Prediction of amyloid and tau brain deposition and cognitive decline in people with Down syndrome using plasma biomarkers: a longitudinal cohort study

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Summary

Background Plasma biomarkers associated with Alzheimer's disease could improve prognostic assessment for people with Down syndrome in both clinical practice and research settings. We aimed to identify the plasma biomarkers that most accurately predict longitudinal changes in Alzheimer's disease-related pathology and cognitive functioning in individuals with Down syndrome.

Methods This longitudinal cohort study included data from 258 adults (aged ≥25 years) with Down syndrome who were followed up prospectively every 16 months as part of the longitudinal Alzheimer's Biomarker Consortium–Down Syndrome study (recruited from seven university sites in the USA and UK between July 13, 2016, and Jan 15, 2019). Participants had baseline and longitudinal assessments of plasma tau phosphorylated at threonine 217 (p-tau217), glial fibrillary acidic protein (GFAP), amyloid β ($A\beta_{42/40}$), neurofilament light (NfL), or total tau (t-tau). Associations of baseline plasma biomarkers and longitudinal changes in plasma biomarkers with changes in global cognitive functioning (Down Syndrome Mental Status Examination [DS-MSE] scores), Aβ-PET, and tau-PET were examined using linear regression models. Plasma biomarker-associated risk of progression to dementia was assessed using Cox regression analysis.

Findings Baseline p-tau217, as well as GFAP, NfL, or t-tau, were individually associated with longitudinal changes in DS-MSE, Aβ-PET, and tau-PET, and with progression to dementia. However, in combined models, only baseline p-tau217 remained associated with changes in DS-MSE (β –0·30 [95% CI –0·45 to –0·15], p=0·0001, n=220), tau-PET (0·42 [0·14 to 0·70], p=0·0039, n=88), and progression to dementia (hazard ratio 3·51 [95% CI 1·76–7·00], p=0·0004, n=194), whereas baseline p-tau217 (0·29 [0·14–0·45], p=0·0003) and GFAP (0·37 [0·18–0·56], p=0·0003) were associated with changes in Aβ-PET (n=106 for both). Similar associations were shown between longitudinal p-tau217 or GFAP and changes in DS-MSE (p-tau217: β –0·33 [95% CI–0·52 to –0·13], p=0·0015, n=133), tau-PET (p-tau217: 0·61 [0·40 to 0·83], p<0·0001, n=87), and Aβ-PET (p-tau217: 0·35 [0·19 to 0·50], p<0·0001; GFAP: 0·49 [0·27 to 0·70], p<0·0001, n=88).

Interpretation Baseline and longitudinal plasma p-tau217 were associated with subsequent decline in global cognition, progression to dementia, and increased tau burden, whereas baseline p-tau217 and GFAP were associated with Aβ accumulation. These findings suggest that plasma p-tau217 and GFAP might be valuable for prognostic assessment of Alzheimer's disease in people with Down syndrome in both clinical and research contexts. The results further support evaluation of these biomarkers for monitoring disease progression in clinical trials of Down syndrome-related Alzheimer's disease.

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Introduction

Down syndrome is considered a genetic form of Alzheimer's disease, with more than 90% of adults with Down syndrome developing Alzheimer's disease-related pathological changes by the age of 40 years, likely due to an additional copy of the amyloid precursor protein-encoding gene located on chromosome 21.[1–3] Despite some differences in the timing, spatial distribution, or magnitude, the overall progression of amyloid-β (Aβ) and tau brain deposition (measured with PET) is relatively similar in Down syndrome and autosomal dominant Alzheimer's disease.[4,5] As such, blood biomarkers of Alzheimer's disease-related Aβ and tau pathologies, including tau phosphorylated at threonine 217 (p-tau217), tau phosphorylated at threonine 181 (p-tau181), neurofilament light (NfL; a marker of neurodegeneration), and glial fibrillary acidic protein (GFAP; a marker of astrogliosis) have shown

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See Online for appendix

Research in context

Evidence before the study

The literature was reviewed using PubMed. We searched from database inception to Aug 1, 2024, for articles in English relating to associations between plasma biomarkers, amyloid and tau pathology, cognition and clinical progression in Down syndrome and Alzheimer's disease. Search terms included "amyloid", "Alzheimer's disease", "cognition", "Down syndrome", "plasma biomarker", "positron emission tomography", and "tau". Several plasma biomarkers, including tau phosphorylated at threonine 217 (p-tau217), tau phosphorylated at threonine 181 (p-tau181), neurofilament light (NfL), and glial fibrillary acidic protein (GFAP), have shown promise for detection of Alzheimer's disease-related neuropathological processes in Down syndrome. However, previous studies only examined associations of plasma biomarkers with cross-sectional measures of amyloid and tau pathology and cognitive performance.

Added value of this study

To the best of our knowledge, this is the first longitudinal study of adults with Down syndrome comprehensively assessing the potential of the most promising plasma Alzheimer's disease biomarkers (ie, p-tau217, GFAP, NfL, total tau, amyloid β [$A\beta]_{42/40}$) to predict future clinical progression and accumulation of Aβ and tau pathology in individuals with Down syndrome. Specifically, we studied associations of baseline and longitudinal plasma biomarkers (individually and in combination) with longitudinal changes in global cognitive functioning, Aβ-PET and tau-PET, as well as progression to dementia. We found that baseline and longitudinal plasma p-tau217 were associated with subsequent decline in global cognition, progression to dementia, and increased tau burden, whereas both p-tau217 and GFAP were associated with Aβ accumulation.

