

Naturally occurring serum anti-Aβ1–42 IgG responses are dynamic and relevant to Alzheimer’s disease in adults with Down syndrome



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In adults with **Down syndrome**, serum free and oligomer-reactive anti-Aβ1–42 IgG behaved as distinct antibody pools, not a single marker of **Alzheimer’s disease** (AD). Oligomer-reactive IgG showed the **clearer clinical and longitudinal signal** (lower in confirmed AD dementia, attenuated after age and sex adjustment, and increasing over time), whereas free IgG showed **APOE ε4-dependent coupling with plasma p-tau217**.

INTRODUCTION	METHODS	RESULTS	CONCLUSIONS
Adults with Down syndrome (DS) have a very high lifetime risk of Alzheimer's disease (AD), driven by lifelong amyloid-β (Aβ) overproduction. Naturally occurring anti-Aβ autoantibodies (IgG) form part of the normal immune repertoire and may aid Aβ clearance. Serum contains both free IgG and IgG reactive to toxic Aβ oligomers, but whether these pools behave differently, and how they relate to AD, is largely unknown in DS.	Baseline adults with DS n = 95 serum free + oligomer-reactive anti-Aβ1–42 IgG Clinical status Dementia status n=93 Confirmed AD dementia n=10 Longitudinal serum n=30 Mean follow-up 1.8 years MRI subset n=37 CAA-related markers APOE ε4 Carriers n=21 Interaction analyses ➤ Cohort: LonDownS (London Down Syndrome Consortium); adults with genetically confirmed Down syndrome. ➤ Serum antibodies: free and oligomer-reactive anti-Aβ1–42 IgG, measured with a proprietary AC Immune SA assay (log2 AU/mL). ➤ Plasma biomarkers: selected NULISaseq CNS markers across amyloid, tau, neurodegeneration, glial/immune and synaptic domains. ➤ Analyses: baseline confirmed AD dementia comparison; longitudinal mixed-effects models; exploratory MRI/CAA; APOE ε4 x biomarker interactions. Models adjusted for age and sex (interaction models also for AD dementia status). FDR within antibody pool.	1. Oligomer-reactive IgG: lower in confirmed AD dementia, rising over time A Free anti-Aβ1–42 IgG p = 0.196 B Oligomer-reactive anti-Aβ1–42 IgG p = 0.032 C D ➤ Oligomer-reactive IgG was lower in confirmed AD dementia (attenuated after age and sex adjustment) and rose over time; free IgG showed neither. ➤ Longitudinally, oligomer +0.16 log2/yr vs free +0.04 (mixed-effects). Within-person, oligomer rose more than free (median Δ 0.26, Wilcoxon p=0.002); 79% vs 37% of participants increased (McNemar p<0.001). 2. Oligomer-reactive IgG and CAA-related MRI markers Cortical superficial siderosis (n = 28) CAA diagnosis (n = 28) Cerebral microbleeds (n = 29) Perivascular spaces (n = 34) White-matter hyperintensities (n = 35) Adjusted odds ratio (95% CI) Per 1 log2 AU/mL oligomer-reactive IgG; adjusted for age and sex. ➤ Inverse point estimates for CAA diagnosis, cortical superficial siderosis, and microbleeds; all non-significant. 3. Free IgG: APOE ε4-dependent coupling with p-tau217 A B ➤ In APOE ε4 carriers, higher plasma p-tau217 was associated with higher free IgG. ➤ Interaction β=1.45 (95% CI 0.53–2.38), within-antibody FDR=0.028.	Free and oligomer-reactive anti-Aβ1–42 IgG are distinct pools, not a single AD marker: oligomer-reactive IgG carries the dynamic, clinically relevant signal, whereas free IgG is APOE ε4-dependent. As anti-amyloid immunotherapies are increasingly considered for DS, where amyloid-related imaging abnormalities (ARIA) and CAA are key safety concerns, characterising endogenous anti-Aβ immunity may be increasingly relevant.
RESEARCH QUESTIONS	CONTACT		
In adults with DS, do serum free and oligomer-reactive anti-Aβ1–42 IgG: 1) relate to AD dementia and change over time? 2) associate with MRI markers of cerebral amyloid angiopathy (CAA)? 3) show plasma-biomarker relationships that differ by APOE ε4 status?	Yajing Zhou King's College London yajing.zhou@kcl.ac.uk ALZHEIMER'S ASSOCIATION AAIC>26		