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ASSOCIATION BETWEEN SERUM NEURODEGENERATION BIOMARKERS AND "DUAL DECLINE" IN COGNITIVE AND MOTOR FUNCTIONS: 15-YEAR RESULTS FROM A POPULATION-BASED STUDY

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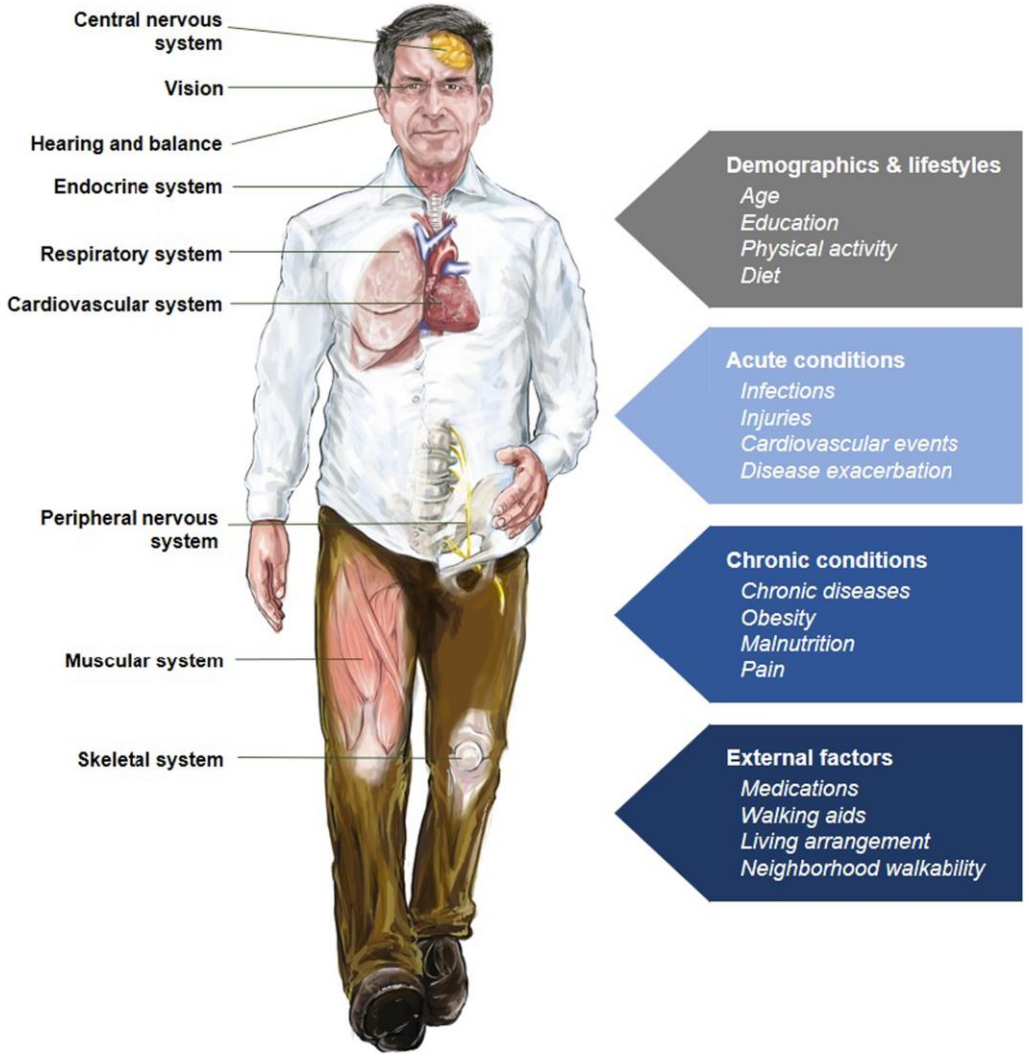
Background

- Cognitive and motor function share **common brain areas**
- **Brain damage and systemic conditions** may affect both motor and cognitive functioning
- Slow gait speed precede **cognitive decline** and predicts **incident dementia**



