

Supplementary Information for “Bidirectional relationship between epigenetic age and stroke, dementia, and late-life depression”

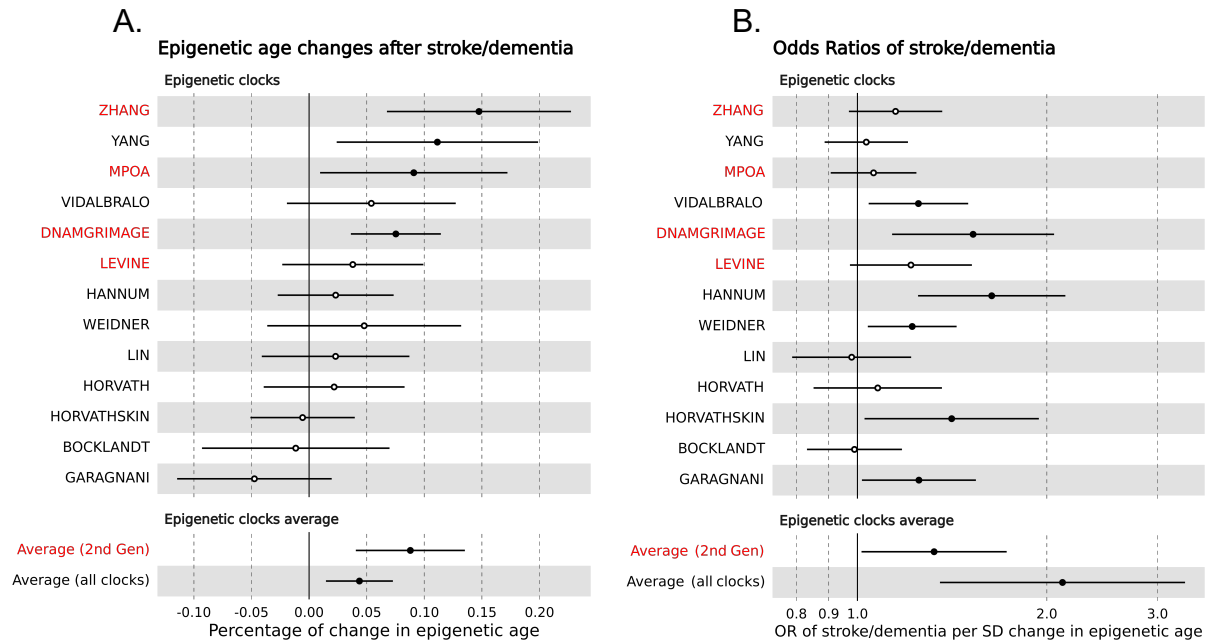
This appendix provides supplementary figures and tables for “Bidirectional relationship between epigenetic age and stroke, dementia, and late-life depression”.

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Supplementary Figures

Figure S1 | Associations between epigenetic ages and stroke or dementia events.



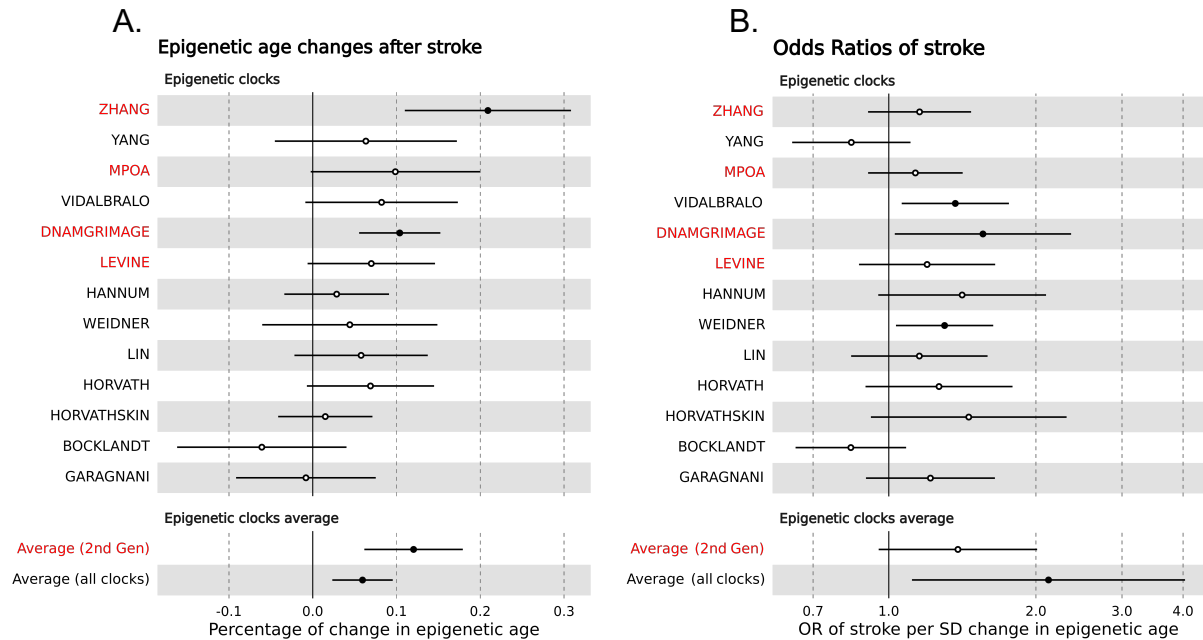
A. Cross-sectional analysis: percentage of change in epigenetic ages following a stroke or dementia after adjusting for chronological age, sex, race and ethnicity, hypertension, diabetes, smoking, BMI, history of heart attack, coronary artery disease, angina, or congestive heart failure. N = 4,018. Data are presented as linear regression coefficients and 95% confidence intervals.

B. Longitudinal analysis: Odds Ratios of stroke or dementia per one standard deviation increase in epigenetic age adjusting for chronological age, sex, race and ethnicity. N = 2,967. Data are presented as odds ratios and 95% confidence intervals.

The second-generation epigenetic clocks are highlighted in red.

Source data are provided as a Source Data file.

Figure S2 | Associations between epigenetic ages and stroke.



