

Longitudinal Changes in Blood-Based Biomarkers of Alzheimer’s Disease Across Age Groups and Their Associations with Cognitive Function



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TAKE HOME MESSAGE

- ✓ Longitudinal changes in plasma biomarkers measured by HISCL may reflect biomarker cascade in the AD continuum, with plasma Aβ showing the earliest changes, followed by p-tau181, and NfL increasing more broadly with aging as a marker of neurodegeneration. These pattern may follow with the ATN biomarker cascade.
- ✓ The HISCL platform enables simultaneous measurement of multiple biomarkers and may be useful for large-scale clinical research in the general population.

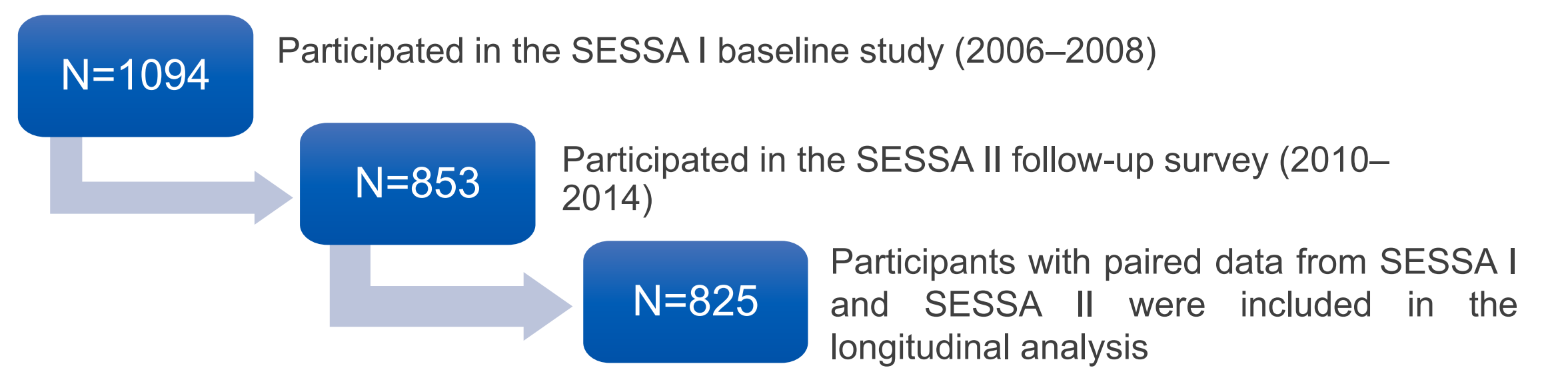
Background

- With the expanding clinical use of disease-modifying therapies, there is increasing demand to identify Alzheimer’s disease (AD) pathology in the general population before the onset of clinical symptoms, and blood-based biomarkers (BBMs) have emerged as a promising approach.
- However, BBM levels are known to be affected by ageing and comorbidities, and it remains unclear how their longitudinal changes differ across age groups or how such changes relate to cognitive function.
- In this study, we investigated age-related longitudinal changes in BBMs and their associations with cognitive function in a general population.

Participants and methods

- Plasma samples were obtained from 825 community-dwelling Japanese men participating in the Shiga Epidemiological Study of Subclinical Atherosclerosis (SESSA) I (baseline: 2006–2008) and SESSA II (follow-up: 2010–2014).

Flow diagram of study participants



- Plasma Aβ40, Aβ42, p-tau181, total-tau and NfL were measured using the Automated Immunoassay System HISCL™-5000.
- Association between longitudinal changes in plasma AD biomarkers and Cognitive Abilities Screening Instrument (CASI) score at follow-up were examined (n=788).

Result 1: Longitudinal changes in plasma biomarkers across age groups

- To confirm the age dependency on their change, we divided the participants into 4 age groups at 10 years intervals based on baseline age (40s: n=80; 50s: n=155; 60s: n=340; 70s: n=250) , and compared median biomarker levels between baseline and follow-up within each group, as shown in Figure 1.
- Plasma Aβ40 and Aβ42 levels increased from the 40s, with the Aβ42/40 ratio showing a consistent shift toward abnormal direction across all age groups.
- p-tau181 demonstrated age-dependent increases, with more pronounced elevation in participants in their 70s.
- Total-tau did not demonstrate a clear age-related shift toward abnormality across age groups.
- NfL exhibited age-dependent increases, with more prominent elevations observed from the 60s
- **Each biomarker showed distinct age-dependent longitudinal trajectories.**
- **Especially, plasma Aβ showed the earliest longitudinal changes from 40s, with a consistent shift toward an abnormal Aβ42/40 ratio.**