Implications of all the available evidence

Our findings are consistent with previous evidence from sporadic and autosomal dominant Alzheimer's disease and add to earlier cross-sectional studies of Down syndrome. We suggest that blood p-tau217, potentially together with GFAP, might be useful in the prognostic workup of Alzheimer's disease in individuals with Down syndrome in both clinical practice and trials.

promise for assessment of Alzheimer's disease in people with Down syndrome.[6–10] For example, in two separate studies that included people with Down syndrome,[8,9] plasma p-tau181 and GFAP were associated with baseline measures of Aβ-PET and brain atrophy in brain regions typically associated with Alzheimer's disease pathology, and accurately discriminated individuals with Down syndrome who had symptoms of Alzheimer's disease from those without symptoms. At the same time, in a cross-sectional investigation comparing different plasma biomarkers (ie, $A\beta_{42/40}$, GFAP, NfL, p-tau217, and total tau [t-tau]), p-tau217 had the best performance to detect abnormal Aβ-PET or tau-PET status and was the only plasma biomarker independently associated with cognitive scores at baseline.[7] Although these findings are encouraging, an important step forward will be to develop blood biomarkers for predicting subsequent cognitive decline and changes in tau burden, where the latter is more related to onset of neurodegeneration and cognitive decline than changes in Aβ pathology. The complexity of cognitive testing in Down syndrome, which is challenging due to differences in baseline levels of intellectual disability and cognitive function, together with highly variable age at onset of dementia caused by Alzheimer's disease (spanning 32 years),[11] highlights the pivotal need for biomarker-supported detection of Alzheimer's disease-related cognitive decline. Such biomarkers could be implemented in the prognostic workup of people with Down syndrome in clinical practice, to enable proper care and health policy decisions for this population. The biomarkers might also facilitate enrolment of participants with Down syndrome, who are at high risk of subsequent tau accumulation and cognitive decline, in clinical trials testing the effects of disease-modifying therapies on these two outcomes. Additionally, plasma biomarkers of Aβ pathology could be useful for the screening and selection of individuals with Down syndrome in clinical trials of amyloid-targeting drugs. Importantly, relations between plasma biomarkers and changes in Aβ-PET or tau-PET over time in people with Down syndrome are currently unknown. Furthermore, although plasma NfL and GFAP have been linked to clinical progression in people with Down syndrome along the Alzheimer's disease continuum,[9,12] associations between other plasma biomarkers (eg, p-tau217) and longitudinal cognition in this population remain largely unexplored. Therefore, we aimed to establish which of a number of promising plasma biomarkers associated with Alzheimer's disease best predict and track cognitive decline and changes in Aβ and tau pathology in people with Down syndrome. We measured plasma concentrations of $A\beta_{42/40}$, GFAP, NfL, p-tau217, and t-tau at baseline and follow-up in a cohort of participants with Down syndrome who had longitudinal cognitive and PET assessments.

Methods

Study design and participants

In this longitudinal cohort study, we analysed data collected at seven university sites in the USA and UK. This study included adults (aged ≥25 years) with Down syndrome who were followed up prospectively every 16 months as part of the Alzheimer Biomarker Consortium-Down Syndrome (ABC-DS) study[13] and who

all had baseline plasma quantification, baseline and longitudinal clinical diagnosis, and global cognitive assessment at baseline and at least one follow-up visit (appendix p 2). Participants were enrolled between July 13, 2016, and Jan 15, 2019 (date of data download: May 2, 2024).

ABC-DS was conducted under institutional review board-approved protocols (Advarra Pro00044843), and participants or their caregivers provided written informed consent to participate. The study followed the STROBE reporting guidelines for longitudinal studies.

Procedures

Sex and race data were collected based on caregiver reports or medical records. Longitudinal global cognitive functioning was assessed using the Down Syndrome Mental Status Examination (DS-MSE), with the DS-MSE scores ranging from 0 to 87 (higher scores indicated better cognitive performance).[13] Premorbid intellectual disability level was determined before any concerns regarding Alzheimer's disease as part of the study or as recorded in clinical records.[14] Participants with Down syndrome were classified as being asymptomatic, or received a diagnosis of mild cognitive impairment or dementia caused by Alzheimer's disease, or were classified as "unable to determine". Diagnosis was determined by clinical consensus diagnosis conferences generally in accordance with the recommendations of the AAMR–IASSID Working Group for the Establishment of Criteria for the Diagnosis of Dementia in Individuals with Developmental Disability and was based on medical, clinical, and cognitive testing considered in reference to baseline intellectual disability and any recent major life transitions or events.[15] A detailed overview of performed tests has been published previously.[13] No genetic findings (eg, apolipoprotein E [*APOE*] gene status) or biomarker results (eg, biofluid or neuroimaging) were available to the consensus team members for diagnosis. Participants were classified as cognitively asymptomatic when they were without cognitive or functional decline, beyond what would be expected with ageing in a person with Down syndrome, per se. Participants were classified as having mild cognitive impairment when they had some cognitive or functional decline over and above what would be expected with ageing per se, but not severe enough to indicate the presence of dementia. Participants were categorised as having dementia caused by Alzheimer's disease when there was evidence of substantial progressive decline in cognitive functioning and daily living skills. An "unable to determine" category was used to indicate that declines were observed but could be caused by major life circumstance (eg, staff changes or family death) or conditions unrelated to Alzheimer's disease (eg, severe sensory loss or active medical or current untreated psychiatric symptoms).

Blood collection and processing were harmonised across all ABC–DS clinical sites. Plasma samples were analysed for p-tau217 (proprietary assay developed by Lilly Research Laboratories [Indianapolis, IN, USA] on a Mesoscale Discovery platform), GFAP (GFAP Discovery Simoa kit, Quanterix [Billerica, MA, USA]), NfL (NF-light Advantage Simoa kit, Quanterix), and t-tau, $A\beta_{42}$, and $A\beta_{40}$ (Neurology 3-Plex Simoa kit, Quanterix), as previously described.[7,10] Further details of sample collection, plasma analysis, and the analytical performance of the assays are in the appendix (pp 3–4).