Grande et al, Exp. Gerontol. 2019

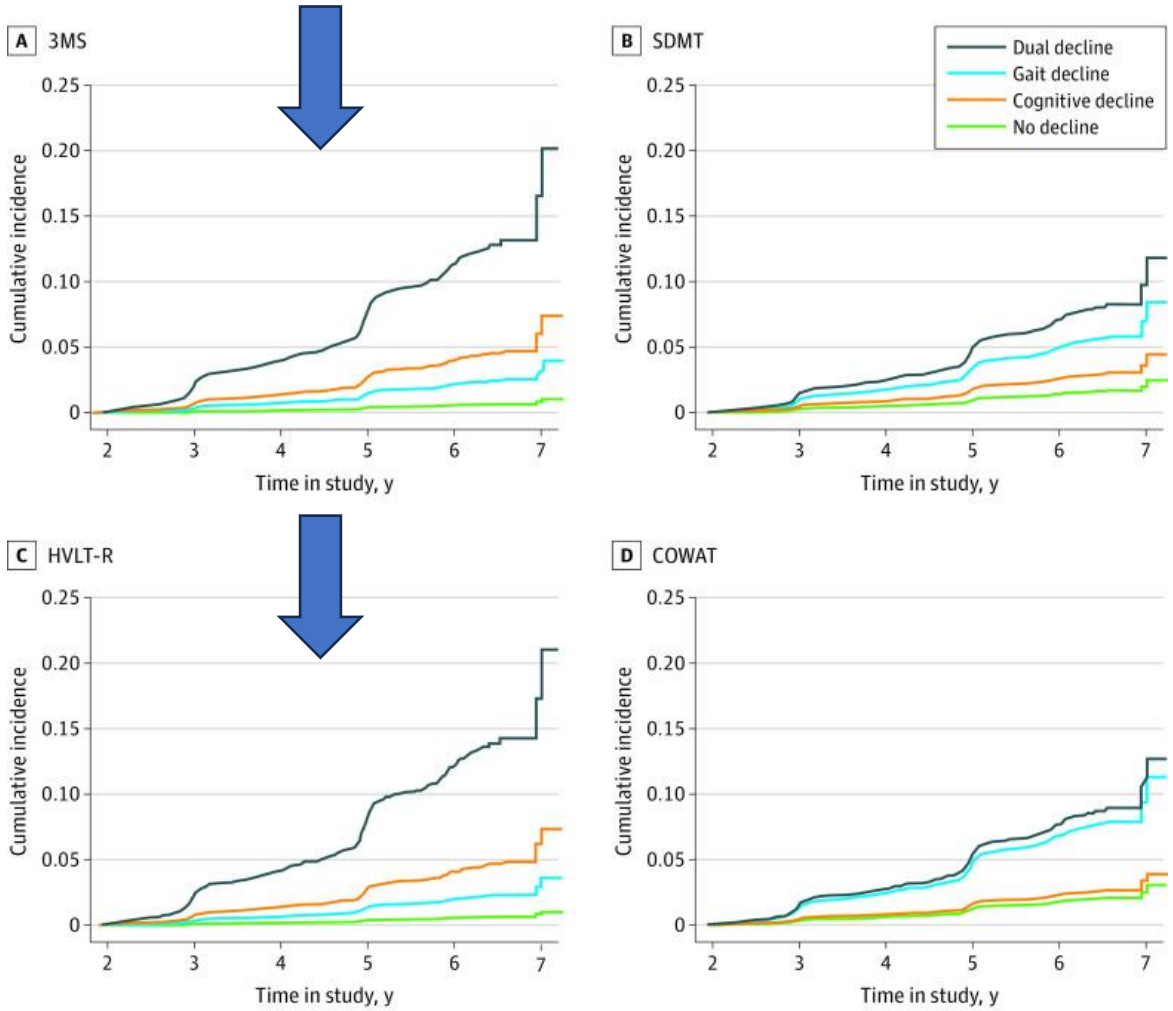
Randomized Controlled Trial > JAMA Netw Open. 2022 May 2;5(5):e2214647.
doi: 10.1001/jamanetworkopen.2022.14647.

Association of Dual Decline in Cognition and Gait Speed With Risk of Dementia in Older Adults

Taya A Collyer [1], Anne M Murray [2], Robyn L Woods [3], Elsdon Storey [3], Trevor T-J Chong [4 5 6], Joanne Ryan [3], Suzanne G Orchard [3], Amy Brodtmann [7 8], Velandai K Srikanth [1], Raj C Shah [9], Michele L Callisaya [1]

Results: Of 19 114 randomized participants, 16 855 (88.2%) had longitudinal gait and cognitive data for inclusion in this study (mean [SD] age, 75.0 [4.4] years; 9435 women [56.0%], 7558 participants [44.8%] with 12 or more years of education). Compared with nondecliners, risk of dementia was highest in the gait plus HVLT-R decliners (hazard ratio [HR], 24.7; 95% CI, 16.3-37.3), followed by the gait plus 3MS (HR, 22.2; 95% CI, 15.0-32.9), gait plus COWAT-F (HR, 4.7; 95% CI, 3.5-6.3), and gait plus SDMT (HR, 4.3; 95% CI, 3.2-5.8) groups. Dual decliners had a higher risk of dementia than those with either gait or cognitive decline alone for 3MS and HVLT-R.

