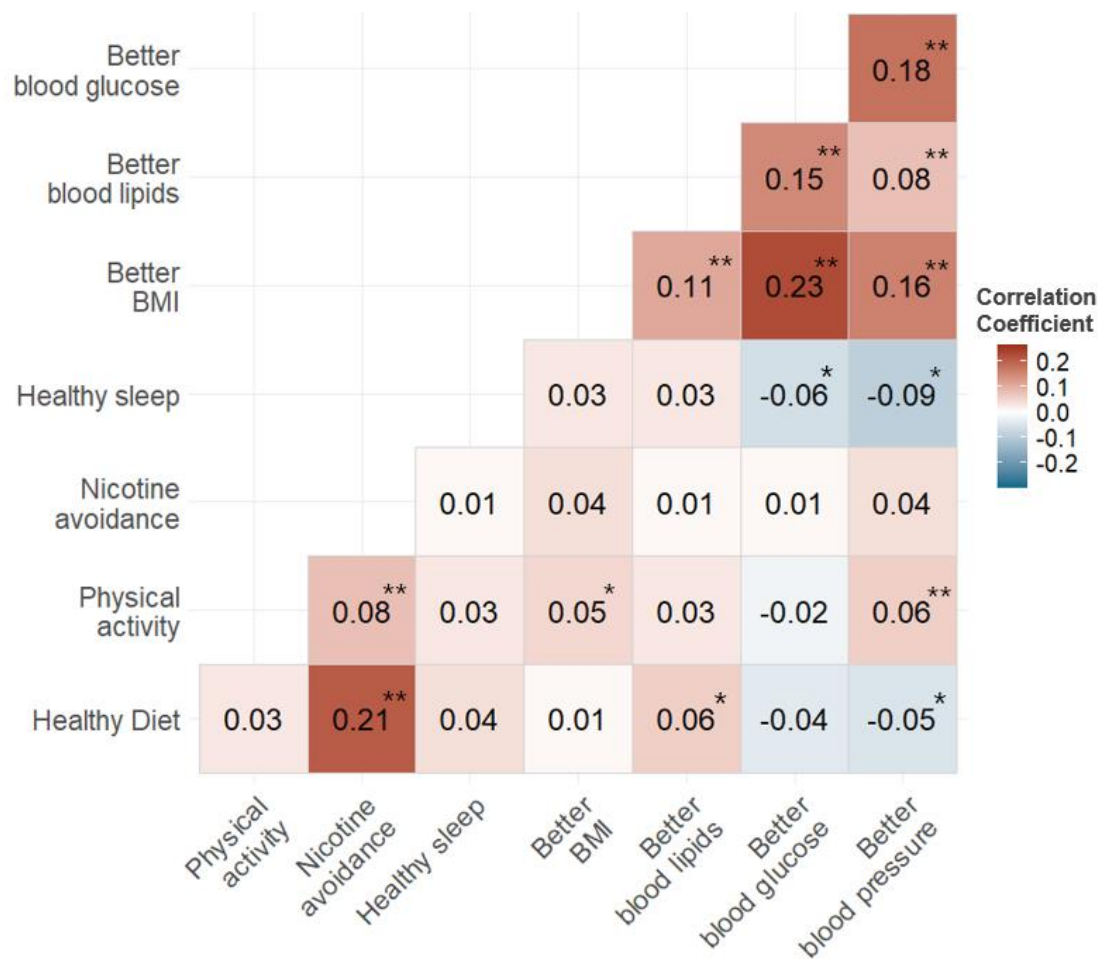


Figure S1. Spearman's correlations among CVH components

* $P < .05$; ** $P < .001$

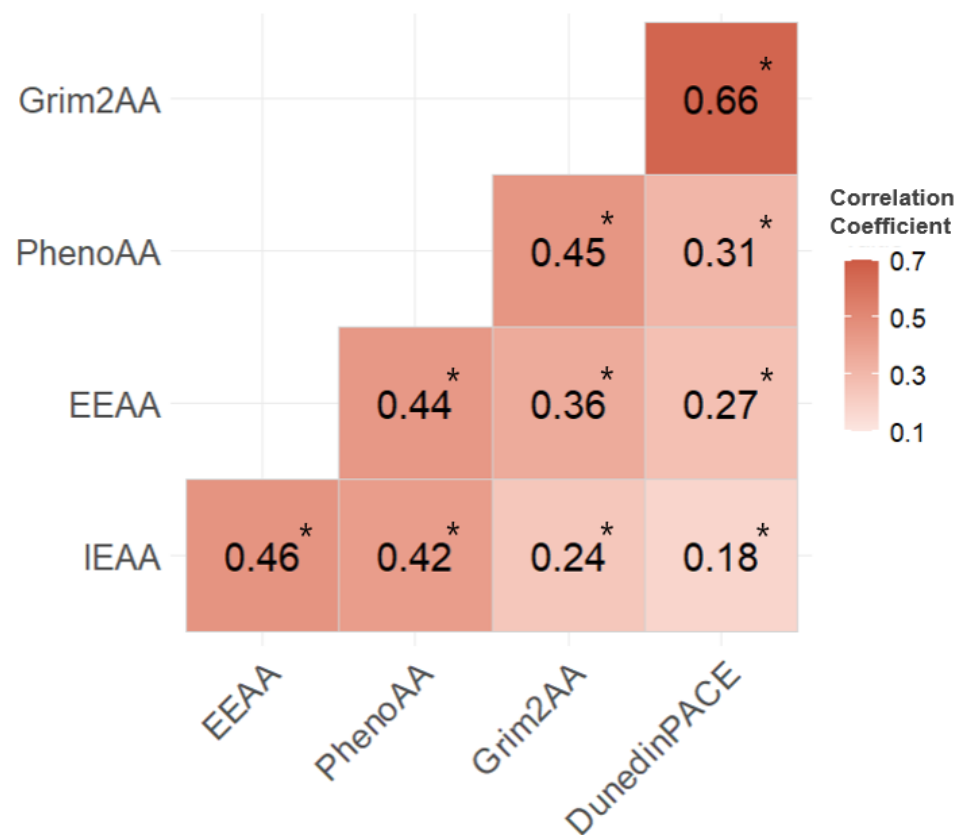


Figure S2. Correlation coefficients among EAA measures