Brain Aβ and tau deposition were measured using Aβ-PET and tau-PET imaging. Of the participants, a subset had longitudinal Aβ-PET ([^{11}C]Pittsburgh compound B, n=63 [one baseline and one follow-up scan per participant] or [^{18}F]florbetapir (AV45), n=43 [n=26 with two scans and n=17 with three scans]) and tau-PET ([^{18}F]flortaucipir, n=89, one baseline and one follow-up scan per participant; appendix pp 2, 5). PET imaging has been described in detail previously.[16,17] For Aβ-PET, a global standard uptake value ratio was determined for each participant from the tracer concentration in a standard cortical region of interest (including anterior cingulate, frontal cortex, parietal cortex, precuneus, temporal cortex, and striatum) normalised to the concentration in the whole cerebellum as the reference. To account for tracer differences, global standard uptake value ratios were transformed into the standardised Centiloid metric.[18,19] Aβ-PET positivity was defined as a Centiloid value of more than 20, on the basis of the inclusion criteria of the AHEAD-4 secondary prevention trial[20] and consistent with a previously derived threshold for Down syndrome.[17] For tau-PET, the target region of interest consisted of the commonly used temporal meta-region of interest (entorhinal cortex, inferior and middle temporal cortices, fusiform gyrus, parahippocampal cortex, and amygdala)[21] using the cerebellar grey matter as the reference region. MRI scans were parcellated using FreeSurfer version 6.0 or 7.2 (the same version was used for scans from the same individual). Observed longitudinal PET data are shown in the appendix (p 6).

Statistical analysis

All analyses were performed in R version 4.4.0. Demographic differences were assessed using the χ^2 and Kruskal-Wallis tests (continuous measures were non-normally distributed on visual inspection). Linear mixed models were used to calculate individual DS-MSE, Aβ-PET, tau-PET, and plasma biomarker slopes. When calculating plasma biomarker slopes, we included a plasma measurement wave as the covariate to adjust for potential batch-to-batch variability in assay performance. Associations of baseline plasma biomarkers with DS-MSE, Aβ-PET, and tau-PET slopes were examined using linear regression models with each model including a single baseline plasma biomarker as a

predictor. Subsequently, we performed a combined model including all significant plasma biomarkers from single-biomarker models as predictors. To explore potential bias associated with the inclusion of participants with fast cognitive decline, we performed a post-hoc sensitivity analysis in a sub-cohort of participants with follow-ups longer than the mean follow-up time in the entire cohort. To determine whether the associations of baseline plasma biomarkers with DS-MSE slopes were driven by Aβ status, we also included an interaction between baseline plasma biomarkers and Aβ status as a predictor in the models. The predictive value of baseline plasma biomarkers on progression to dementia or mild cognitive impairment was investigated using Cox regression and Kaplan-Meier survival analyses. Participants without a dementia or mild cognitive impairment diagnosis were censored at the last follow-up visit. Cox regression models were used to calculate hazard ratios (HRs) and 95% CIs. Participants with undetermined cognitive status at any of the visits were excluded from these analyses. Associations of plasma biomarker slopes with DS-MSE, Aβ-PET, and tau-PET slopes were tested in linear regression models. Plasma biomarker slopes were compared between groups categorised by cognitive status using Wilcoxon rank sum test. Log-transformed plasma biomarker data were used in regression and survival analysis. To aid interpretability, all continuous predictors and outcome measures were scaled to retrieve standardised regression coefficients (referred to as β) that are interpreted as the change in the outcome measures (ie, DS-MSE, Aβ-PET, and tau-PET slopes) per each SD increase in log-transformed plasma biomarker data. Model fit and performance were assessed with adjusted coefficient of determination (adjusted R^2). All linear regression models were corrected for baseline age, sex, premorbid intellectual disability, *APOE*ε4 status, and site. Cox regression models were corrected for baseline age, sex, premorbid intellectual disability, and *APOE*ε4 as there were too few events (ie, progression to either dementia or mild cognitive impairment) per site (three events or less for four of seven sites) to include site as a covariate. We also performed a post-hoc sensitivity analysis adjusting for site, baseline age, sex, premorbid intellectual disability, and *APOE*ε4 in a subsample only including sites with more than three events. A p value threshold of <0·05 was used to determine statistical significance.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

The study included 258 participants with Down syndrome recruited between July 13, 2016, and Jan 15, 2019 (mean age 44·9 [SD 9·33] years; 138 [53%] were female and 120 [47%] were male; 249 [96%] were White, two [1%] were Black or African American, five [2%] were Asian, and two [1%] were of unknown race). Of these 258 participants, 195 participants were cognitively asymptomatic, 57 participants were diagnosed with cognitive impairment (34 with mild cognitive impairment and 23 with dementia), and six participants had undetermined cognitive status at baseline. There were significant differences in age (p<0·0001), sex (0·0042), and global cognition (DS-MSE score; p=0·0001) but not in the levels of premorbid intellectual disability between the groups (table 1). Baseline plasma concentrations of all biomarkers (ie, p-tau217 [p<0·0001], GFAP [p<0·0001], NfL [p<0·0001], and t-tau [p=0·0003]) except $A\beta_{42/40}$ also significantly varied across the groups. Participant characteristics in subcohorts with Aβ-PET and tau-PET are presented in the appendix (p 5). There were significant differences in age (p=0·011), global cognition (p=0·020), and diagnosis (p=0·040) between the cohorts with cognitive data (n=258), tau-PET data (n=89), and Aβ-PET data (n=106). The PET cohorts were younger, had higher DS-MSE scores, and included higher numbers of participants with asymptomatic Down syndrome, compared with the overall cohort with cognitive data, all indicative of less severe disease.