Conclusions and relevance: Of domains examined, the combination of decline in gait speed with memory had the strongest association with dementia risk. These findings support the inclusion of gait speed in dementia risk screening assessments.



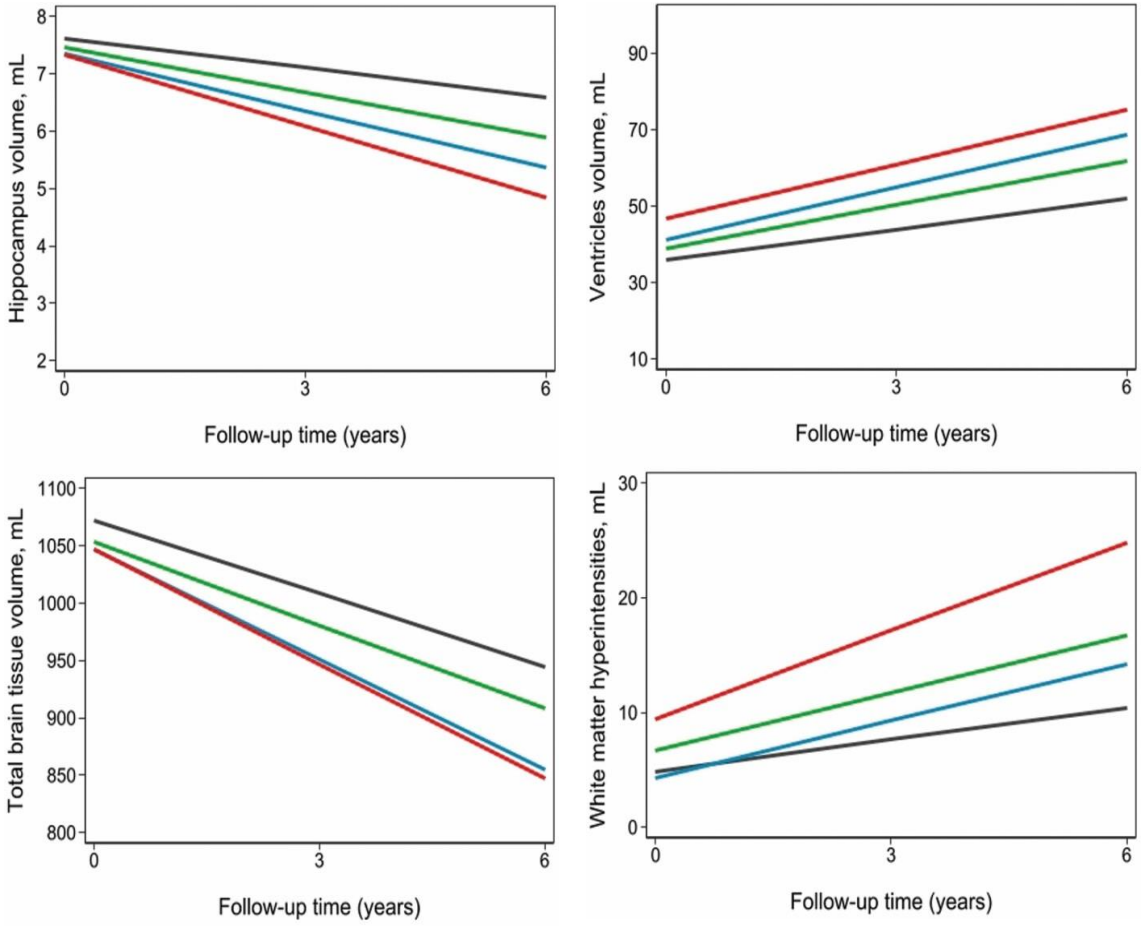
J Gerontol A Biol Sci Med Sci. 2023 Feb 24;78(2):326-332. doi: 10.1093/gerona/glac177.

Brain Changes and Fast Cognitive and Motor Decline in Older Adults

Giulia Grande [1], Davide Liborio Vetrano [1 2], Grégoria Kalpouzos [1], Anna-Karin Welmer [1 3], Erika J Laukka [1 2], Anna Marseglia [1 4], Laura Fratiglioni [1 2], Debora Rizzuto [1 2]

According to our findings, individuals who were free from dementia, cognitive impairment, and disability at baseline who rapidly declined in both cognitive and motor functions experienced the steepest loss in total brain tissue and HV, the greatest ventricular enlargement, and the largest accumulation of white matter lesions. The subanalyses, including DTI measures, further supported these findings by showing lower microstructural white matter integrity in people with co-occurring cognitive and motor decline, beyond the presence of macrostructural white matter lesions.