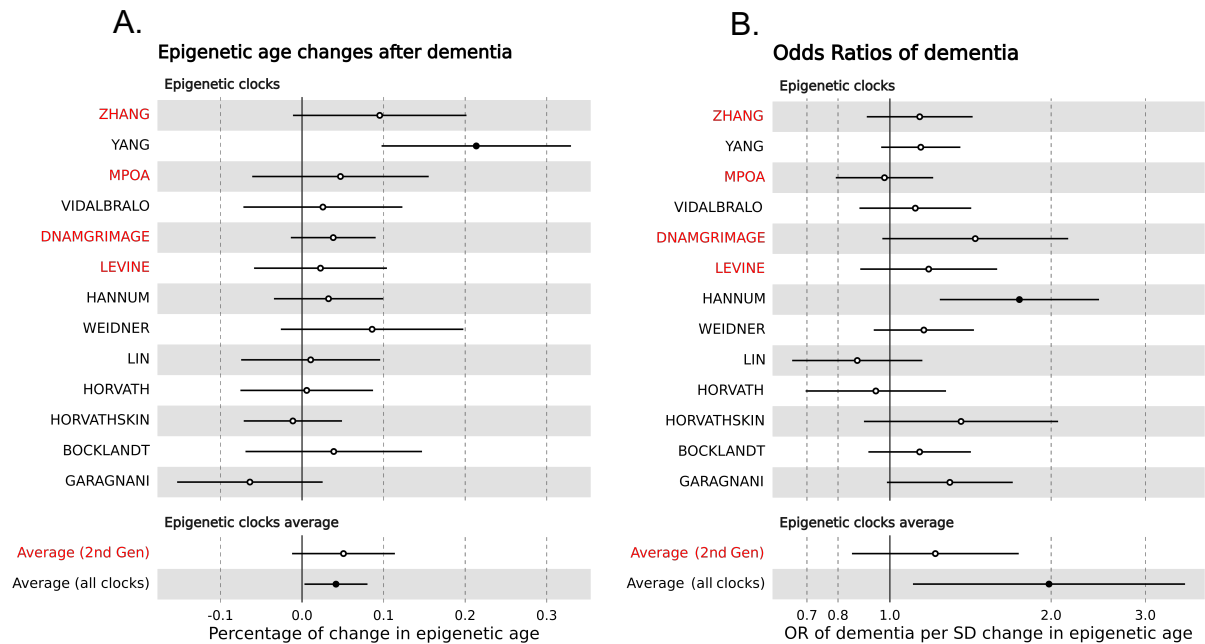
A. Cross-sectional analysis: percentage of change in epigenetic ages following a stroke after adjusting for chronological age, sex, race and ethnicity, hypertension, diabetes, smoking, BMI, history of heart attack, coronary artery disease, angina, or congestive heart failure. N = 4,018. Data are presented as linear regression coefficients and 95% confidence intervals.

B. Longitudinal analysis: Odds Ratios of stroke per one standard deviation increase in epigenetic age adjusting for chronological age, sex, race and ethnicity. N = 2,967. Data are presented as odds ratios and 95% confidence intervals.

The second-generation epigenetic clocks are highlighted in red.

Source data are provided as a Source Data file.

Figure S3 | Associations between epigenetic ages and dementia.



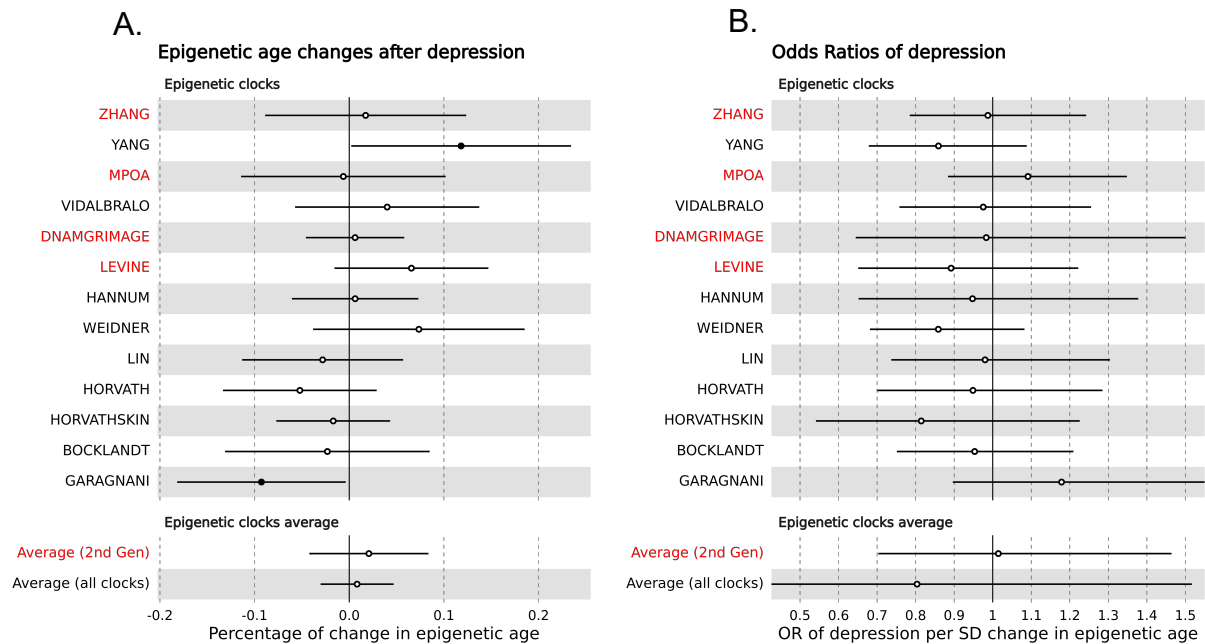
A. Cross-sectional analysis: percentage of change in epigenetic ages following dementia after adjusting for chronological age, sex, race and ethnicity, hypertension, diabetes, smoking, BMI, history of heart attack, coronary artery disease, angina, or congestive heart failure. N = 4,018. Data are presented as linear regression coefficients and 95% confidence intervals.

B. Longitudinal analysis: Odds Ratios of dementia per one standard deviation increase in epigenetic age adjusting for chronological age, sex, race and ethnicity. N = 2,967. Data are presented as odds ratios and 95% confidence intervals.

The second-generation epigenetic clocks are highlighted in red.

Source data are provided as a Source Data file.

Figure S4 | Associations between epigenetic ages and depression.



A. Cross-sectional analysis: percentage of change in epigenetic ages following a depression after adjusting for chronological age, sex, race and ethnicity, hypertension, diabetes, smoking, BMI, history of heart attack, coronary artery disease, angina, or congestive heart failure. N = 4,018. Data are presented as linear regression coefficients and 95% confidence intervals.

B. Longitudinal analysis: Odds Ratios of depression per one standard deviation increase in epigenetic age adjusting for chronological age, sex, race and ethnicity. N = 2,967. Data are presented as odds ratios and 95% confidence intervals.

The second-generation epigenetic clocks are highlighted in red.

Source data are provided as a Source Data file.

