

# Supplementary Material

## Factors Influencing Change in Brain-Predicted Age Difference in a Cohort of Healthy Older Individuals

**Supplementary Table 1.** Mixed models measuring the association between participants' characteristics at baseline and the change in brain-PAD (n=497) over time.

<b>Characteristics:</b>	<b><sup>a</sup>Estimate</b>	<b><sup>b</sup>b (95% CI)</b>	<b>p</b>
<b>Sex, female</b>	Baseline	0.18 (-0.87, 1.23)	0.74
	Longitudinal	-0.16 (-0.31, -0.004)	0.04
<b>Education, &lt;12 y</b>	Baseline	0.13 (-0.95, 1.22)	0.81
	Longitudinal	-0.02 (-0.18, 0.13)	0.76
<b>SES, below median</b>	Baseline	-0.25 (-1.31, 0.80)	0.64
	Longitudinal	0.08 (-0.08, 0.23)	0.32
<b>3MS</b>	Baseline	-0.04 (-0.17, 0.08)	0.50
	Longitudinal	-0.01 (-0.03, 0.01)	0.19
<b>COWAT</b>	Baseline	-0.12 (-0.24, -0.002)	0.05
	Longitudinal	0.02 (0.001, 0.03)	0.04
<b><sup>c</sup>SDMT</b>	Baseline	-0.10 (-0.16, -0.03)	0.002
	Longitudinal	0.01 (-0.003, 0.01)	0.21
<b><sup>c</sup>HVLT-R, delayed recall</b>	Baseline	-0.20 (-0.39, 0.002)	0.06
	Longitudinal	-0.02 (-0.05, 0.01)	0.19
<b>Depression</b>	Baseline	0.99 (-0.83, 2.81)	0.29
	Longitudinal	-0.27 (-0.53, -0.01)	0.04
<b>Physical HRQoL</b>	Baseline	-0.05 (-0.11, 0.02)	0.15
	Longitudinal	0.01 (0.0004, 0.02)	0.04
<b>Mental HRQoL</b>	Baseline	-0.05 (-0.13, 0.03)	0.20
	Longitudinal	0.01 (-0.01, 0.02)	0.42
<b><sup>c</sup>Body mass index (kg/m<sup>2</sup>):</b>			
<b>25-29</b>	Baseline	-0.94 (-2.23, 0.34)	0.15
	Longitudinal	0.10 (-0.08, 0.28)	0.29
<b>≥30</b>	Baseline	-0.57 (-2.02, 0.88)	0.44
	Longitudinal	-0.02 (-0.23, 0.19)	0.85
<b><sup>c</sup>Weak grip strength</b>	Baseline	0.73 (-0.63, 2.10)	0.29
	Longitudinal	-0.08 (-0.28, 0.12)	0.45
<b><sup>c</sup>Slow gait speed</b>	Baseline	0.65 (-0.69, 1.99)	0.34
	Longitudinal	-0.16 (-0.36, 0.04)	0.11
<b>Pre-frail/Frail</b>	Baseline	0.93 (-0.24, 2.10)	0.12
	Longitudinal	-0.09 (-0.26, 0.08)	0.28
<b>Diabetes</b>	Baseline	0.19 (-1.52, 1.89)	0.83
	Longitudinal	-0.07 (-0.32, 0.18)	0.61
<b>Dyslipidemia</b>	Baseline	0.53 (-0.56, 1.62)	0.34
	Longitudinal	0.04 (-0.11, 0.19)	0.62

<b>Hypertensive</b>	Baseline	-0.28 (-1.43, 0.88)	0.64
	Longitudinal	0.05 (-0.11, 0.21)	0.55
<b>Aspirin treatment</b>	Baseline	0.19 (-0.87, 1.24)	0.73
	Longitudinal	0.07 (-0.08, 0.22)	0.38

These models contained the fixed effect of time (baseline, one-year, and three-year visits; results not shown above), and baseline participant characteristics. The 2-way interaction between baseline characteristics and time were also included and reported in the table above. <sup>a</sup>‘Baseline’ represents results from the intercept, while ‘Longitudinal’ defines the interaction between the fixed effect and time. <sup>b</sup>A separate mixed-effect linear regression model was performed for each baseline participant characteristic, adjusting for sex, age, and age<sup>2</sup>. <sup>c</sup>Number of total participants who are missing data from SDMT (n=2), and HVLT-R (n=1), weak grip strength (n=4), slow gait speed (n=3), body mass index (n=3). HVLT-R, Hopkins Verbal Learning Test-Revised, delayed memory recall; SES, socioeconomic status.