Regardless of the specific pathways behind cognitive and motor decline, it is plausible that established cognitive, and motor impairments are characterized by complex and mixed (white and gray matter, including atrophy and vascular lesions) brain deterioration.



Slow/no decliners-black line, isolated motor decliners-green line, isolated cognitive decliners-blue line, and cognitive and motor decliners-red line.

Aim

To test the association between serum neurodegeneration biomarkers and different patterns of decline in cognition and motor function in an aging population

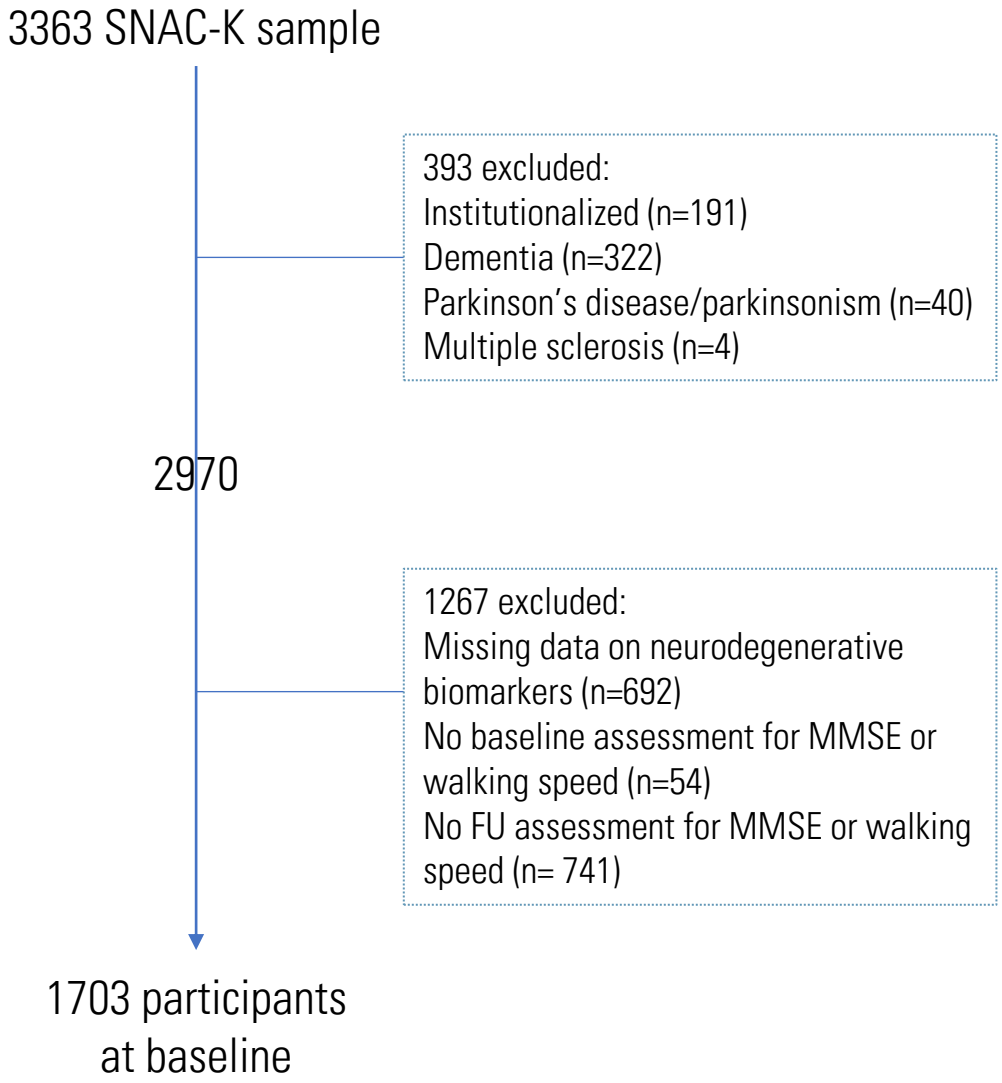
Materials and Methods

Setting and Participants

SNAC-K

Swedish National Study on Aging and Care in Kungsholmen:

- Aged 60+
- Urban-dwellers
- With up to 17 years of follow-up

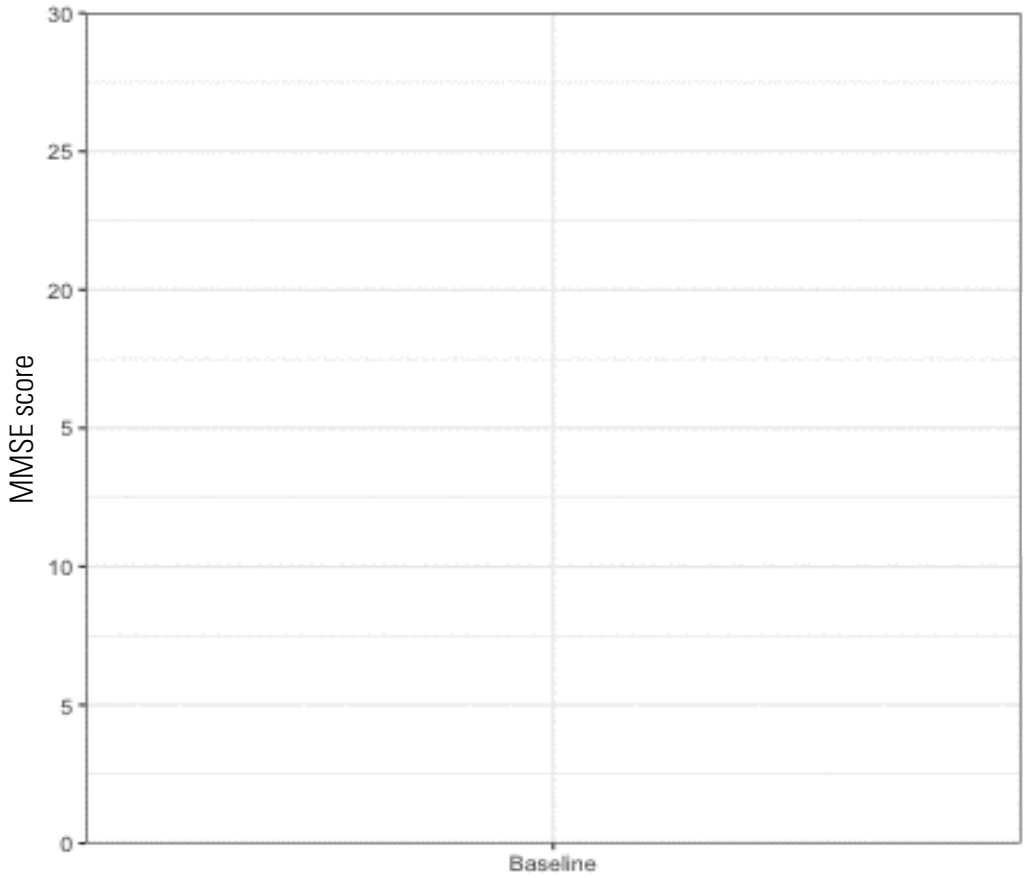


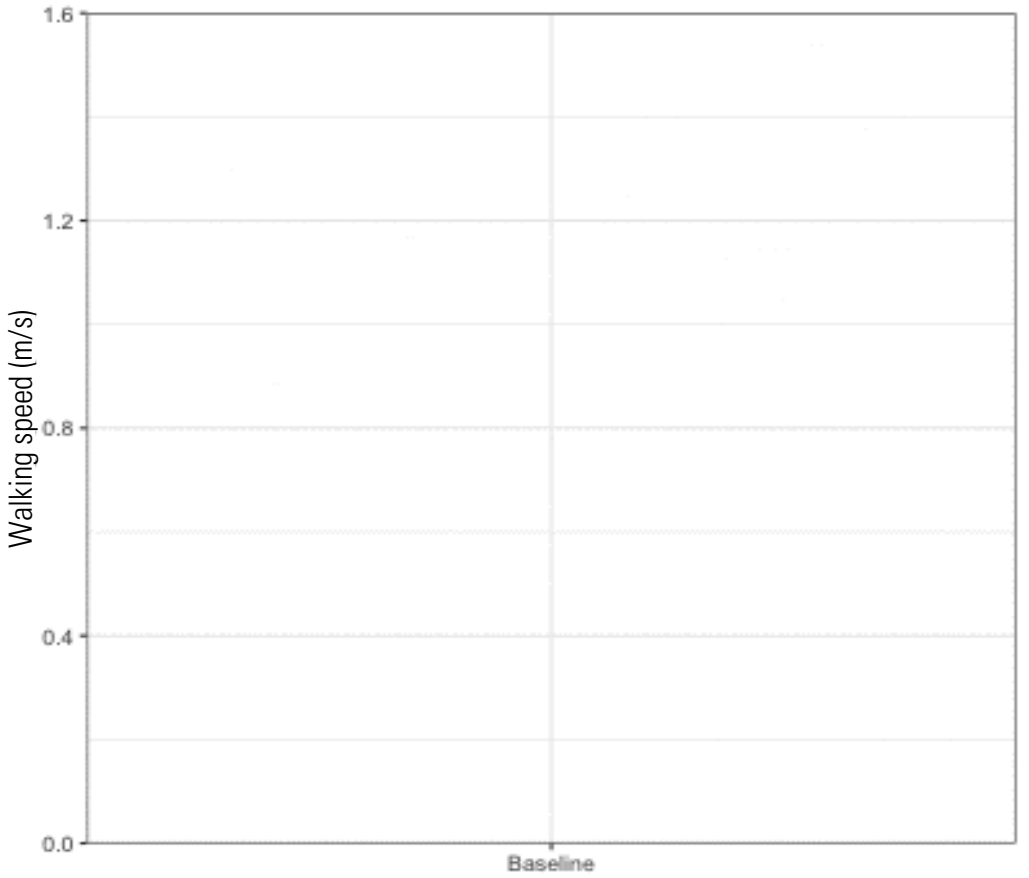
Statistical Analysis

- **Descriptive statistics** to summarize sample baseline characteristics
- **Linear mixed models** with random intercept and slope to estimate the rate of motor and cognitive decline for each participant