Supplementary Tables

Table S1 | Comparison between HRS whole cohort and subset with DNAm data

			Whole HRS cohort	Cohort with epigenetic data
N			42,406	4,018
Demographics				
Age at wave 13 (mean (SD))			66.16 (11.79)	69.94 (9.62)
Male gender			18643 (44.0)	1669 (41.5)
Race	White		30667 (72.3)	3013 (75.0)
	Black		8086 (19.1)	674 (16.8)
	Hispanic		2027 (4.8)	207 (5.2)
	Other		1590 (3.7)	122 (3.0)
Risk factors				
Smoking at wave 13	Non-missing	Past	8245 (39.6)	1776 (44.2)
		Never	9526 (45.7)	1764 (43.9)
		Current	3053 (14.7)	455 (11.3)
	Missing		21582 (50.9)	0 (0)
BMI at wave 13 (mean (SD))			27.76 (6.01)	29.30 (6.74)
Comorbidities				
Prevalent hypertension			25538 (60.2)	2559 (63.7)
Prevalent diabetes			10732 (25.3)	1151 (28.6)
Prevalent heart condition*			12946 (30.5)	1098 (27.3)

*Heart conditions include: heart attack, coronary artery disease, angina, congestive heart failure

Notes: The terms prevalent, respectively incident, refer to conditions having occurred before, respectively after, the epigenetic age estimation performed during wave 13 (2016). The smoking and BMI statistics were obtained after excluding participants missing these values at wave 13.

Table S2 | Descriptive Statistics of Epigenetic Clocks in our cohort (n=4,018).

Epigenetic Clock	mean	std	min	25%	50%	75%	max
HORVATH	65.72	9.62	23.31	59.16	65.28	72.03	114.52
HANNUM	54.59	9.23	25.06	47.81	53.91	60.65	107.79
LEVINE	57.48	10.08	26.72	50.37	56.85	63.96	101.68
HORVATHSKIN	69.61	8.85	36.97	63.00	69.04	75.97	101.29
LIN	58.41	11.08	1.91	50.97	57.73	65.12	133.27
WEIDNER	67.29	11.62	25.22	58.91	65.56	73.96	148.87
VIDALBRALO	63.76	6.19	36.47	59.48	63.37	67.42	109.95
YANG	0.07	0.02	0.03	0.06	0.07	0.08	0.23
ZHANG	-1.08	0.46	-2.53	-1.41	-1.10	-0.78	0.60
BOCKLANDT	0.39	0.08	0.10	0.34	0.39	0.44	0.89
GARAGNANI	0.72	0.07	0.43	0.67	0.71	0.76	0.99
DNAMGRIMAGE	68.13	8.63	42.67	61.35	67.71	74.42	99.61
MPOA	1.08	0.09	0.74	1.01	1.07	1.13	1.46

Table S3 | Multivariable linear regression results of epigenetic age changes in survivors of brain health events (stroke, dementia or late-life depression).

Model	Model 1		Model 2		Model 3	
Epigenetic clock	Beta (SE)	P value	Beta (SE)	P value	Beta (SE)	P value
<i>ZHANG</i>	0.41 (0.04)	4.28e-26	0.23 (0.04)	1.37e-09	0.13 (0.04)	3.60e-04
<i>YANG</i>	0.31 (0.04)	1.88e-15	0.12 (0.04)	0.002	0.12 (0.04)	0.003
<i>MPOA</i>	0.24 (0.04)	8.80e-10	0.21 (0.04)	2.65e-07	0.10 (0.04)	0.009
<i>VIDALBRALO</i>	0.45 (0.04)	9.71e-31	0.09 (0.03)	0.006	0.07 (0.03)	0.045
<i>DNAMGRIMAGE</i>	0.72 (0.04)	1.05e-77	0.15 (0.02)	3.05e-12	0.07 (0.02)	1.80e-04
<i>LEVINE</i>	0.60 (0.04)	4.71e-53	0.10 (0.03)	3.72e-04	0.05 (0.03)	0.051
<i>HANNUM</i>	0.60 (0.04)	7.42e-54	0.06 (0.02)	0.005	0.04 (0.02)	0.093
<i>WEIDNER</i>	0.30 (0.04)	2.27e-14	0.04 (0.04)	0.324	0.03 (0.04)	0.372
<i>LIN</i>	0.50 (0.04)	1.68e-37	0.03 (0.03)	0.385	0.01 (0.03)	0.660
<i>HORVATH</i>	0.52 (0.04)	5.03e-41	0.02 (0.03)	0.453	0.01 (0.03)	0.753
<i>HORVATHSKIN</i>	0.60 (0.04)	5.22e-54	0.02 (0.02)	0.428	-0.00 (0.02)	0.902
<i>BOCKLANDT</i>	-0.27 (0.04)	3.75e-12	-0.04 (0.04)	0.291	-0.03 (0.04)	0.394
<i>GARAGNANI</i>	0.44 (0.04)	4.68e-29	-0.03 (0.03)	0.367	-0.05 (0.03)	0.109
<i>Average (2nd Gen)</i>	0.49 (0.03)	1.80e-61	0.17 (0.02)	9.81e-13	0.09 (0.02)	5.53e-05
<i>Average (all clocks)</i>	0.42 (0.02)	2.42e-71	0.08 (0.01)	2.06e-08	0.04 (0.01)	0.002

Model 1: Unadjusted; Model 2: Adjusted for age, sex and race/ethnicity; Model 3: Adjusted for age, sex, race/ethnicity, hypertension, diabetes, smoking, BMI, history of heart attack, coronary artery disease, angina, congestive heart failure
P-values provided are unadjusted and based on two-sided t-tests.

Table S4 | Multivariable logistic regression results: Odds Ratios of brain health events (stroke, dementia or late-life depression) per one standard deviation increase in epigenetic age

Model	Model 1		Model 2		Model 3	
Epigenetic clock	OR (95%CI)	P value	OR (95%CI)	P value	OR (95%CI)	P value
<i>ZHANG</i>	1.30 (1.14-1.48)	6.53e-05	1.10 (0.95-1.27)	0.195	1.03 (0.89-1.20)	0.699
<i>YANG</i>	1.14 (1.01-1.29)	0.033	1.00 (0.88-1.14)	0.984	1.00 (0.88-1.14)	0.990
<i>MPOA</i>	1.09 (0.96-1.24)	0.172	1.08 (0.94-1.23)	0.268	1.00 (0.86-1.16)	0.992
<i>VIDALBRALO</i>	1.52 (1.34-1.73)	1.02e-10	1.19 (1.02-1.39)	0.031	1.17 (1.00-1.37)	0.052
<i>DNAMGRIMAGE</i>	1.80 (1.57-2.06)	2.25e-17	1.37 (1.07-1.77)	0.014	1.21 (0.89-1.64)	0.232
<i>LEVINE</i>	1.59 (1.40-1.82)	2.44e-12	1.12 (0.93-1.36)	0.232	1.07 (0.88-1.30)	0.497
<i>HANNUM</i>	1.79 (1.57-2.05)	5.43e-18	1.44 (1.14-1.81)	0.002	1.38 (1.09-1.75)	0.007
<i>WEIDNER</i>	1.35 (1.19-1.53)	1.95e-06	1.12 (0.98-1.29)	0.098	1.13 (0.98-1.30)	0.090
<i>LIN</i>	1.47 (1.29-1.68)	8.17e-09	0.96 (0.80-1.16)	0.679	0.95 (0.79-1.15)	0.611
<i>HORVATH</i>	1.57 (1.37-1.79)	5.68e-11	1.04 (0.85-1.26)	0.727	1.02 (0.84-1.24)	0.840
<i>HORVATHSKIN</i>	1.73 (1.51-1.99)	2.47e-15	1.17 (0.90-1.53)	0.236	1.13 (0.86-1.48)	0.370
<i>BOCKLANDT</i>	0.78 (0.68-0.89)	2.43e-04	0.97 (0.84-1.13)	0.695	0.98 (0.84-1.13)	0.752
<i>GARAGNANI</i>	1.67 (1.47-1.90)	4.68e-15	1.29 (1.09-1.54)	0.004	1.28 (1.07-1.52)	0.006
<i>Average (2nd Gen)</i>	1.81 (1.53-2.15)	1.21e-11	1.24 (0.99-1.56)	0.060	1.09 (0.84-1.40)	0.527
<i>Average (all clocks)</i>	2.62 (2.10-3.25)	5.48e-18	1.70 (1.16-2.50)	0.007	1.48 (0.99-2.21)	0.057