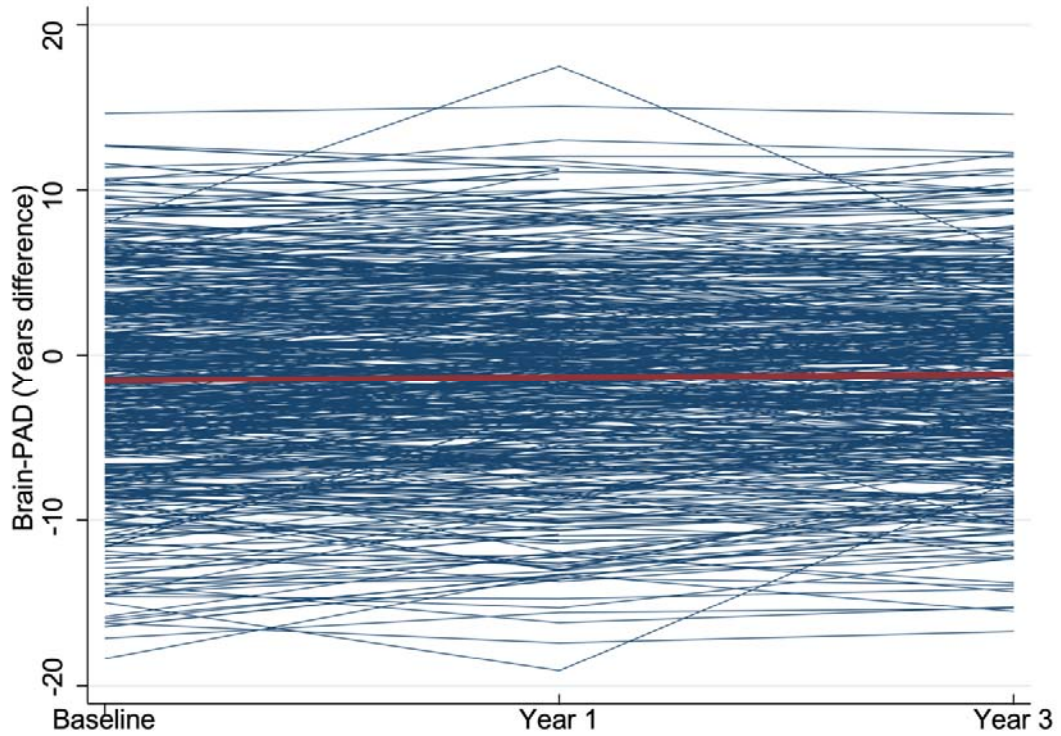
**Supplementary Table 2.** Multinomial logistic regression analyzing the association between baseline participant characteristics and the relative risk of the change in brain-PAD accelerating (n=105) or decelerating (n=61) rather than remaining stable (n=274).