- **Multinomial logistic regression models** to estimate ORs and 95% CIs for the different patterns of decline in relation to serum biomarkers concentration at baseline

Study Population

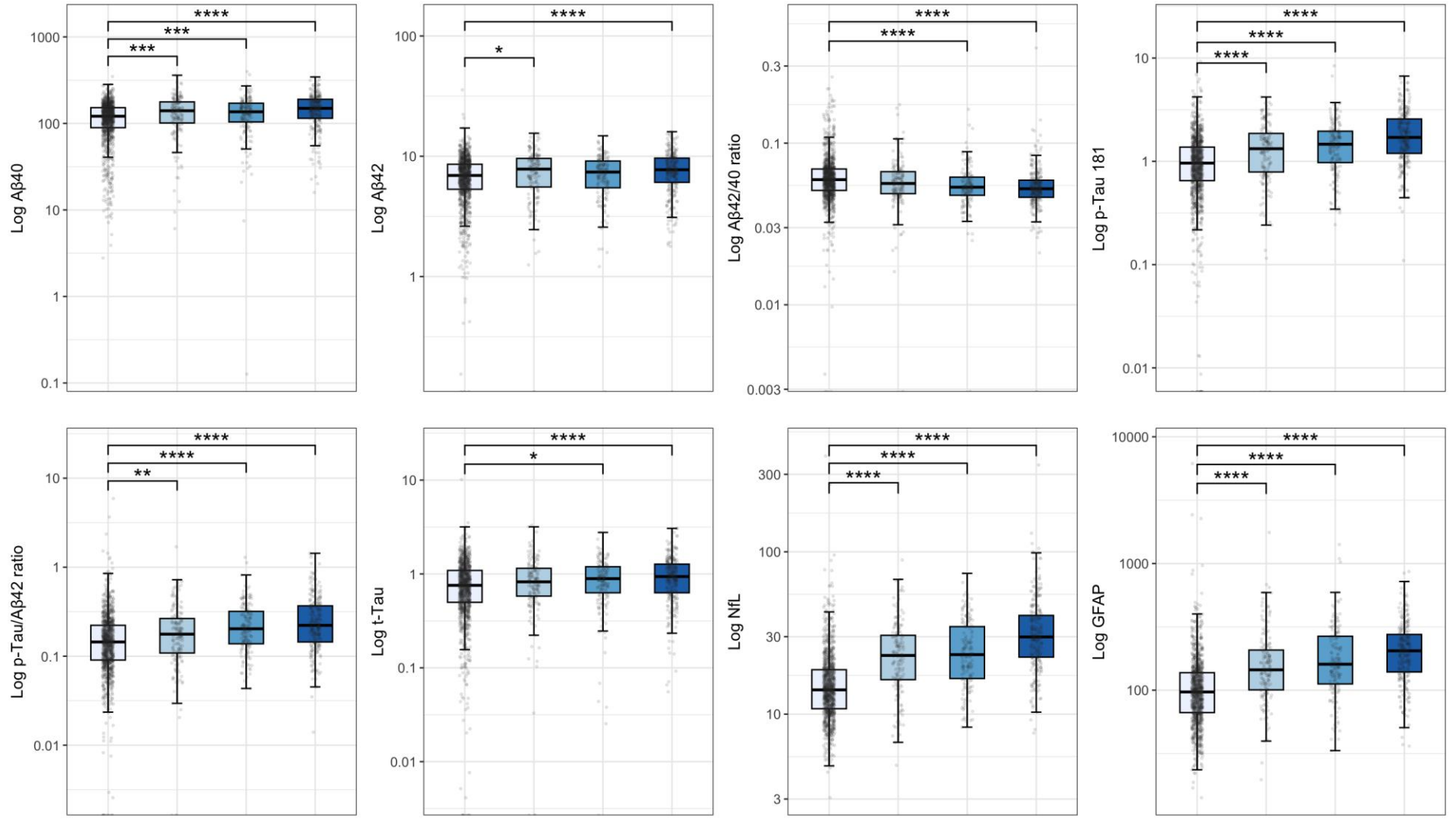
Slow/Non decliners	Fast motor decliners	Fast cognitive decliners	Dual decliners
N = 1115	N = 162	N = 162	N = 264