Model 1: Unadjusted; Model 2: Adjusted for age, sex and race/ethnicity; Model 3: Adjusted for age, sex, race/ethnicity, hypertension, diabetes, smoking, BMI, history of heart attack, coronary artery disease, angina, congestive heart failure
P-values provided are unadjusted and based on two-sided Wald tests.

Table S5 | Multivariable linear regression results of epigenetic age changes in participants with stroke or dementia

Model	Model 1		Model 2		Model 3	
Epigenetic clock	Beta (SE)	P value	Beta (SE)	P value	Beta (SE)	P value
<i>ZHANG</i>	0.36 (0.04)	1.43e-15	0.25 (0.04)	1.63e-09	0.15 (0.04)	3.01e-04
<i>YANG</i>	0.27 (0.04)	1.22e-09	0.12 (0.04)	0.007	0.11 (0.04)	0.013
<i>MPOA</i>	0.27 (0.04)	2.07e-09	0.21 (0.05)	3.22e-06	0.09 (0.04)	0.029
<i>VIDALBRALO</i>	0.26 (0.04)	4.01e-09	0.08 (0.04)	0.031	0.05 (0.04)	0.149
<i>DNAMGRIMAGE</i>	0.51 (0.04)	1.24e-29	0.16 (0.02)	7.18e-12	0.08 (0.02)	1.60e-04
<i>LEVINE</i>	0.37 (0.04)	2.76e-16	0.09 (0.03)	0.006	0.04 (0.03)	0.225
<i>HANNUM</i>	0.34 (0.04)	5.31e-14	0.05 (0.03)	0.044	0.02 (0.03)	0.369
<i>WEIDNER</i>	0.19 (0.04)	1.57e-05	0.05 (0.04)	0.235	0.05 (0.04)	0.265
<i>LIN</i>	0.29 (0.04)	8.12e-11	0.03 (0.03)	0.295	0.02 (0.03)	0.482
<i>HORVATH</i>	0.31 (0.04)	3.36e-12	0.03 (0.03)	0.274	0.02 (0.03)	0.486
<i>HORVATHSKIN</i>	0.34 (0.04)	6.74e-14	0.01 (0.02)	0.531	-0.01 (0.02)	0.807
<i>BOCKLANDT</i>	-0.12 (0.05)	0.010	-0.02 (0.04)	0.657	-0.01 (0.04)	0.780
<i>GARAGNANI</i>	0.23 (0.04)	4.36e-07	-0.02 (0.03)	0.489	-0.05 (0.03)	0.166
<i>Average (2nd Gen)</i>	0.38 (0.03)	9.72e-28	0.18 (0.03)	2.78e-11	0.09 (0.02)	2.77e-04
<i>Average (all clocks)</i>	0.28 (0.03)	6.79e-25	0.08 (0.02)	1.05e-07	0.04 (0.01)	0.003

Model 1: Unadjusted; Model 2: Adjusted for age, sex and race/ethnicity; Model 3: Adjusted for age, sex, race/ethnicity, hypertension, diabetes, smoking, BMI, history of heart attack, coronary artery disease, angina, congestive heart failure
P-values provided are unadjusted and based on two-sided t-tests.

Table S6 | Multivariable logistic regression results: Odds Ratios of stroke or dementia per one standard deviation increase in epigenetic age

Model	Model 1		Model 2		Model 3	
Epigenetic clock	OR (95%CI)	P value	OR (95%CI)	P value	OR (95%CI)	P value
<i>ZHANG</i>	1.33 (1.14-1.55)	3.29e-04	1.15 (0.97-1.36)	0.109	1.06 (0.88-1.27)	0.547
<i>YANG</i>	1.19 (1.03-1.37)	0.015	1.03 (0.89-1.20)	0.677	1.03 (0.88-1.20)	0.750
<i>MPOA</i>	1.10 (0.95-1.28)	0.219	1.06 (0.91-1.24)	0.461	0.96 (0.80-1.14)	0.605
<i>VIDALBRALO</i>	1.50 (1.30-1.74)	5.50e-08	1.25 (1.04-1.50)	0.016	1.23 (1.02-1.48)	0.028
<i>DNAMGRIMAGE</i>	1.79 (1.53-2.10)	9.60e-13	1.53 (1.14-2.05)	0.005	1.29 (0.90-1.85)	0.164
<i>LEVINE</i>	1.59 (1.36-1.85)	3.10e-09	1.22 (0.97-1.52)	0.086	1.16 (0.92-1.45)	0.214
<i>HANNUM</i>	1.77 (1.51-2.06)	6.31e-13	1.63 (1.25-2.14)	3.53e-04	1.57 (1.20-2.06)	0.001
<i>WEIDNER</i>	1.41 (1.22-1.63)	4.24e-06	1.22 (1.04-1.44)	0.016	1.23 (1.05-1.45)	0.012
<i>LIN</i>	1.42 (1.22-1.66)	8.89e-06	0.98 (0.79-1.22)	0.849	0.97 (0.78-1.21)	0.821
<i>HORVATH</i>	1.53 (1.30-1.79)	1.68e-07	1.08 (0.85-1.36)	0.535	1.07 (0.84-1.35)	0.583
<i>HORVATHSKIN</i>	1.72 (1.47-2.02)	3.71e-11	1.41 (1.03-1.94)	0.034	1.37 (0.99-1.88)	0.057
<i>BOCKLANDT</i>	0.82 (0.70-0.96)	0.016	0.99 (0.83-1.18)	0.903	1.00 (0.84-1.19)	0.969
<i>GARAGNANI</i>	1.57 (1.35-1.83)	4.45e-09	1.25 (1.02-1.54)	0.035	1.22 (0.99-1.51)	0.061
<i>Average (2nd Gen)</i>	1.83 (1.49-2.24)	6.17e-09	1.32 (1.02-1.73)	0.038	1.12 (0.83-1.51)	0.476
<i>Average (all clocks)</i>	2.62 (2.02-3.38)	1.84e-13	2.12 (1.35-3.32)	0.001	1.79 (1.12-2.87)	0.015

Model 1: Unadjusted; Model 2: Adjusted for age, sex and race/ethnicity; Model 3: Adjusted for age, sex, race/ethnicity, hypertension, diabetes, smoking, BMI, history of heart attack, coronary artery disease, angina, congestive heart failure
P-values provided are unadjusted and based on two-sided Wald tests.