Longitudinal measures of global cognition (DS-MSE) were available in 221–258 participants with baseline plasma biomarker data (mean follow-up time 2·75 years [SD 0·93]; maximum 4·66 years). All baseline plasma biomarkers, except for $A\beta_{42/40,}$ were associated with subsequent longitudinal change in global cognitive functioning (p-tau217: β –0·40 [95% CI –0·51 to –0·28], p<0·0001, adjusted R^2=0·34; GFAP: –0·41 [–0·56 to –0·25], p<0·0001, adjusted R^2=0·29; NfL: –0·36 [–0·52 to –0·19], p<0·0001, adjusted R^2=0·27; t-tau: –0·19 [–0·31 to –0·07], p=0·0016, adjusted R^2=0·24; $A\beta_{42/40}$: –0·02 [–0·14 to 0·10], p=0·71, adjusted R^2=0·20; table 2, figure 1).

The models including baseline plasma p-tau217, GFAP, NfL, or t-tau individually explained more variance than the corresponding basic models (ie, models only including age, sex, premorbid intellectual disability, *APOE*ε4 status, and site as independent variables). However, the strongest effect was shown for p-tau217 (ΔR^2=0·12), followed by GFAP (ΔR^2=0·07), NfL (ΔR^2=0·06), and t-tau (ΔR^2=0·03); table 2). Furthermore, in a model combining the four significant baseline plasma biomarkers, only p-tau217 remained significantly associated with change in global cognition over time (β –0·30 [95% CI –0·45 to –0·15], p=0·0001, adjusted R^2=0·34; table 2). To explore potential bias associated with the inclusion of patients with fast cognitive decline, we performed a post-hoc sensitivity analysis in a subcohort of 139 participants with follow-ups of longer than 2·75 years (mean follow-up 3·42 years [SD 0·56]). In this analysis, plasma p-tau217 was the only significant

biomarker in the combined model, whereas plasma p-tau217, GFAP, and NfL were all individually associated with future cognitive decline (appendix p 7).

Subsequently, we ran regression models with an interaction between baseline plasma biomarkers and baseline Aβ status to test whether abnormal brain Aβ concentrations affect the associations between the biomarkers and cognitive changes (appendix pp 8–9). In the subcohort of study participants who had Aβ-PET (n=177–192), we found a significant interaction between Aβ status and p-tau217 (β –0·72 [95% CI –0·98 to –0·45], p<0·0001, adjusted R^2=0·42), GFAP (–0·50 [–0·82 to –0·18], p=0·0025, adjusted R^2=0·33), NfL (–0·56 [–0·86 to –0·25], p=0·0005, adjusted R^2=0·33), and t-tau (–0·28 [–0·54 to –0·01], p=0·041, adjusted R^2=0·30). However, in a combined model, again only the p-tau217 and Aβ interaction remained a significant predictor of global cognitive functioning slope (β –0·61 [95% CI –0·96 to –0·27], p=0·0006, adjusted R^2=0·39). Results were highly similar when restricting analyses to the Aβ-positive subpopulation (n=90–94), in which only p-tau217 remained a significant predictor in a combined model (β –0·44 [0·73 to –0·16], p=0·0030, adjusted R^2=0·30, appendix p 10).

Consistent with findings in sporadic Alzheimer's disease,[22] baseline tau-PET was the strongest predictor of future cognitive decline in individuals with Down syndrome whereas no added value was seen for plasma biomarkers in this combined statistical model (appendix p 11).

Overall progression rate to a clinical diagnosis of dementia was 13% (28 of 222 participants). Higher baseline p-tau217 (HR 4·15 [95% CI 2·45–7·02] per SD increase of log-transformed data, p<0·0001), GFAP (4·39 [2·35–8·21], p<0·0001), NfL (1·91 [1·08–3·38], p=0·027), t-tau (2·03 [1·29–3·19], p=0·0022), and $A\beta_{42/40}$ (0·54 [0·35–0·84], p=0·0059) were associated with a higher risk of subsequent progression to dementia (appendix p 12). Similar to the findings on changes in cognition, only p-tau217 remained a significant predictor of progression to dementia in a combined model (HR 3·51 [1·76–7·00], p=0·0004; appendix pp 12–13) and of progression to mild cognitive impairment (2·06 [1·17–3·62], p=0·012; appendix p 14). Similar results were seen in a post-hoc sensitivity analysis adjusting for site (in addition to baseline age, sex, premorbid intellectual disability, and *APOE*ε4) that only included sites with more than three events (appendix pp 15–16).

In participants with available longitudinal tau-PET (n=87–89; mean time between the scans 2·77 years [SD 1·14]), p-tau217 (β 0·40 [95% CI 0·18–0·62], p=0·0006, adjusted R^2=0·29), GFAP (0·32 [0·04–0·61], p=0·028, adjusted R^2=0·22), and t-tau (0·21 [0·02–0·41], p=0·035, adjusted R^2=0·22) were associated with subsequent longitudinal changes in tau-PET. However, only p-tau217 (β=0·42 [0·14–0·70], p=0·0039, adjusted

