

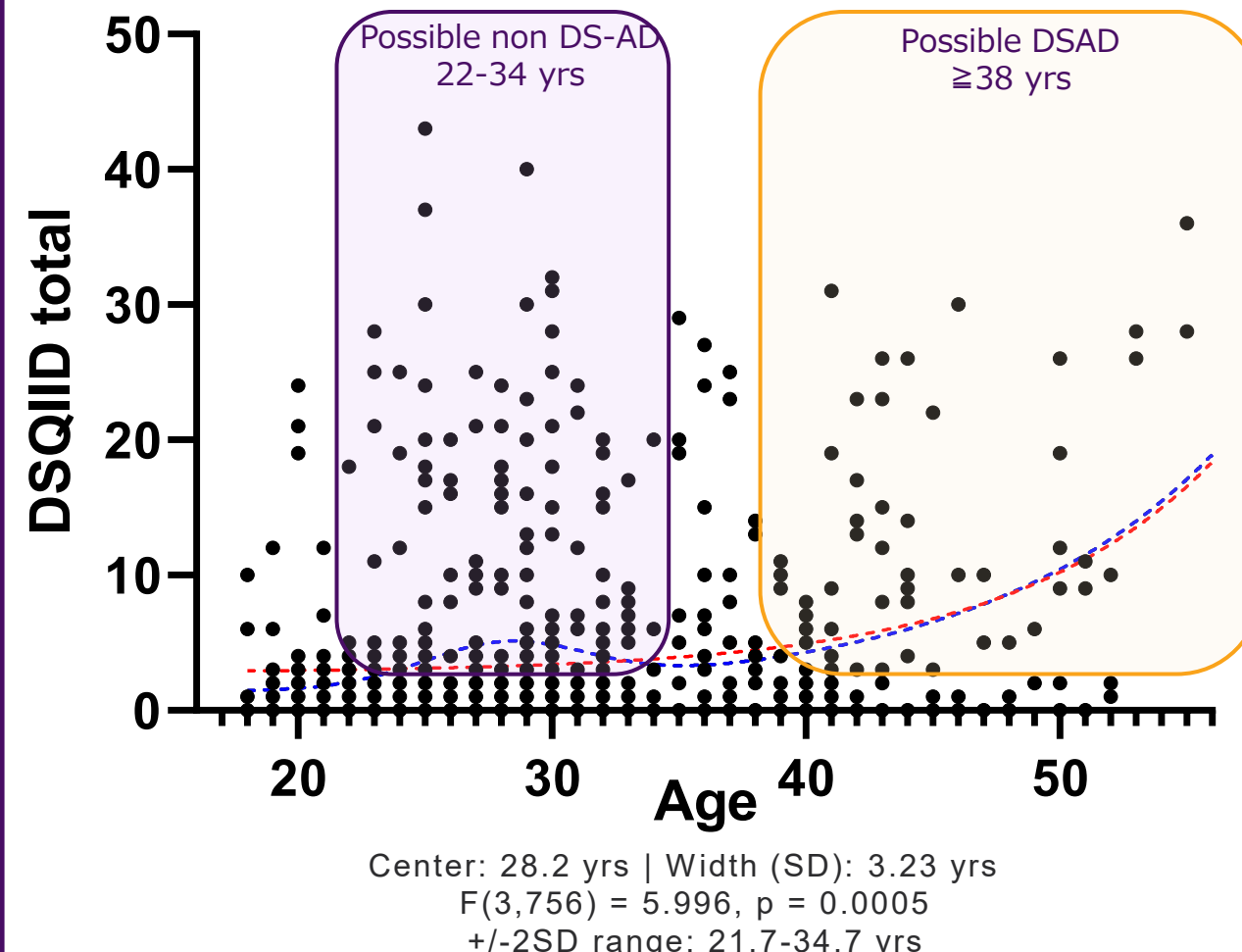
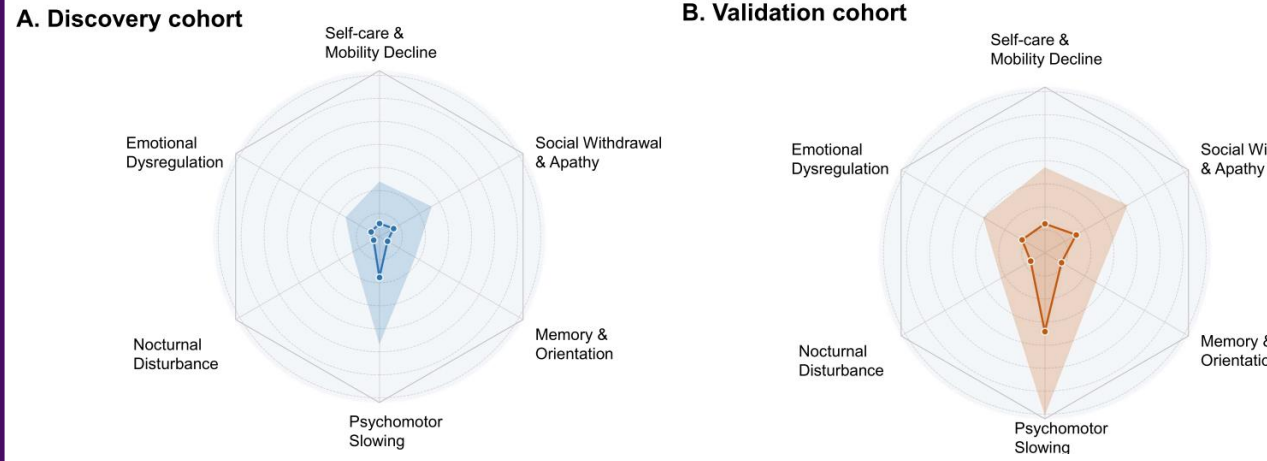
Characteristics of Alzheimer's Disease in Down Syndrome: Insights from a Nationwide Survey Using the DSQIID in Japan