Table S7 | Multivariable linear regression results of epigenetic age changes in participants with stroke

Model	Model 1		Model 2		Model 3	
Epigenetic clock	Beta (SE)	P value	Beta (SE)	P value	Beta (SE)	P value
<i>ZHANG</i>	0.47 (0.06)	6.04e-17	0.34 (0.05)	4.63e-11	0.21 (0.05)	3.69e-05
<i>YANG</i>	0.17 (0.06)	0.003	0.05 (0.05)	0.348	0.06 (0.06)	0.253
<i>MPOA</i>	0.31 (0.06)	2.57e-08	0.26 (0.06)	2.43e-06	0.10 (0.05)	0.056
<i>VIDALBRALO</i>	0.31 (0.06)	3.86e-08	0.12 (0.05)	0.011	0.08 (0.05)	0.077
<i>DNAMGRIMAGE</i>	0.54 (0.06)	4.06e-22	0.22 (0.03)	1.50e-13	0.10 (0.02)	2.77e-05
<i>LEVINE</i>	0.40 (0.06)	2.28e-12	0.14 (0.04)	4.33e-04	0.07 (0.04)	0.072
<i>HANNUM</i>	0.34 (0.06)	2.01e-09	0.06 (0.03)	0.055	0.03 (0.03)	0.371
<i>WEIDNER</i>	0.18 (0.06)	0.001	0.04 (0.05)	0.410	0.04 (0.05)	0.407
<i>LIN</i>	0.32 (0.06)	1.56e-08	0.07 (0.04)	0.066	0.06 (0.04)	0.155
<i>HORVATH</i>	0.35 (0.06)	7.51e-10	0.08 (0.04)	0.026	0.07 (0.04)	0.075
<i>HORVATHSKIN</i>	0.34 (0.06)	1.34e-09	0.04 (0.03)	0.155	0.02 (0.03)	0.601
<i>BOCKLANDT</i>	-0.20 (0.06)	5.06e-04	-0.08 (0.05)	0.126	-0.06 (0.05)	0.239
<i>GARAGNANI</i>	0.24 (0.06)	2.35e-05	0.02 (0.04)	0.717	-0.01 (0.04)	0.848
<i>Average (2nd Gen)</i>	0.43 (0.04)	1.77e-23	0.24 (0.03)	4.66e-13	0.12 (0.03)	6.11e-05
<i>Average (all clocks)</i>	0.29 (0.03)	1.51e-17	0.11 (0.02)	2.49e-08	0.06 (0.02)	0.001

Model 1: Unadjusted; Model 2: Adjusted for age, sex and race/ethnicity; Model 3: Adjusted for age, sex, race/ethnicity, hypertension, diabetes, smoking, BMI, history of heart attack, coronary artery disease, angina, congestive heart failure
P-values provided are unadjusted and based on two-sided t-tests.

Table S8 | Multivariable logistic regression results: Odds Ratios of stroke per one standard deviation increase in epigenetic age

Model	Model 1		Model 2		Model 3	
Epigenetic clock	OR (95%CI)	P value	OR (95%CI)	P value	OR (95%CI)	P value
<i>ZHANG</i>	1.21 (0.97-1.52)	0.093	1.16 (0.91-1.47)	0.241	1.08 (0.83-1.40)	0.552
<i>YANG</i>	0.91 (0.69-1.18)	0.462	0.84 (0.63-1.11)	0.215	0.81 (0.61-1.08)	0.147
<i>MPOA</i>	1.14 (0.92-1.42)	0.231	1.13 (0.91-1.42)	0.270	1.06 (0.82-1.37)	0.648
<i>VIDALBRALO</i>	1.40 (1.14-1.72)	0.001	1.37 (1.06-1.76)	0.015	1.35 (1.04-1.74)	0.023
<i>DNAMGRIMAGE</i>	1.42 (1.13-1.78)	0.003	1.56 (1.03-2.36)	0.036	1.49 (0.88-2.51)	0.139
<i>LEVINE</i>	1.31 (1.05-1.64)	0.018	1.20 (0.87-1.65)	0.270	1.13 (0.81-1.57)	0.484
<i>HANNUM</i>	1.36 (1.08-1.70)	0.008	1.41 (0.95-2.10)	0.087	1.33 (0.89-1.99)	0.169
<i>WEIDNER</i>	1.36 (1.10-1.68)	0.004	1.30 (1.03-1.64)	0.025	1.31 (1.04-1.64)	0.022
<i>LIN</i>	1.29 (1.03-1.61)	0.028	1.15 (0.84-1.59)	0.380	1.16 (0.83-1.60)	0.384
<i>HORVATH</i>	1.35 (1.08-1.70)	0.010	1.27 (0.90-1.79)	0.181	1.26 (0.89-1.78)	0.199
<i>HORVATHSKIN</i>	1.38 (1.10-1.74)	0.006	1.46 (0.92-2.31)	0.109	1.38 (0.87-2.20)	0.176
<i>BOCKLANDT</i>	0.79 (0.63-1.00)	0.053	0.84 (0.64-1.09)	0.179	0.84 (0.64-1.08)	0.176
<i>GARAGNANI</i>	1.32 (1.06-1.65)	0.014	1.22 (0.90-1.65)	0.205	1.18 (0.87-1.60)	0.281
<i>Average (2nd Gen)</i>	1.50 (1.11-2.01)	0.007	1.38 (0.95-2.01)	0.087	1.24 (0.80-1.92)	0.328
<i>Average (all clocks)</i>	1.81 (1.25-2.62)	0.002	2.12 (1.12-4.04)	0.022	1.81 (0.92-3.57)	0.088

Model 1: Unadjusted; Model 2: Adjusted for age, sex and race/ethnicity; Model 3: Adjusted for age, sex, race/ethnicity, hypertension, diabetes, smoking, BMI, history of heart attack, coronary artery disease, angina, congestive heart failure
P-values provided are unadjusted and based on two-sided Wald tests.