	Asymptomatic (n=195)	Mild cognitive impairment (n=34)	Dementia (n=23)	p value
Age, years	42·0 (36·0–50·0)	52·0 (46·2–53·8)	54·0 (51·0–57·0)	<0·0001
Sex				0·0042
Female	97 (50%)	7 (21%)	13 (57%)	..
Male	98 (50%)	27 (79%)	10 (43%)	..
Race				0·0091
White	189 (97%)	31 (91%)	23 (100%)	..
Black or African American	0	2 (6%)	0	..
Asian	4 (2%)	1 (3%)	0	..
Unknown	2 (1%)	0	0	..
*APOE*ε4 carrier				0·0021
Yes	37 (19%)	12 (35%)	11 (48%)	..
No	158 (81%)	22 (65%)	12 (52%)	..
Cognition				
DS-MSE score	68·0 (58·0–74·0)	56·2 (43·2–64·2)	43·0 (29·5–54·0)	0·0001
Premorbid intellectual impairment				0·29
Mild	112 (57%)	13 (38%)	13 (57%)	..
Moderate	64 (33%)	18 (53%)	8 (35%)	..
Severe	19 (10%)	3 (9%)	2 (9%)	..
Plasma				
p-tau217, pg/mL	0·46 (0·35–0·65)	0·91 (0·51–1·32)	1·24 (0·72–1·74)	<0·0001
GFAP, pg/mL	130 (89–216)	235 (146–386)	371 (307–482)	<0·0001
NfL, pg/mL†	12·6 (8·9–21·9)	22·9 (16·3–28·2)	32·4 (24·6–45·5)	<0·0001
t-tau, pg/mL†	2·22 (1·79–2·71)	2·56 (2·17–2·92)	3·10 (2·46–3·81)	0·0003
$A\beta_{42/40}$†	0·034 (0·031–0·036)	0·032 (0·030–0·036)	0·034 (0·031–0·039)	0·37

Data are n (%) or median (IQR). The study included six participants with undetermined cognitive status at baseline not shown in the table. Aβ=amyloid β. *APOE*ε4=apolipoprotein E ε4. DS-MSE=Down Syndrome Mental Status Examination. GFAP=glial fibrillary acidic protein. NfL=neurofilament light. p-tau217=tau phosphorylated at threonine 217. t-tau=total tau. *Group differences were tested using the χ^2 and Kruskal-Wallis tests. †NfL, t-tau, and $A\beta_{42/40}$ data were missing for 33 participants, 37 participants, and 37 participants, respectively.

Table 1: **Baseline demographics**

	n	Single biomarker models β (95% CI), p value	Adjusted R^2 full model (basic model)	Combined model (n=220) β (95% CI), p value
p-tau217	258	–0·40 (–0·51 to –0·28), p<0·0001	0·34 (0·22)	–0·30 (–0·45 to –0·15), 0·0001
GFAP	258	–0·41 (–0·56 to –0·25), <0·0001	0·29 (0·22)	–0·12 (–0·32 to 0·08), 0·25
NfL	225	–0·36 (–0·52 to –0·19), <0·0001	0·27 (0·21)	–0·14 (–0·31 to 0·04), 0·12
t-tau	221	–0·19 (–0·31 to –0·07), 0·0016	0·24 (0·20)	–0·08 (–0·20 to 0·04), 0·17
$A\beta_{42/40}$	221	–0·02 (–0·14 to 0·10), 0·71	0·20 (0·20)	NA

β estimates and p values are from the linear regression model, including log-transformed plasma biomarkers either individually (single biomarker models) or in combination (combined model) as independent variables and slopes of DS-MSE as outcome, adjusting for baseline age, sex, premorbid intellectual disability, *APOE*ε4 status, and site. All continuous predictors and outcome measures were scaled to retrieve the standardised βs. The combined model included only plasma biomarkers that were significant in the single biomarker models. The basic model included baseline age, sex, premorbid intellectual disability, *APOE*ε4 status, and site as the independent variables. Aβ=amyloid β. *APOE*ε4=apolipoprotein E ε4. DS-MSE=Down Syndrome Mental Status Examination. GFAP=glial fibrillary acidic protein. NA=not applicable. NfL=neurofilament light. p-tau217=tau phosphorylated at threonine 217. t-tau=total tau.

Table 2: **Associations between baseline plasma biomarkers and change in global cognitive functioning (DS-MSE)**