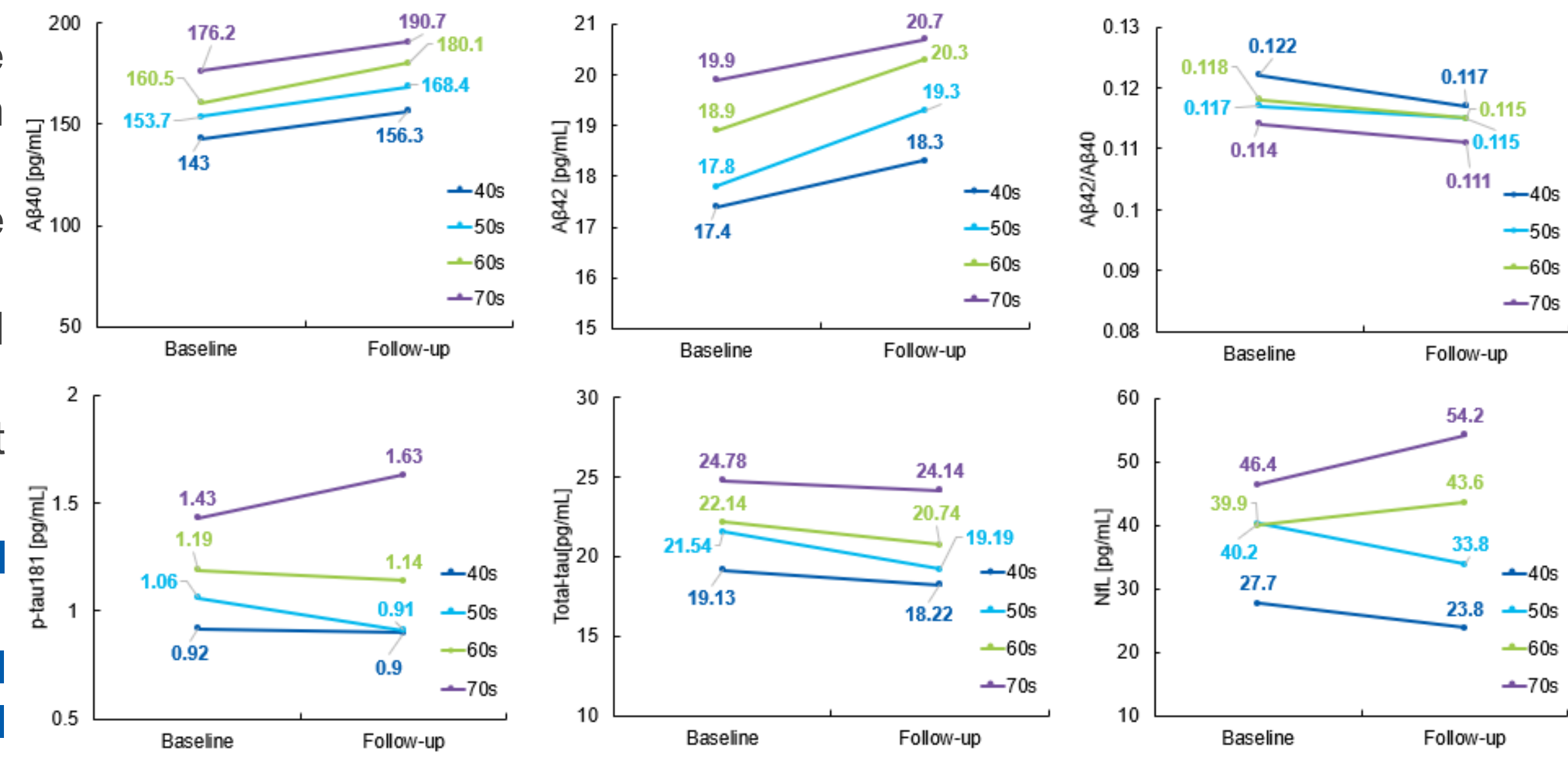


Figure 1. Longitudinal changes of each biomarkers' levels.

Result 2: Exploratory analysis of classification by plasma Aβ status

Plasma Aβ status in different age group

- To characterize age-related shifts of plasma Aβ status, participants were classified into longitudinal Aβ status groups across baseline age categories.
- Plasma Aβ status was defined based on a previously defined cut-off value (0.102, Yamashita K. et al, 2022.), and participants were classified into groups using the cut-off (Table 1).
- Plasma Aβ positivity was observed in individuals from participants in their 40s at both baseline and follow-up, and its frequency increased with age.