Table S9 | Multivariable linear regression results of epigenetic age changes in participants with dementia

Model	Model 1		Model 2		Model 3	
Epigenetic clock	Beta (SE)	P value	Beta (SE)	P value	Beta (SE)	P value
<i>ZHANG</i>	0.25 (0.06)	3.42e-05	0.15 (0.06)	0.006	0.10 (0.05)	0.079
<i>YANG</i>	0.44 (0.06)	2.77e-13	0.24 (0.06)	3.91e-05	0.21 (0.06)	3.16e-04
<i>MPOA</i>	0.19 (0.06)	0.002	0.10 (0.06)	0.087	0.05 (0.06)	0.394
<i>VIDALBRALO</i>	0.21 (0.06)	3.91e-04	0.03 (0.05)	0.485	0.03 (0.05)	0.607
<i>DNAMGRIMAGE</i>	0.46 (0.06)	3.27e-14	0.09 (0.03)	0.007	0.04 (0.03)	0.149
<i>LEVINE</i>	0.34 (0.06)	1.20e-08	0.04 (0.04)	0.343	0.02 (0.04)	0.586
<i>HANNUM</i>	0.35 (0.06)	1.00e-08	0.05 (0.03)	0.142	0.03 (0.03)	0.341
<i>WEIDNER</i>	0.24 (0.06)	7.62e-05	0.09 (0.06)	0.122	0.09 (0.06)	0.132
<i>LIN</i>	0.28 (0.06)	2.97e-06	0.01 (0.04)	0.801	0.01 (0.04)	0.808
<i>HORVATH</i>	0.30 (0.06)	4.46e-07	0.01 (0.04)	0.837	0.01 (0.04)	0.890
<i>HORVATHSKIN</i>	0.34 (0.06)	2.02e-08	-0.00 (0.03)	0.920	-0.01 (0.03)	0.714
<i>BOCKLANDT</i>	-0.03 (0.06)	0.563	0.04 (0.05)	0.415	0.04 (0.06)	0.481
<i>GARAGNANI</i>	0.23 (0.06)	1.68e-04	-0.05 (0.05)	0.317	-0.06 (0.05)	0.160
<i>Average (2nd Gen)</i>	0.31 (0.05)	2.38e-11	0.10 (0.04)	0.008	0.05 (0.03)	0.114
<i>Average (all clocks)</i>	0.28 (0.04)	3.01e-14	0.06 (0.02)	0.002	0.04 (0.02)	0.035

Model 1: Unadjusted; Model 2: Adjusted for age, sex and race/ethnicity; Model 3: Adjusted for age, sex, race/ethnicity, hypertension, diabetes, smoking, BMI, history of heart attack, coronary artery disease, angina, congestive heart failure
P-values provided are unadjusted and based on two-sided t-tests.

Table S10 | Multivariable logistic regression results: Odds Ratios of dementia per one standard deviation increase in epigenetic age

Model	Model 1		Model 2		Model 3	
Epigenetic clock	OR (95%CI)	P value	OR (95%CI)	P value	OR (95%CI)	P value
<i>ZHANG</i>	1.43 (1.17-1.75)	4.44e-04	1.14 (0.91-1.43)	0.270	1.05 (0.82-1.33)	0.716
<i>YANG</i>	1.36 (1.16-1.58)	1.00e-04	1.14 (0.96-1.35)	0.126	1.14 (0.96-1.36)	0.125
<i>MPOA</i>	1.04 (0.85-1.27)	0.699	0.98 (0.79-1.20)	0.828	0.87 (0.69-1.09)	0.215
<i>VIDALBRALO</i>	1.54 (1.28-1.85)	4.55e-06	1.12 (0.88-1.42)	0.373	1.11 (0.87-1.41)	0.418
<i>DNAMGRIMAGE</i>	2.14 (1.74-2.65)	1.49e-12	1.44 (0.97-2.15)	0.072	1.15 (0.72-1.85)	0.555
<i>LEVINE</i>	1.80 (1.48-2.19)	3.01e-09	1.18 (0.88-1.59)	0.267	1.14 (0.85-1.54)	0.387
<i>HANNUM</i>	2.13 (1.74-2.60)	9.47e-14	1.75 (1.24-2.46)	0.001	1.71 (1.21-2.42)	0.002
<i>WEIDNER</i>	1.45 (1.20-1.75)	1.12e-04	1.16 (0.93-1.44)	0.184	1.17 (0.94-1.45)	0.149
<i>LIN</i>	1.55 (1.27-1.89)	1.84e-05	0.87 (0.66-1.15)	0.326	0.87 (0.65-1.15)	0.317
<i>HORVATH</i>	1.68 (1.37-2.06)	8.55e-07	0.94 (0.70-1.27)	0.694	0.93 (0.69-1.26)	0.660
<i>HORVATHSKIN</i>	2.06 (1.66-2.54)	2.66e-11	1.36 (0.89-2.06)	0.151	1.34 (0.88-2.04)	0.178
<i>BOCKLANDT</i>	0.84 (0.68-1.04)	0.109	1.14 (0.91-1.42)	0.256	1.15 (0.92-1.43)	0.223
<i>GARAGNANI</i>	1.80 (1.48-2.18)	2.40e-09	1.29 (0.99-1.70)	0.062	1.28 (0.98-1.69)	0.072
<i>Average (2nd Gen)</i>	2.10 (1.61-2.73)	3.82e-08	1.22 (0.85-1.74)	0.285	1.00 (0.67-1.49)	0.997
<i>Average (all clocks)</i>	3.39 (2.44-4.70)	3.53e-13	1.98 (1.10-3.56)	0.022	1.72 (0.94-3.16)	0.079

Model 1: Unadjusted; Model 2: Adjusted for age, sex and race/ethnicity; Model 3: Adjusted for age, sex, race/ethnicity, hypertension, diabetes, smoking, BMI, history of heart attack, coronary artery disease, angina, congestive heart failure
P-values provided are unadjusted and based on two-sided Wald tests.

Table S11 | Multivariable linear regression results of epigenetic age changes in participants with late-life depression

Model	Model 1		Model 2		Model 3	
Epigenetic clock	Beta (SE)	P value	Beta (SE)	P value	Beta (SE)	P value
<i>ZHANG</i>	0.43 (0.06)	1.45e-13	0.08 (0.06)	0.160	0.02 (0.05)	0.749
<i>YANG</i>	0.38 (0.06)	6.19e-11	0.12 (0.06)	0.050	0.12 (0.06)	0.046
<i>MPOA</i>	0.09 (0.06)	0.142	0.07 (0.06)	0.264	-0.01 (0.06)	0.910
<i>VIDALBRALO</i>	0.73 (0.06)	1.28e-36	0.06 (0.05)	0.248	0.04 (0.05)	0.420
<i>DNAMGRIMAGE</i>	1.05 (0.06)	3.08e-76	0.06 (0.03)	0.059	0.01 (0.03)	0.816
<i>LEVINE</i>	0.97 (0.06)	3.73e-65	0.09 (0.04)	0.028	0.07 (0.04)	0.113
<i>HANNUM</i>	1.00 (0.06)	8.75e-69	0.02 (0.03)	0.553	0.01 (0.03)	0.855
<i>WEIDNER</i>	0.54 (0.06)	7.69e-21	0.08 (0.06)	0.182	0.07 (0.06)	0.197
<i>LIN</i>	0.84 (0.06)	1.54e-48	-0.02 (0.04)	0.665	-0.03 (0.04)	0.517
<i>HORVATH</i>	0.86 (0.06)	1.05e-50	-0.04 (0.04)	0.300	-0.05 (0.04)	0.208
<i>HORVATHSKIN</i>	1.04 (0.06)	5.94e-75	-0.00 (0.03)	0.873	-0.02 (0.03)	0.582
<i>BOCKLANDT</i>	-0.50 (0.06)	5.64e-18	-0.03 (0.05)	0.577	-0.02 (0.06)	0.675
<i>GARAGNANI</i>	0.76 (0.06)	2.97e-40	-0.08 (0.05)	0.070	-0.09 (0.05)	0.041
<i>Average (2nd Gen)</i>	0.63 (0.04)	5.54e-47	0.07 (0.04)	0.038	0.02 (0.03)	0.518
<i>Average (all clocks)</i>	0.63 (0.03)	5.73e-75	0.03 (0.02)	0.143	0.01 (0.02)	0.673