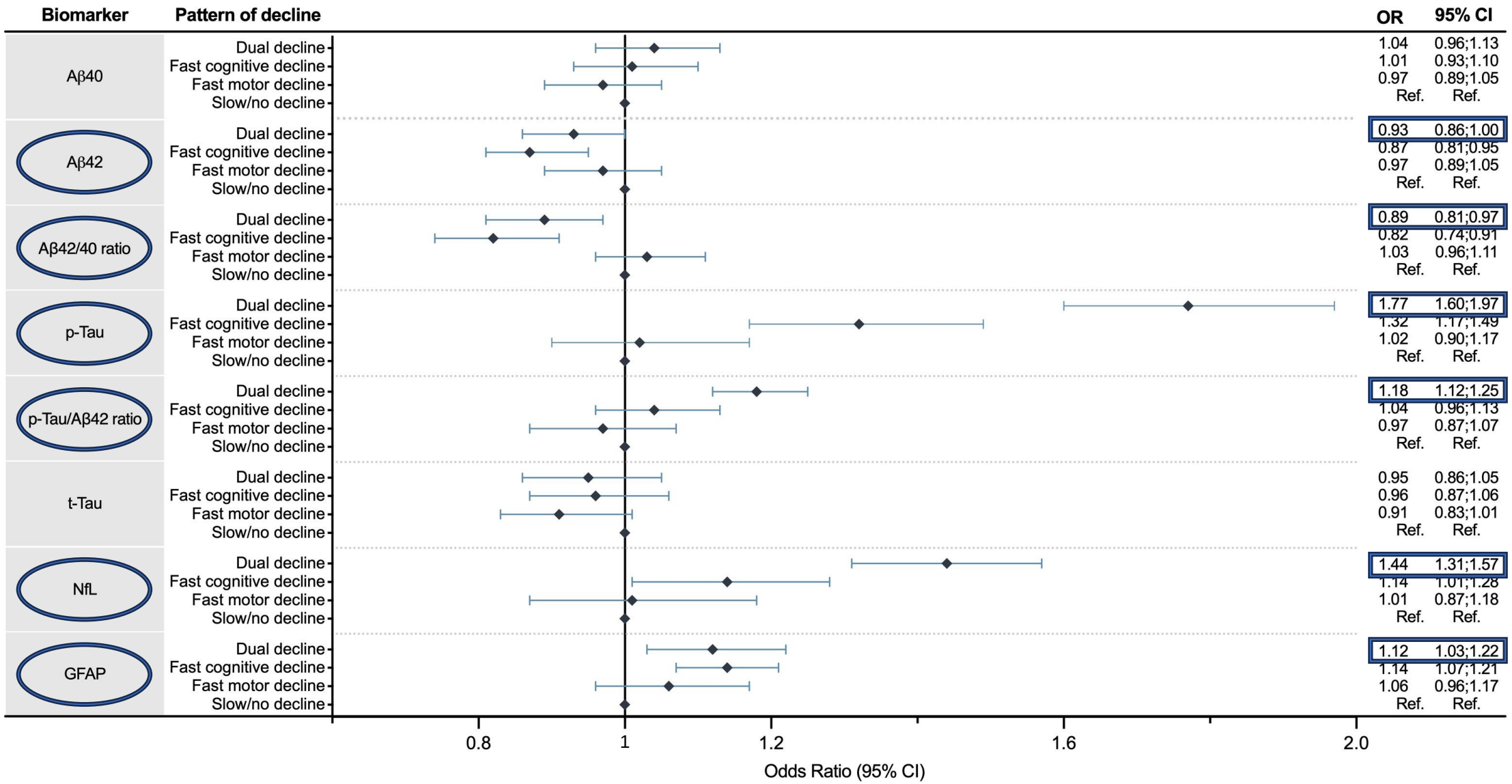

30
25
20
5
10
5
0
MMSE score
Baseline
Follow-up time


1.6
1.2
0.8
0.4
0.0
Walking speed (m/s)
Baseline
Follow-up time

Results

	Patterns of motor/cognitive decline				
	Slow/Non decliners	Fast motor decliners	Fast cognitive decliners	Dual decliners	p-value
Age (mean (SD))	66.6 (7.2)	77.1 (8.2)	77.4 (8.8)	82.5 (7.6)	<0.001
Female (%)	670 (60.1)	111 (68.5)	92 (56.8)	191 (72.3)	<0.001
Education					<0.001
Elementary school (%)	91 (8.2)	21 (13.0)	38 (23.5)	64 (24.2)	
High school (%)	494 (44.3)	94 (58.0)	93 (57.4)	146 (55.3)	
University (%)	530 (47.5)	47 (29.0)	31 (19.1)	54 (20.5)	
Physical activity level					<0.001
Inadequate (%)	193 (17.3)	44 (27.2)	34 (21.0)	117 (44.3)	
Health-enhancing (%)	574 (51.5)	91 (56.2)	96 (59.3)	113 (42.8)	
Fitness-enhancing (%)	348 (31.2)	27 (16.7)	32 (19.8)	34 (12.9)	
MMSE score (mean (SD))	29.4 (0.8)	29.1 (1.0)	28.1 (1.6)	27.8 (2.2)	<0.001
Gait speed (m/s; mean (SD))	1.3 (0.3)	1.0 (0.4)	1.0 (0.3)	0.7 (0.4)	<0.001
No. of chronic diseases (mean (SD))	2.9 (1.9)	4.9 (2.3)	3.7 (2.0)	4.9 (2.3)	<0.001
IL-6 (pg/ ml; median [IQR])	1.21 [0.75, 2.16]	2.03 [1.26, 3.27]	1.69 [1.00, 2.85]	1.87 [1.28, 3.25]	<0.001
APOE ε4 (%)	323 (29.1)	30 (18.5)	51 (31.5)	90 (35.0)	0.004


Log Aβ40
Log Aβ42
Log Aβ42/40 ratio
Log p-Tau 181
Log p-Tau/Aβ42 ratio
Log t-Tau
Log NfL
Log GFAP
Patterns of motor/cognitive decline
Slow/no decline
Fast motor decline
Fast cognitive decline
Dual decline


Biomarker
Pattern of decline
OR
95% CI
Aβ40
Dual decline 1.04 0.96;1.13
Fast cognitive decline 1.01 0.93;1.10
Fast motor decline 0.97 0.89;1.05
Slow/no decline Ref. Ref.
Aβ42
Dual decline 0.93 0.86;1.00
Fast cognitive decline 0.87 0.81;0.95
