SUPPLEMENTARY TABLES

Supplementary Table 1. Descriptive data of the three generations DNA methylation.

	Total	Age <65	Age ≥65
	(*n* = 1789)	(*n* = 804)	(*n* = 985)
Chronological age(years)	58 (± 12)	48 (± 7.3)	67 (± 6.5)
First generation			
Hannum	62 (± 9.0)	55 (± 6.3)	68 (± 5.8)
Horvath2	53 (± 7.9)	47 (± 5.6)	58 (± 5.7)
Second generation			
PhenoAge	52 (± 9.7)	45 (± 7.1)	59 (± 6.7)
GrimAge	69 (± 9.5)	61 (± 6.6)	75 (± 6.0)
Third generation			
DunedinPACE	1.1 (± 0.12)	1.0 (± 0.11)	1.1 (± 0.11)

The chronological age, first−generation and second−generation epigenetic clock measure age in years. The third−generation epigenetic clock measure aging in pace of aging. Mean with standard deviation is reported for each cell.

Supplementary Table 2. Descriptive data of advance aging in different sex groups.

	Total	Male	Female
	(*n* = 1789)	(*n* = 834)	(*n* = 955)
First Generation			
Hannum	49.6	66.2	35.1
Horvath	49.1	56.2	42.8
Second Generation			
PhenoAge	47.6	53.7	42.3
GrimAge	40.4	57.4	25.4
Third Generation			
DunedinPACE	65.0	67.6	62.7

This table shows the percentage of participants with advanced aging.

Supplementary Table 3. Interaction analysis between epigenetic age residual and age at dDCT age.

	Coefficient of interaction term	Coefficient of DNAm age residual	Coefficient of age at dCDT	*P*−Value of interaction term
DunedinPACE	−0.9	41.6	0.42	0.004*
Hannum	−0.002	−0.06	−0.50	0.880
Horvath	−0.009	0.40	−0.50	0.302
PhenoAge	−0.0007	−0.23	−0.50	0.931
GrimAge	0.001	−0.40	−0.50	0.928

Supplementary Table 4. Interaction analysis between epigenetic age residual and sex.

	Coefficient of interaction term	Coefficient of DNAm age residual	Coefficient of sex	*P*−Value of interaction term
DunedinPACE	−0.3	−17.0	4.00	0.967
Hannum	−0.004	−0.16	4.04	0.989
Horvath	0.04	−0.30	4.20	0.844

PhenoAge	−0.04	−0.20	4.04	0.835
GrimAge	0.13	−0.50	3.65	0.629

Supplementary Table 5. Association analysis between dCDT scores and DNA methylation−based plasma protein levels in GrimAge estimation.