Table 1. Association between age and longitudinal changes in plasma Aβ status.

	Negative →Negative (N→N)	Negative →Positive (N→P)	Positive →Negative (P→N)	Positive →Positive (P→P)
40s (n=80)	n=77 (96.3 %)	n=1 (1.3 %)	n=1 (1.3 %)	n=1 (1.3 %)
50s (n=155)	n=134 (86.5 %)	n=12 (7.7 %)	n=4 (2.6 %)	n=5 (3.2 %)
60s (n=340)	n=270 (79.4 %)	n=32 (9.4 %)	n=4 (1.2 %)	n=34 (10.0 %)
70s (n=250)	n=157 (62.8 %)	n=33 (13.2 %)	n=8 (3.2 %)	n=52 (20.8 %)

Biomarker trajectory across different Aβ status groups

- To assess whether downstream biomarker trajectories differed by plasma Aβ status, we examined longitudinal changes in p-tau181 and NfL across plasma Aβ status groups. Given the limited longitudinal signal of total-tau in this community-based cohort, subsequent analyses focused on p-tau181 and NfL.
- P-tau181 showed no clear changes in the N→N group; however, abnormal increases emerged in the N→P and P→P groups starting in the 60s (Figure 2A).
- **P-tau181 typically increases after Aβ abnormality and may reflect tau-related biological change. Our results were consistent with this temporal pattern.**
- NfL levels began to increase with aging, regardless of Aβ status (Figure 2B).
- **NfL is a general neurodegenerative biomarker that increase with age. Our results were consistent with the expected age-related increase in NfL.**

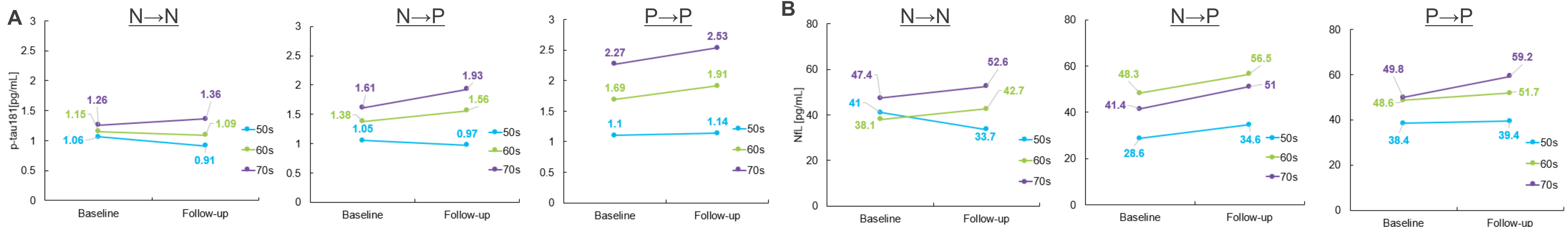


Figure 2. Longitudinal biomarker levels of (A) p-tau181 and (B) NfL in groups defined by the plasma Aβ cut-off. Data are presented as median values. Age groups with small sample sizes were excluded from the figures.

Result 3: Associations between biomarker changes and cognitive function

- To assess the clinical relevance of longitudinal biomarker changes, we examined their associations with cognitive function at follow-up
- In unadjusted analyses, longitudinal changes in several biomarkers except Aβ42 were associated with CASI score. However, these associations were largely attenuated after adjusting for age. Notably, only increases in NfL remained significantly associated with cognitive performance.
- **This pattern suggests that NfL may capture aspects of neurodegeneration related to cognitive decline that are not fully explained by the effect of age.**

Table 2. Associations of longitudinal changes in each biomarker and CASI score at the follow-up (n=788). Each value represents standardized regression coefficients. 95% confidence intervals (95% CI) are shown in parentheses.

	Unadjusted	Age-adjusted
ΔAβ40 (pg/mL)	-0.084 (-0.152 to -0.015)	-0.058 (-0.12 to 0.005)
ΔAβ42 (pg/mL)	-0.014 (-0.084 to 0.056)	-0.030 (-0.094 to 0.033)
ΔAβ42/Aβ40	0.087 (0.018 to 0.157)	0.060 (-0.003 to 0.123)
Δp-tau181 (pg/mL)	-0.123 (-0.193 to -0.054)	-0.042 (-0.106 to 0.023)
ΔNfL (pg/mL)	-0.087 (-0.155 to -0.019)	-0.075 (-0.137 to -0.013)