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DSQIID scores show a bimodal age distribution in adults with DS: an early local peak (~28 yrs, reflecting non-DS-AD functional decline) and a later rise (>38 yrs, reflecting DS-AD). A weighted model combining age with DS-AD-specific DSQIID subscores (memory/orientation, psychomotor/activity) significantly outperforms total score alone for early DS-AD detection (AUC 0.888 vs. 0.643), enabling scalable caregiver-based pre-hospital screening from age 35.

INTRODUCTION	METHODS	RESULTS	REFERENCES	
Background Adults with Down syndrome (DS) are at high risk of Alzheimer's disease (DS-AD), typically manifesting after age 40. However, functional decline in adults with DS is not limited to DS-AD; non-DS-AD functional decline, including DS-associated regression disorder (DS-RD), may also cause significant ability loss in younger individuals. The prevalence, age distribution, and symptom characteristics of functional decline across adulthood in DS remain poorly understood, and appropriate screening strategies have not been established. Two major recognized causes of cognitive decline in adults with DS: DS Regression Disorder (DS-RD) - Onset in adolescence/early adulthood - Acute-subacute functional loss - Mechanisms: over-adaptation, immune dysregulation DS-Alzheimer's Disease (DS-AD) - Onset >=40 yr. ; <i>APP</i> overexpression - Early: executive dysfunction, apathy, behavioral change - Late: memory loss, disorientation, ADL decline, seizures Unrecognized functional decline in adult DS, neither related to DS-AD nor DS-RD, is possibly present. Objectives: - Age-dependent pattern of decline: Is caregiver-reported functional decline in DS monotonically age-related, or does it show a distinct local peak in younger adults reflecting non-AD etiology? - Symptom profile comparison: Using factor analysis of DSQIID items, compare domain profiles between possible non-DS-AD decline and possible DS-AD.	Multi-cohort design (1 discovery + 2 validation) Discovery Cohort Nationwide caregiver survey via Japan Down Syndrome Association (Jul–Oct 2025); postal + online 2,355 eligible members → 769 consented (349F/419M; mean age 29.5±8.1 yrs, range 18–59) Respondents: 99.2% mothers; mean age 62.7 yrs Validation Cohort 1 — Institutional Outpatients DS outpatients, Kyoto Prefectural Univ. of Medicine n=82 (44F/38M; mean age 31.3±11.6 yrs) Plasma p-tau181 measured as AD biomarker DS-AD: biomarker-confirmed + specialist diagnosis Non-DS-AD: age 22–34, DSQIID ≥6, no AD progression on follow-up Validation Cohort 2 — Residential Care (INDIGO-2019) Cross-sectional data from welfare facilities across Japan Dementia diagnosed by consensus panel (DSM-5/ICD-10/DC-LD) n=40 clinically confirmed DS-AD; used for symptom profile analysis Statistical Analyses: - Age-stratified DSQIID score distribution - Gaussian + logistic model comparison (F-test for local peak) - Exploratory factor analysis → 6 DSQIID subscale domains	Finding 1: Local Peak Phenomenon DSQIID scores did NOT increase monotonically with age. A statistically significant local peak was identified:  Center: 28.2 yrs Width (SD): 3.23 yrs F(3,756) = 5.996, p = 0.0005 +/-2SD range: 21.7-34.7 yrs Finding 2: Exploratory Factor Analysis (EFA) Identified Six Clinically Interpretable DSQIID Domains EFA of all 53 DSQIID items (discovery cohort, n=769) using principal axis factoring with oblique rotation (Oblimin) identified six latent domains:  A. Discovery cohort B. Validation cohort	Finding 3: While Psychomotor Slowing was prominent in both groups, Memory & Orientation impairment emerged as the key domain distinguishing DS-AD from non-DS-AD across all three cohorts.  CONCLUSION - Non-monotonic age pattern supports two distinct decline etiologies. A local DSQIID peak at ~28 yrs (non-AD) and a later rise after 38 yrs (DS-AD) suggest that early-adulthood decline in DS should not be attributed to Alzheimer's disease. - Memory & Orientation distinguishes DS-AD from non-AD decline. This domain was consistently elevated in DS-AD across discovery and both validation cohorts, while Psychomotor Slowing was shared by both etiologies. - A caregiver questionnaire-based model enables early DS-AD detection from age 35. Combining age with DS-AD-specific subscores achieved AUC 0.888 in biomarker-validated data, supporting feasible pre-hospital screening in the anti-amyloid treatment era.	1. Santoro JD, et al. Front Neurol. 2022;13:940175. 2. Fortea J, et al. Lancet Neurol. 2021. 3. Deb S. Br J Psychiatry. 2007. 4. Shinomoto M, Takeuchi C, Kasai T, et al. PLoS One. 2024;e0311878. 5. Kinoshita D, et al. Nozomi-no-sono Research Bulletin. 2011;5. CONTACT  Takashi Kasai, MD, PhD Dept. of Neurology Kyoto Prefectural University of Medicine kasaita@koto.kpu-m.ac.jp ALZHEIMER'S ASSOCIATION AAIC>26