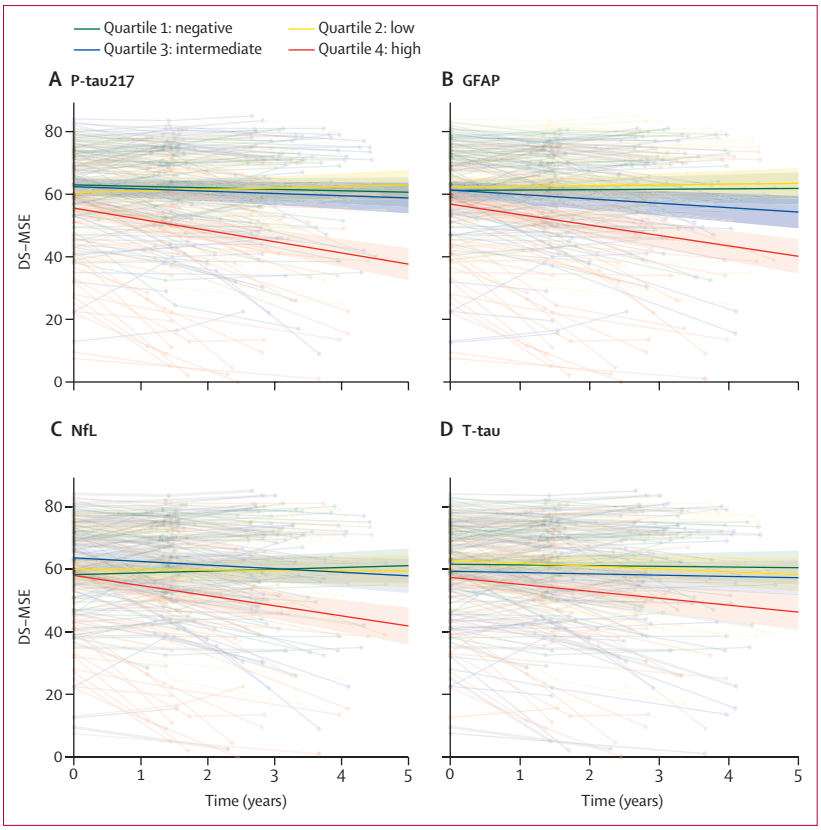

Figure 1: **Association between baseline plasma biomarkers and longitudinal cognition**
Spaghetti plots visualise associations of plasma p-tau217 (A), GFAP (B), NfL (C), and t-tau (D) with cognitive decline. Each transparent line represents an independent individual connecting longitudinal DS-MSE observations. Solid lines represent the estimated cognitive trajectories for plasma biomarker quartiles (with shaded areas representing 95% CI) that were derived using linear mixed effects models and the "ggeffects" package of R software. Linear mixed effects models included longitudinal DS-MSE as the outcome and interaction between plasma biomarker quartiles and time as the predictor adjusting for age, sex, premorbid intellectual disability, *APOE*ε4 status, and site. Plasma NfL and t-tau data were missing for 33 and 37 participants, respectively. Further results for the associations between plasma biomarkers and cognition are presented in table 2. *APOE*ε4=apolipoprotein E ε4. DS-MSE=Down Syndrome Mental Status Examination. GFAP=glial fibrillary acidic protein. NfL=neurofilament light. p-tau217=tau phosphorylated at threonine 217. t-tau=total tau.

	n	Single biomarker models β (95% CI), p value	Adjusted R^2 full model (basic model)	Combined model (n=88) β (95% CI), p value
p-tau217	89	0·40 (0·18 to 0·62), 0·0006	0·29 (0·18)	0·42 (0·14 to 0·70), 0·0039
GFAP	89	0·32 (0·04 to 0·61), 0·028	0·22 (0·18)	0·18 (–0·14 to 0·50), 0·26
NfL	87	–0·11 (–0·41 to 0·19), 0·46	0·18 (0·19)	NA
t-tau	88	0·21 (0·02 to 0·41), 0·035	0·22 (0·18)	0·21 (–0·07 to 0·50), 0·14
$A\beta_{42/40}$	88	0·00 (–0·20 to 0·21), 0·97	0·17 (0·18)	NA

β estimates and p values are from the linear regression model, including log-transformed plasma biomarkers either individually (single biomarker models) or in combination (combined model) as the independent variables and slopes of tau-PET standard uptake value ratio as outcome, adjusting for baseline age, sex, premorbid intellectual disability, *APOE*ε4 status, and site. All continuous predictors and outcome measures were scaled to retrieve the standardised β. The combined model included only plasma biomarkers that were significant in the single biomarker models. The basic model included baseline age, sex, premorbid intellectual disability, *APOE*ε4 status, and site as the independent variables. Aβ=amyloid β. *APOE*ε4=apolipoprotein E ε4. GFAP=glial fibrillary acidic protein. NA=not applicable. NfL=neurofilament light. p-tau217=tau phosphorylated at threonine 217. t-tau=total tau.

Table 3: **Associations between baseline plasma biomarkers and tau accumulation (tau-PET, temporal meta-region of interest)**

R^2=0·31) remained a significant predictor of changes in tau-PET in a combined model (table 3).

The associations between baseline p-tau217 and longitudinal tau-PET were more apparent for the Aβ-positive participants, with the interaction between plasma biomarker and Aβ status being significant for only p-tau217 (β 0·74 [95% CI 0·32–1·20], p=0·0008, adjusted R^2=0·42; figure 2A, appendix p 17).

Aβ-PET data were available in 103–106 participants (mean time between the scans 2·80 years [SD 0·89]). In this subcohort, p-tau217 (β 0·40 [95% CI 0·25–0·56], p<0·0001, adjusted R^2=0·60) and GFAP (0·50 [0·31–0·69], p<0·0001, adjusted R^2=0·60) were significantly associated with longitudinal changes in Aβ-PET individually and when combined in one model (p-tau217: 0·29 [0·14–0·45], p=0·0003; GFAP: 0·37 [0·18–0·56], p=0·0003, adjusted R^2=0·65; table 4). Although associations of these biomarkers as well as NfL with Aβ-PET slopes differed by Aβ status individually (figure 2B–D), only the interaction between p-tau217 and Aβ status was significant in a combined model (appendix p 18).

We investigated whether changes in plasma biomarkers over time were associated with disease progression in subcohorts of participants who also had longitudinal cognitive and PET assessments (appendix p 2). The results from the combined model revealed that accelerated increase in plasma concentrations of p-tau217, but no other plasma biomarkers, was significantly associated with worsening of global cognition (β –0·33 [95% CI –0·52 to –0·13], p=0·0015, adjusted R^2=0·36; appendix p 19). Furthermore, higher slopes of plasma p-tau217 but not other plasma biomarkers were associated with a heightened increase in tau-PET signal (β 0·61 [95% CI 0·40 to 0·83], p<0·0001, adjusted R^2=0·42; appendix p 20). We also observed significant independent effects of p-tau217 and GFAP slopes (p-tau217: β 0·35 [95% CI 0·19 to 0·50], p<0·0001; GFAP: 0·49 [0·27 to 0·70], p<0·0001; adjusted R^2=0·70) on longitudinal change in Aβ-PET (appendix p 21). As shown in the appendix (p 22), slopes of p-tau217, GFAP, and NfL were lower in participants with Down syndrome who were asymptomatic than those with Down syndrome who were asymptomatic and progressed to mild cognitive impairment, those with Down syndrome who were asymptomatic and progressed to dementia, those with Down syndrome with mild cognitive impairment who progressed to dementia, and those with Down syndrome and dementia. However, only p-tau217 slopes were increased in participants with Down syndrome and mild cognitive impairment compared with those with Down syndrome who were asymptomatic.