Pearson correlation was used for the IEAA–EEAA pair; Spearman correlation was applied for all other pairs.

* P < .001

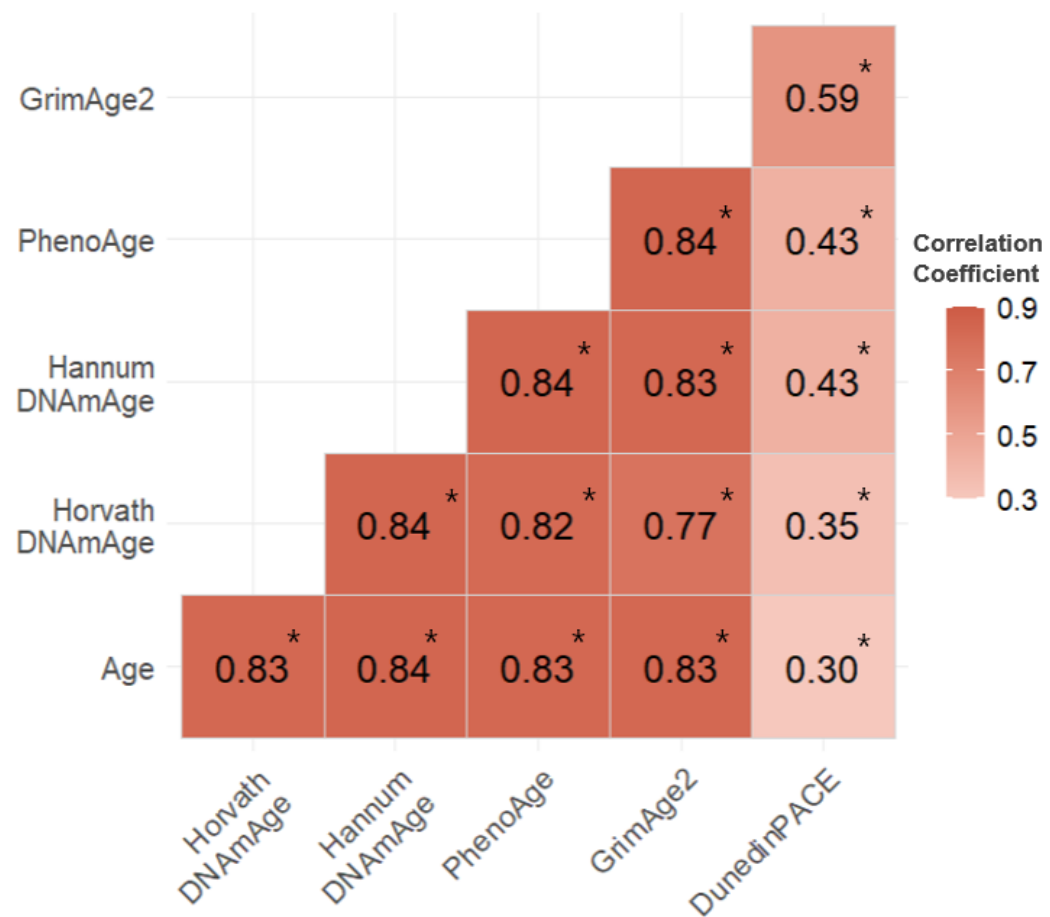


Figure S3. Spearman's correlations among epigenetic age measures and chronological age