Model 1: Unadjusted; Model 2: Adjusted for age, sex and race/ethnicity; Model 3: Adjusted for age, sex, race/ethnicity, hypertension, diabetes, smoking, BMI, history of heart attack, coronary artery disease, angina, congestive heart failure
P-values provided are unadjusted and based on two-sided t-tests.

Table S12 | Multivariable logistic regression results: Odds Ratios of late-life depression per one standard deviation increase in epigenetic age

Model	Model 1		Model 2		Model 3	
Epigenetic clock	OR (95%CI)	P value	OR (95%CI)	P value	OR (95%CI)	P value
<i>ZHANG</i>	1.21 (0.99-1.48)	0.069	0.99 (0.78-1.24)	0.914	0.97 (0.76-1.23)	0.791
<i>YANG</i>	0.95 (0.76-1.20)	0.668	0.86 (0.68-1.09)	0.208	0.88 (0.69-1.11)	0.276
<i>MPOA</i>	1.07 (0.88-1.32)	0.484	1.09 (0.88-1.35)	0.417	1.09 (0.86-1.38)	0.486
<i>VIDALBRALO</i>	1.37 (1.13-1.66)	0.001	0.98 (0.76-1.26)	0.846	0.97 (0.75-1.25)	0.791
<i>DNAMGRIMAGE</i>	1.60 (1.31-1.97)	6.67e-06	0.98 (0.64-1.50)	0.938	0.92 (0.56-1.51)	0.739
<i>LEVINE</i>	1.45 (1.19-1.77)	2.83e-04	0.89 (0.65-1.22)	0.476	0.85 (0.61-1.18)	0.335
<i>HANNUM</i>	1.58 (1.30-1.93)	4.22e-06	0.95 (0.65-1.38)	0.778	0.93 (0.63-1.37)	0.725
<i>WEIDNER</i>	1.12 (0.91-1.37)	0.287	0.86 (0.68-1.08)	0.197	0.86 (0.68-1.09)	0.206
<i>LIN</i>	1.50 (1.22-1.83)	8.59e-05	0.98 (0.74-1.30)	0.891	0.96 (0.72-1.29)	0.796
<i>HORVATH</i>	1.52 (1.23-1.87)	8.82e-05	0.95 (0.70-1.28)	0.734	0.92 (0.68-1.25)	0.603
<i>HORVATHSKIN</i>	1.59 (1.29-1.96)	1.56e-05	0.81 (0.54-1.23)	0.325	0.77 (0.51-1.17)	0.229
<i>BOCKLANDT</i>	0.73 (0.59-0.91)	0.005	0.95 (0.75-1.21)	0.693	0.96 (0.76-1.21)	0.723
<i>GARAGNANI</i>	1.61 (1.33-1.96)	1.62e-06	1.18 (0.90-1.55)	0.239	1.20 (0.91-1.59)	0.202
<i>Average (2nd Gen)</i>	1.59 (1.22-2.07)	5.89e-04	1.01 (0.70-1.46)	0.938	0.96 (0.64-1.45)	0.851
<i>Average (all clocks)</i>	2.06 (1.48-2.87)	2.03e-05	0.80 (0.43-1.52)	0.500	0.74 (0.38-1.45)	0.386

Model 1: Unadjusted; Model 2: Adjusted for age, sex and race/ethnicity; Model 3: Adjusted for age, sex, race/ethnicity, hypertension, diabetes, smoking, BMI, history of heart attack, coronary artery disease, angina, congestive heart failure
P-values provided are unadjusted and based on two-sided Wald tests.

Table S13 | Multivariable linear regression results of epigenetic age changes in survivors of brain health events (stroke, dementia or late-life depression) with late-life depression ascertained with a cutoff of 60 years.

Model	Model 1		Model 2		Model 3	
Epigenetic clock	Beta (SE)	P value	Beta (SE)	P value	Beta (SE)	P value
<i>ZHANG</i>	0.40 (0.04)	1.02e-28	0.25 (0.03)	1.63e-12	0.15 (0.03)	1.61e-05
<i>YANG</i>	0.30 (0.04)	1.27e-16	0.12 (0.04)	8.66e-04	0.12 (0.04)	0.001
<i>MPOA</i>	0.26 (0.04)	1.82e-12	0.23 (0.04)	7.14e-10	0.11 (0.03)	0.001
<i>VIDALBRALO</i>	0.40 (0.04)	1.54e-28	0.08 (0.03)	0.008	0.06 (0.03)	0.064
<i>DNAMGRIMAGE</i>	0.66 (0.03)	7.27e-77	0.15 (0.02)	1.55e-14	0.06 (0.02)	9.54e-05
<i>LEVINE</i>	0.56 (0.04)	1.27e-54	0.11 (0.03)	1.49e-05	0.07 (0.03)	0.010
<i>HANNUM</i>	0.55 (0.04)	2.69e-53	0.07 (0.02)	9.70e-04	0.05 (0.02)	0.032
<i>WEIDNER</i>	0.28 (0.04)	1.35e-14	0.04 (0.03)	0.215	0.04 (0.04)	0.242
<i>LIN</i>	0.46 (0.04)	7.84e-37	0.03 (0.03)	0.240	0.02 (0.03)	0.451
<i>HORVATH</i>	0.47 (0.04)	4.80e-39	0.02 (0.03)	0.457	0.01 (0.03)	0.790
<i>HORVATHSKIN</i>	0.56 (0.04)	2.62e-54	0.03 (0.02)	0.105	0.01 (0.02)	0.517
<i>BOCKLANDT</i>	-0.25 (0.04)	3.24e-12	-0.05 (0.03)	0.151	-0.04 (0.03)	0.240
<i>GARAGNANI</i>	0.42 (0.04)	1.96e-31	0.00 (0.03)	0.984	-0.02 (0.03)	0.471
<i>Average (2nd Gen)</i>	0.47 (0.03)	1.96e-65	0.18 (0.02)	7.26e-17	0.10 (0.02)	1.37e-06
<i>Average (all clocks)</i>	0.39 (0.02)	6.39e-73	0.08 (0.01)	3.18e-11	0.05 (0.01)	7.95e-05

Model 1: Unadjusted; Model 2: Adjusted for age, sex and race/ethnicity; Model 3: Adjusted for age, sex, race/ethnicity, hypertension, diabetes, smoking, BMI, history of heart attack, coronary artery disease, angina, congestive heart failure
P-values provided are unadjusted and based on two-sided t-tests.