<b>Characteristics:</b>	<b>Group</b>	<b><sup>a</sup>RR (95% CI)</b>	<b><i>p</i></b>
<b>Sex, female</b>	Decelerate	0.66 (0.37, 1.17)	0.15
	Accelerate	0.50 (0.31, 0.80)	0.004
<b>Education, &lt;12 y</b>	Decelerate	1.35 (0.76, 2.40)	0.31
	Accelerate	0.95 (0.58, 1.54)	0.82
<b>SES, below median</b>	Decelerate	1.24 (0.70, 2.19)	0.47
	Accelerate	1.66 (1.04, 2.67)	0.03
<b>3MS</b>	Decelerate	1.01 (0.94, 1.08)	0.76
	Accelerate	0.94 (0.89, 0.99)	0.02
<b>COWAT</b>	Decelerate	1.00 (0.93, 1.06)	0.92
	Accelerate	1.05 (0.99, 1.10)	0.09
<b><sup>b</sup>SDMT</b>	Decelerate	1.00 (0.97, 1.03)	0.92
	Accelerate	1.00 (0.97, 1.03)	0.91
<b><sup>b</sup>HVLT-R, delayed recall</b>	Decelerate	0.97 (0.87, 1.07)	0.52
	Accelerate	0.91 (0.83, 1.00)	0.05
<b>Depression</b>	Decelerate	1.48 (0.63, 3.46)	0.37
	Accelerate	1.11 (0.48, 2.56)	0.80
<b>Physical HRQoL</b>	Decelerate	1.01 (0.98, 1.05)	0.58
	Accelerate	1.02 (0.99, 1.05)	0.26
<b>Mental HRQoL</b>	Decelerate	1.01 (0.97, 1.05)	0.63
	Accelerate	1.01 (0.98, 1.05)	0.45
<b><sup>b</sup>Body mass index (kg/m<sup>2</sup>):</b>			
25-29	Decelerate	1.45 (0.73, 2.89)	0.29
	Accelerate	1.54 (0.87, 2.74)	0.14
≥30	Decelerate	1.24 (0.56, 2.75)	0.60
	Accelerate	0.97 (0.49, 1.91)	0.93
<b><sup>b</sup>Weak grip strength</b>	Decelerate	1.71 (0.69, 4.24)	0.24
	Accelerate	0.98 (0.39, 2.47)	0.97
<b><sup>b</sup>Slow gait speed</b>	Decelerate	1.32 (0.52, 3.36)	0.56
	Accelerate	0.70 (0.25, 1.96)	0.50
<b>Pre-frail/Frail</b>	Decelerate	1.56 (0.86, 2.83)	0.14
	Accelerate	0.94 (0.55, 1.62)	0.83
<b>Diabetes</b>	Decelerate	1.46 (0.63, 3.37)	0.38
	Accelerate	0.87 (0.39, 1.95)	0.74
<b>Dyslipidemia</b>	Decelerate	1.03 (0.57, 1.85)	0.93
	Accelerate	1.00 (0.61, 1.63)	0.99
<b>Hypertensive</b>	Decelerate	1.31 (0.69, 2.49)	0.41
	Accelerate	1.26 (0.75, 2.13)	0.38
<b>Aspirin treatment</b>	Decelerate	0.92 (0.52, 1.64)	0.79
	Accelerate	1.45 (0.91, 2.33)	0.12

<sup>a</sup>A separate multinomial linear regression model was performed for each baseline participant characteristic, adjusting for baseline brain-PAD, sex, age, and age<sup>2</sup>. <sup>b</sup>Number of participants who

are missing data from SDMT (stable: n=2), and HVLTR (incline: n=1), weak grip strength (stable: n=3), slow gait speed (stable: n=2), body mass index (stable: n=2). COWAT, Controlled Oral Word Association Test; HVLTR, Hopkins Verbal Learning Test-Revised, delayed memory recall; SDMT, Symbol-Digit Modalities Test; SES, socioeconomic status; 3MS, Modified-Mini-Mental State examination.

**Supplementary Figure 1.** Individual longitudinal trajectories of the brain-predicted age difference (brain-PAD) measured over one and three years of follow-up (n=497).



**Supplementary Figure 2.** Marginal plots comparing the change in brain-predicted age difference (brain-PAD) between groups for verbal fluency (COWAT) (a), depression (b), and physical health related quality of life (HRQoL) (c). Plots represent the predictive margins and 95% confidence intervals (CI) for groups, taken from linear mixed models adjusting for sex, age, and age<sup>2</sup>. Groups were defined for COWAT and physical HRQoL using a median split, and represent individuals below (COWAT: baseline (BL)=227, year 1=225; year 3=201; physical HRQoL: BL=246; year 1=239; year 3=210), or above the median score (COWAT: BL=270; year 1=262; year 3=239; physical HRQoL: BL=251; year 1=248; year 3=230). People above the median score had a better verbal fluency (COWAT) or physical well-being (HRQoL). At baseline, one-year, and three-year follow-up, there were 46, 45, and 42 participants diagnosed with depression, while 451, 442, and 398 were not, respectively.