	Total	**Age < 65**	**Age ≥65**
	(*n* = 1789)	**(*n* = 804)**	**(*n* = 985)**
dCDTScore			
ADM	−2.86 (−4.69, −1.04)	−2.93 (−5.38, −0.49)	−3.11 (−5.63, −0.59)
B2M	−0.87 (−1.95, 0.21)	−1.13 (−2.55, 0.28)	−1.37 (−2.88, 0.14)
CystatinC	−0.58 (−1.67, 0.50)	−0.12 (−1.41, 1.16)	−1.94 (−3.69, −0.20)
GDF15	−1.02 (−2.10, 0.06)	−0.86 (−2.24, 0.52)	−1.73 (−3.33, −0.13)
Leptin	−2.25 (−5.80, 1.29)	−0.88 (−6.63, 4.84)	−2.33 (−6.86, 2.20)
PAI1	−2.33 (−3.53, −1.13)	−1.91 (−3.49, −0.34)	−2.54 (−4.20, −0.88)
TIMP1	−1.47 (−3.00, 0.05)	−1.22 (−3.29, 0.85)	−2.82 (−4.96, −0.68)
COPDrawingEfficiency			
ADM	−0.49 (−1.30, 0.31)	−0.36 (−1.60, −0.87)	−0.81(−1.85, 0.23)
B2M	0.01 (−0.47, 0.49)	0.36 (−0.35, 1.08)	−0.42 (−1.04, 0.21)
CystatinC	−0.16 (−0.64, 0.32)	−0.28 (−0.94, 0.37)	−0.35 (−1.07, 0.37)
GDF15	−0.03 (−0.51, 0.44)	−0.34 (−1.04, 0.36)	−0.11 (−0.78, 0.55)
Leptin	−0.26 (−1.83, 1.30)	−0.81 (−3.69, 2.05)	−0.25 (−2.13, 1.63)
PAI1	−0.56 (−1.09, −0.03)	−0.37 (−1.17, 0.43)	−0.64 (−1.32, 0.05)
TIMP1	−0.25 (−0.92, 0.42)	−0.17 (−1.21, 0.87)	−0.51 (−1.40, 0.38)
COPSimpleMotor			
ADM	−0.99 (−1.57, −0.40)	−1.30 (−2.18, −0.43)	−0.94 (−1.73, −0.15)
B2M	−0.39 (−0.74, −0.04)	−0.43 (−0.94, 0.07)	−0.46 (−0.94, 0.01)
CystatinC	−0.29 (−0.64, 0.06)	−0.46 (−0.93, 0.01)	−0.25 (−0.80, 0.29)
GDF15	−0.60 (−0.95, −0.25)	−0.78 (−1.28, −0.28)	−0.61 (−1.12, −0.11)
Leptin	0.12 (−1.03, 1.26)	−0.39 (−2.43, 1.65)	0.08 (−1.34, 1.50)
PAI1	−0.74 (−1.13, −0.35)	−0.82 (−1.38, −0.25)	−0.66 (−1.18, −0.14)
TIMP1	−0.42 (−0.91, 0.07)	−0.70 (−1.45, 0.04)	−0.37 (−1.04, 0.31)
COPInformationProcessing			
ADM	−0.02 (−1.00, 0.97)	1.16 (−0.29, −2.61)	−0.80 (−2.12, 0.52)
B2M	0.11 (−0.49, 0.69)	0.80 (−0.04, 1.64)	−0.50 (−1.30, 0.29)
CystatinC	0.12 (−0.47, 0.69)	0.07 (−0.70, 0.85)	−0.37 (−1.28, 0.55)
GDF15	0.17 (−0.41, 0.76)	0.09 (−0.73, 0.91)	−0.11 (−0.95, 0.73)
Leptin	−0.53 (−2.45, 1.38)	−0.28 (−3.66, 3.10)	−0.77 (−3.14, 1.60)
PAI1	−0.60 (−1.25, 0.05)	−0.004 (−0.93, 0.94)	−0.94 (−1.81, −0.07)
TIMP1	−0.38 (−1.20, 0.44)	0.04 (−1.19, 1.27)	−1.15 (−2.27, −0.03)
COPSpatialReasoning			
ADM	−3.02 (−4.65, −1.39)	−2.86 (−5.29, −0.44)	−3.23 (−5.41, −1.06)
B2M	−1.04 (−2.01, −0.08)	−1.44 (−2.85, −0.04)	−1.14 (−2.45, 0.17)
CystatinC	−0.58 (−1.55, 0.39)	−0.74 (−0.54, 2.03)	−1.59 (−3.10, −0.07)
GDF15	−0.70 (−1.68, 0.27)	0.13 (−1.24, 1.51)	−1.07 (−2.47, 0.32)
Leptin	−5.79 (−8.95, −2.63)	−6.21 (−11.87, −0.58)	−5.09 (−9.01, −1.17)
PAI1	−1.71 (−2.78, −0.63)	−2.10 (−3.67, −0.54)	−1.42 (−2.86, 0.02)
TIMP1	−1.57 (−2.93, −0.21)	−0.99 (−3.05, 1.06)	−2.05 (−3.91, −0.19)