Discussion

In this longitudinal study of adults with Down syndrome who were followed up for up to 4·7 years, we found that baseline plasma p-tau217 predicted future cognitive

decline and accumulation of tau pathology. Additionally, higher baseline p-tau217 concentrations were associated with increased risk for progression to dementia. Although other plasma biomarkers (ie, GFAP, NfL, and t-tau) individually showed significant associations with longitudinal change in cognition and tau-PET, as well as progression to dementia, none of these associations was independent of the effects of p-tau217. That is, in the models combining the different plasma biomarkers, only p-tau217 remained a significant predictor of clinical progression and tau deposition. We also found that higher baseline plasma p-tau217 and GFAP both significantly and independently predicted future Aβ pathology. Finally, longitudinal increases in plasma p-tau217 were independently associated with faster rates of cognitive decline and changes in tau-PET over time, whereas longitudinal plasma p-tau217 and GFAP were both independently associated with the accumulation of Aβ proteinopathy.

Previous studies in people with Down syndrome have suggested associations of plasma NfL and t-tau with measures of episodic memory and visuospatial function at baseline[23] and increased risk of change in clinical diagnosis during follow-up in individuals with Down syndrome who were asymptomatic or with mild cognitive impairment and also had higher baseline concentrations of NfL and GFAP.[9,12] Data on plasma $A\beta_{42/40}$ have been inconsistent,[23–26] which is possibly due, in part, to substantial variability in the performance of the plasma Aβ immunoassays used in different studies.[27] In the current work, we found that higher baseline plasma concentrations of GFAP, NfL, p-tau217, and t-tau, individually, were all predictive of future cognitive deterioration and progression to dementia. However, one important question when considering the use of plasma biomarkers for diagnosis and prognosis of Alzheimer's disease is whether combining several biomarkers in one model provides any added value. Currently available evidence suggests that plasma p-tau217 is a key plasma biomarker independently associated with clinical progression in sporadic Alzheimer's disease, whereas other plasma biomarkers such as $A\beta_{42/40}$, NfL, and GFAP do not meaningfully improve prognostic information.[28,29] In line with these observations, we found that, in people with Down syndrome, only baseline p-tau217 was significantly associated with rates of cognitive decline in models also including other plasma biomarkers. These results were consistent in the entire sample and in Aβ-positive individuals with Down syndrome, suggesting that plasma p-tau217 as a standalone biomarker could support prediction of future cognitive decline and progression to dementia in individuals with Down syndrome and have an important role as a much-needed biomarker of disease onset.

Notably, models testing association between individual biomarkers and subsequent longitudinal changes in tau tangle burden (as measured by PET) also revealed significant independent effects of baseline plasma p-tau217 but no other plasma biomarkers. Our findings

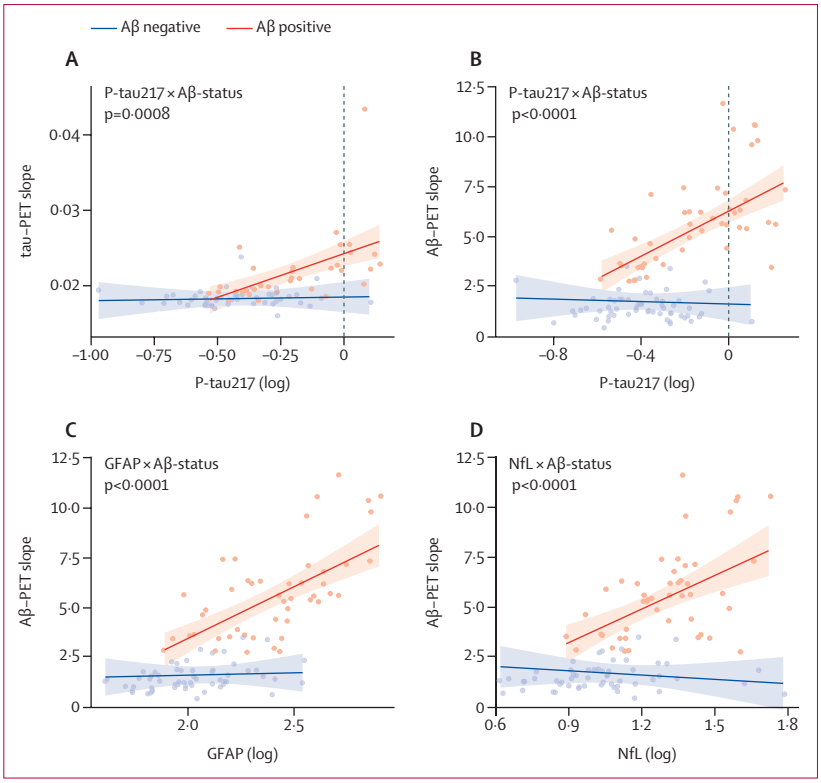

Figure 2: **Association of baseline plasma biomarkers with longitudinal tau-PET and Aβ-PET**
Scatterplots illustrate the association of plasma p-tau217 (A, B), GFAP (C), and NfL (D) with tau-PET slopes (A) and Aβ-PET slopes (B–D) stratified by Aβ status (cutoff point Centiloid >20). Each dot represents an individual biomarker value (log-transformed) and corresponding PET slope value. Regression lines with 95% CI (shaded areas) representing associations between plasma biomarkers and PET slopes were derived using linear regression models and the "ggeffects" package of R software. p values are from linear regression models, including the interaction between each plasma biomarker (log-transformed) and Aβ status as the predictor and subject-specific slopes of tau-PET or Aβ-PET as the outcome adjusted for age, sex, premorbid intellectual disability, *APOE*ε4 status, and site. Plasma NfL data were missing for three participants. Further results for the associations between plasma biomarkers and PET measures are presented in the appendix (pp 17–18). Aβ=amyloid β. *APOE*ε4=apolipoprotein E ε4. GFAP=glial fibrillary acidic protein. NfL=neurofilament light. p-tau217=tau phosphorylated at threonine 217.