Fast motor decline 0.97 0.89;1.05
Slow/no decline Ref. Ref.
Aβ42/40 ratio
Dual decline 0.89 0.81;0.97
Fast cognitive decline 0.82 0.74;0.91
Fast motor decline 1.03 0.96;1.11
Slow/no decline Ref. Ref.
p-Tau
Dual decline 1.77 1.60;1.97
Fast cognitive decline 1.32 1.17;1.49
Fast motor decline 1.02 0.90;1.17
Slow/no decline Ref. Ref.
p-Tau/Aβ42 ratio
Dual decline 1.18 1.12;1.25
Fast cognitive decline 1.04 0.96;1.13
Fast motor decline 0.97 0.87;1.07
Slow/no decline Ref. Ref.
t-Tau
Dual decline 0.95 0.86;1.05
Fast cognitive decline 0.96 0.87;1.06
Fast motor decline 0.91 0.83;1.01
Slow/no decline Ref. Ref.
NfL
Dual decline 1.44 1.31;1.57
Fast cognitive decline 1.14 1.01;1.28
Fast motor decline 1.01 0.87;1.18
Slow/no decline Ref. Ref.
GFAP
Dual decline 1.12 1.03;1.22
Fast cognitive decline 1.14 1.07;1.21
Fast motor decline 1.06 0.96;1.17
Slow/no decline Ref. Ref.
0.8
1
1.2
1.6
2.0
Odds Ratio (95% CI)

Conclusions

- Dual decliners present **unique profiles** of serum neurodegeneration biomarkers
- Robust associations were found between **p-Tau181** and **NfL** and the concurrent decline in cognitive and motor functions, even after adjusting for covariates
- Gait impairment seems to be related to a **wider neurodegenerative involvement** beyond specific AD pathology
- Variations in the association between serum biomarkers and dual decline were evident based on **age** and **ApoE ε4 carrier status** in our stratified analyses
- **Future research** is needed to deepen our knowledge of the mechanisms involved in brain damage, possibly encompassing vascular and neuroinflammatory pathways as well

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