* P< .001

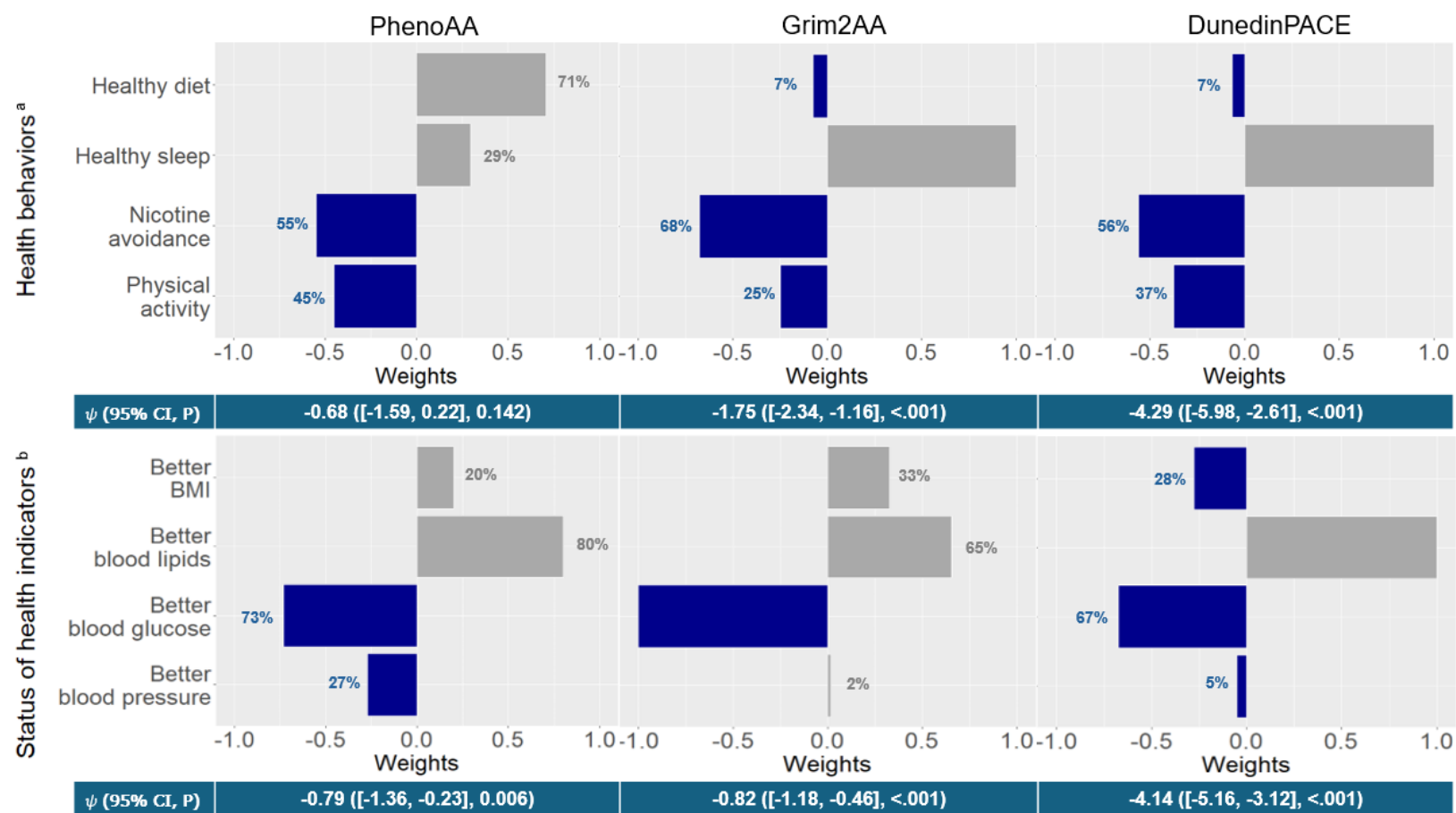


Figure S4. Collective association and relative contribution of CVH components to EAA in total participants

† *Blue*: negative contribution of health components to association; *Grey*: positive contribution of health components to association

ψ represents the mixture association.

^a Adjusted for chronological age, sex, marital status, education level, household income, job, current drinking, no. of comorbidities, and four health behaviours.

^b Adjusted for chronological age, sex, marital status, education level, household income, job, current drinking, no. of comorbidities, and four health indicators.