	n	Single biomarker models β (95% CI), p value	Adjusted R^2 full model (basic model)	Combined model (n=106) β (95% CI), p value
p-tau217	106	0·40 (0·25 to 0·56), <0·0001	0·60 (0·49)	0·29 (0·14 to 0·45), 0·0003
GFAP	106	0·50 (0·31 to 0·69), <0·0001	0·60 (0·49)	0·37 (0·18 to 0·56), 0·0003
NfL	103	0·16 (–0·06 to 0·38), 0·15	0·49 (0·48)	NA
t-tau	104	0·08 (–0·07 to 0·22), 0·29	0·48 (0·48)	NA
$A\beta_{42/40}$	104	–0·13 (–0·28 to 0·03), 0·10	0·49 (0·48)	NA

β estimates and p values are from linear regression models, including log-transformed plasma biomarkers individually (single biomarker models) or in combination (combined model) as the independent variables and slopes of Aβ-PET Centiloid as the outcome, adjusting for baseline age, sex, premorbid intellectual disability, *APOE*ε4 status, and site. Plasma biomarkers were log-transformed and all continuous predictors and outcome measures were scaled to retrieve the standardised β. The combined model included only plasma biomarkers that were significant in the single biomarker models. The basic model included baseline age, sex, premorbid intellectual disability, *APOE*ε4 status, and site as the independent variables. Aβ=amyloid β. *APOE*ε4=apolipoprotein E ε4. GFAP=glial fibrillary acidic protein. NA=not applicable. NfL=neurofilament light. p-tau217=tau phosphorylated at threonine 217. t-tau=total tau.

Table 4: **Associations between baseline plasma biomarkers and amyloid accumulation (global Aβ-PET)**

on p-tau217 are in agreement with earlier studies showing that higher p-tau217 concentration at baseline was related to accelerated increase in tau-PET signal over time in sporadic Alzheimer's disease and autosomal dominant Alzheimer's disease.[30,31] In one of these studies,[31] no association with longitudinal tau-PET was reported for plasma $A\beta_{42/40}$ or NfL, which is also in line with the present results. In contrast with the findings on clinical progression and tau deposition, baseline plasma p-tau217 and GFAP both predicted future accumulation of Aβ aggregates in the brain. Earlier cross-sectional work in sporadic Alzheimer's disease has linked plasma GFAP with brain Aβ pathology.[32,33] However, it has been reported that combining baseline plasma p-tau217 and $A\beta_{42/40}$ measured using state-of-the art mass spectrometry-based assays improved prediction of future Aβ accumulation in cognitively unimpaired individuals with no added value of GFAP.[34] Further investigations using high performance mass spectrometry methods are needed to assess the use of plasma biomarkers, especially p-tau217, $A\beta_{42/40}$, and GFAP (all of which are affected by brain Aβ deposition), to predict longitudinal changes in Aβ burden in Down syndrome.

Although published data on longitudinal plasma biomarkers, cognitive performance, and PET imaging in Alzheimer's disease are scarce, existing evidence suggests that change over time in plasma concentrations of p-tau217 but no other plasma biomarkers, including GFAP, NfL, and $A\beta_{42/40}$, is associated with cognitive decline.[35] Our longitudinal plasma biomarker results in people with Down syndrome (that were clearly congruent with the cross-sectional analysis) further support the use of plasma p-tau217 measures to monitor cognitive decline. The findings also indicate the usefulness of longitudinal plasma p-tau217 alone to predict the development of tau pathology and suggest a benefit of combining plasma p-tau217 and GFAP for monitoring Aβ deposition.

Strengths of the current work include the longitudinal design, relatively large sample size of well phenotyped individuals with Down syndrome with longitudinal plasma assessments and availability of longitudinal cognitive, clinical, and PET imaging data. However, there are some limitations to consider. First, the number of participants with available longitudinal PET scans was limited to a portion of the ABC-DS participants; hence, these results should be interpreted with caution. Nevertheless, this cohort represents one of the largest Down syndrome cohorts worldwide for which there are any longitudinal PET data. Second, plasma biomarker data, and in particular longitudinal GFAP data, were missing for some participants. However, we do not consider that the missing samples introduced bias in the study since combined models included subcohorts in which all plasma biomarkers were available. Nevertheless, studies in larger Down syndrome cohorts should perform an in-depth examination of the association between changes in plasma biomarkers, cognitive function, and Aβ and tau pathologies, and how these associations depend on the brain amyloid concentrations. Finally, plasma samples were analysed using immunoassays, and it is yet to be determined if more accurate mass spectrometry-based approaches could improve biomarker performance.

In conclusion, plasma p-tau217 is a promising standalone biomarker that can predict cognitive decline, progression to dementia, and changes in tau burden in Down syndrome, and plasma p-tau217 and GFAP might be useful for monitoring the accumulation of Aβ pathology. Our findings support the implementation of especially plasma p-tau217, and potentially also GFAP, in the prognostic workup of Alzheimer's disease in people with Down syndrome in both clinical practice and drug trials. The ability of these biomarkers to track disease progression and serve as surrogate endpoints in clinical trials of Down syndrome-related Alzheimer's disease should be further evaluated. For implementation in clinical practice, however, regulatory approved blood tests with established thresholds for abnormality would be required.

Contributors

All authors participated in the collection of the data, had full access to all the data in the study, and reviewed the manuscript for intellectual content. OH, BLH, BTC, and SJ designed and coordinated the study. SJ and LEC analysed the data and were responsible for writing and submitting the manuscript. BLH and BTC accessed and verified data. SJ, LEC, NM-C, RO, BTC, BLH, and OH contributed to data interpretation. All authors had final responsibility for the decision to submit for publication.

Data sharing

The data used in this analysis are available on request to the Alzheimer's Biomarker Consortium–Down Syndrome investigators, provided data request applications are approved by the studies' committees. The data request application is available at https://pitt.co1.qualtrics.com/jfe/form/SV_cu0pNCZZlrdSxUN.

Declaration of interests

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