COMDrawingEfficiency			
ADM	−0.05 (−1.04, 0.93)	−0.42 (−1.91, 1.07)	−0.04 (−1.33, 1.25)
B2M	0.33 (−0.25, 0.91)	0.15 (−0.72, 1.01)	0.12 (−0.65, 0.89)
CystatinC	0.16 (−0.42, 0.75)	−0.11 (−0.90, 0.67)	−0.08 (−0.97, 0.82)
GDF15	0.10 (−0.49, 0.68)	−0.13 (−0.97, 0.72)	−0.11 (−0.93, 0.71)
Leptin	1.27 (−0.65, 3.18)	3.09 (−0.39, 6.56)	0.54 (−1.77, 2.85)
PAI1	0.08 (−0.57, 0.72)	0.25 (−0.71, 1.22)	0.04 (−0.81, 0.89)
TIMP1	0.29 (−0.54, 1.11)	0.19 (−1.07, 1.45)	−0.07 (−1.17, 1.02)
COMInformationProcessing			
ADM	−1.00 (−1.74, −0.25)	−0.38 (−1.48, 0.71)	−1.58 (−2.58, −0.58)
B2M	−0.45 (−0.89, −0.01)	−0.35 (−0.98, 0.28)	−0.64 (−1.24, −0.04)
CystatinC	−0.65 (−1.09, −0.21)	−0.75 (−1.33, −0.16)	−0.79 (−1.49, −0.10)
GDF15	−0.78 (−1.22, −0.34)	−0.89 (−1.51, −0.27)	−0.89 (−1.53, −0.25)
Leptin	−0.22 (−1.67, 1.22)	0.50 (−2.04, 3.04)	−0.52 (−2.32, 1.29)
PAI1	−0.83 (−1.32, −0.34)	−0.38 (−1.09, 0.33)	−1.07 (−1.74, −0.41)
TIMP1	−0.83 (−1.45, −0.21)	−0.95 (−1.88, −0.02)	−0.94 (−1.79, −0.08)
COMSpatialReasoning			
ADM	−0.33 (−1.20, 0.54)	−0.31 (−1.52, 0.90)	−0.30 (−1.51, 0.91)
B2M	0.19 (−0.32, 0.71)	0.37 (−0.33, 1.08)	−0.12 (−0.85, 0.60)
CystatinC	0.32 (−0.20, 0.84)	0.17 (−0.47, 0.82)	−0.08 (−0.91, 0.76)
GDF15	0.20 (−0.32, 0.72)	0.13 (−0.56, 0.81)	−0.13 (−0.90, 0.64)
Leptin	0.89 (−0.80, 2.57)	1.67 (−1.15, 4.48)	0.46 (−1.72, 2.63)
PAI1	−0.20 (−0.77, 0.37)	−0.13 (−0.91, 0.65)	−0.19 (−0.99, 0.61)
TIMP1	0.03 (−0.69, 0.76)	−0.01 (−1.03, 1.01)	−0.45 (−1.47, 0.58)
COPSpatialReasoning			
ADM	−0.94 (−2.48, 0.60)	−1.86 (−3.85, 0.13)	−0.48 (−2.70, 1.72)
B2M	−0.52 (−1.44, 0.39)	−1.04 (−2.19, 0.11)	−0.52 (−1.84, 0.80)
CystatinC	0.08 (−0.83, 1.00)	−0.25 (−1.30, 0.81)	−0.72 (−2.25, 0.81)
GDF15	−0.25 (−1.17, 0.66)	−0.61 (−1.73, 0.52)	−0.67 (−2.07, 0.74)
Leptin	0.62 (−2.37, 3.61)	0.13 (−4.53, 4.77)	1.14 (−2.82, 5.10)
PAI1	−1.18 (−2.20, −0.17)	−0.83 (−2.12, 0.45)	−1.46 (−2.92, −0.01)
TIMP1	−0.38 (−1.67, 0.91)	−0.87 (−2.55, 0.81)	−1.44 (−3.31, 0.44)

Note: Effect size with 95% confidence intervals is provided for each plasma protein level. Subdomain scores of dCDT copy task start with COP; subdomain scores dCDT command task start with COM. Detailed information about how each plasma protein level was used in GrimAge estimation can be found in a previous study [1].

SUPPLEMENTARY REFERENCE

1. Lu AT, Quach A, Wilson JG, Reiner AP, Aviv A, Raj K, Hou L, Baccarelli AA, Li Y, Stewart JD, Whitsel EA, Assimes TL, Ferrucci L, Horvath S. DNA methylation GrimAge strongly predicts lifespan and healthspan. Aging (Albany NY). 2019; 11:303–27. https://doi.org/10.18632/aging.101684
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