Table S14 | Multivariable logistic regression results: Odds Ratios of brain health events (stroke, dementia or late-life depression) per one standard deviation increase in epigenetic age with late-life depression ascertained with a cutoff of 60 years.

Model	Model 1		Model 2		Model 3	
Epigenetic clock	OR (95%CI)	P value	OR (95%CI)	P value	OR (95%CI)	P value
<i>ZHANG</i>	1.28 (1.12-1.45)	1.85e-04	1.12 (0.98-1.30)	0.106	1.06 (0.91-1.23)	0.456
<i>YANG</i>	1.16 (1.02-1.31)	0.022	1.03 (0.90-1.17)	0.673	1.03 (0.90-1.18)	0.635
<i>MPOA</i>	1.09 (0.96-1.24)	0.182	1.07 (0.94-1.23)	0.284	1.00 (0.86-1.15)	0.980
<i>VIDALBRALO</i>	1.40 (1.24-1.59)	1.14e-07	1.16 (1.00-1.36)	0.057	1.14 (0.98-1.34)	0.093
<i>DNAMGRIMAGE</i>	1.60 (1.40-1.82)	2.97e-12	1.34 (1.04-1.72)	0.024	1.18 (0.87-1.60)	0.279
<i>LEVINE</i>	1.46 (1.29-1.66)	5.42e-09	1.14 (0.94-1.37)	0.178	1.09 (0.90-1.32)	0.394
<i>HANNUM</i>	1.56 (1.37-1.78)	1.50e-11	1.30 (1.03-1.65)	0.026	1.26 (0.99-1.59)	0.058
<i>WEIDNER</i>	1.29 (1.14-1.46)	4.70e-05	1.13 (0.98-1.29)	0.087	1.13 (0.98-1.30)	0.083
<i>LIN</i>	1.33 (1.16-1.51)	1.90e-05	0.94 (0.78-1.13)	0.503	0.93 (0.77-1.11)	0.427
<i>HORVATH</i>	1.38 (1.21-1.58)	1.33e-06	0.98 (0.81-1.19)	0.832	0.96 (0.80-1.17)	0.705
<i>HORVATHSKIN</i>	1.50 (1.31-1.71)	1.76e-09	1.07 (0.82-1.38)	0.636	1.03 (0.79-1.34)	0.820
<i>BOCKLANDT</i>	0.82 (0.72-0.94)	0.003	0.97 (0.84-1.12)	0.707	0.98 (0.85-1.13)	0.773
<i>GARAGNANI</i>	1.45 (1.28-1.65)	9.08e-09	1.16 (0.97-1.39)	0.095	1.15 (0.97-1.38)	0.117
<i>Average (2nd Gen)</i>	1.66 (1.40-1.97)	5.26e-09	1.26 (1.00-1.57)	0.046	1.11 (0.86-1.43)	0.422
<i>Average (all clocks)</i>	2.14 (1.73-2.65)	2.96e-12	1.57 (1.07-2.31)	0.021	1.37 (0.91-2.05)	0.129

Model 1: Unadjusted; Model 2: Adjusted for age, sex and race/ethnicity; Model 3: Adjusted for age, sex, race/ethnicity, hypertension, diabetes, smoking, BMI, history of heart attack, coronary artery disease, angina, congestive heart failure
P-values provided are unadjusted and based on two-sided Wald tests.

Table S15 | Multivariable logistic regression results: Odds Ratios of brain health events (stroke, dementia or late-life depression) per one standard deviation increase in epigenetic age excluding only participants missing one of both follow-up waves (2018 or 2020)

Model	Model 1		Model 2		Model 3	
Epigenetic clock	OR (95%CI)	P value	OR (95%CI)	P value	OR (95%CI)	P value
<i>ZHANG</i>	1.31 (1.14-1.52)	1.67e-04	1.15 (0.98-1.35)	0.080	1.07 (0.90-1.26)	0.437
<i>YANG</i>	1.13 (0.98-1.29)	0.086	1.00 (0.86-1.15)	0.952	0.99 (0.85-1.14)	0.844
<i>MPOA</i>	1.08 (0.94-1.25)	0.268	1.08 (0.93-1.25)	0.319	0.98 (0.83-1.15)	0.809
<i>VIDALBRALO</i>	1.50 (1.29-1.73)	4.09e-08	1.19 (1.00-1.42)	0.049	1.17 (0.98-1.39)	0.085
<i>DNAMGRIMAGE</i>	1.80 (1.54-2.10)	6.61e-14	1.50 (1.13-1.98)	0.004	1.28 (0.91-1.80)	0.158
<i>LEVINE</i>	1.59 (1.37-1.84)	5.46e-10	1.17 (0.95-1.44)	0.143	1.12 (0.90-1.39)	0.309
<i>HANNUM</i>	1.78 (1.53-2.06)	3.01e-14	1.50 (1.16-1.94)	0.002	1.44 (1.11-1.87)	0.006
<i>WEIDNER</i>	1.32 (1.15-1.52)	7.81e-05	1.11 (0.96-1.30)	0.166	1.11 (0.95-1.30)	0.180
<i>LIN</i>	1.42 (1.23-1.65)	2.94e-06	0.95 (0.78-1.16)	0.632	0.94 (0.77-1.16)	0.583
<i>HORVATH</i>	1.54 (1.33-1.79)	1.63e-08	1.06 (0.85-1.32)	0.592	1.05 (0.84-1.31)	0.660
<i>HORVATHSKIN</i>	1.72 (1.47-2.01)	5.46e-12	1.24 (0.92-1.68)	0.155	1.19 (0.88-1.60)	0.268
<i>BOCKLANDT</i>	0.77 (0.66-0.90)	8.32e-04	0.94 (0.80-1.11)	0.456	0.94 (0.80-1.11)	0.486
<i>GARAGNANI</i>	1.61 (1.40-1.86)	3.93e-11	1.26 (1.04-1.52)	0.019	1.23 (1.02-1.50)	0.033
<i>Average (2nd Gen)</i>	1.82 (1.50-2.21)	1.33e-09	1.32 (1.03-1.70)	0.028	1.13 (0.85-1.50)	0.398
<i>Average (all clocks)</i>	2.56 (2.00-3.27)	6.86e-14	1.78 (1.16-2.72)	0.008	1.48 (0.95-2.31)	0.087

Model 1: Unadjusted; Model 2: Adjusted for age, sex and race/ethnicity; Model 3: Adjusted for age, sex, race/ethnicity, hypertension, diabetes, smoking, BMI, history of heart attack, coronary artery disease, angina, congestive heart failure
P-values provided are unadjusted and based on two-sided Wald tests.