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RESEARCH ARTICLE

Plasma p-tau212 as a biomarker of sporadic and Down syndrome Alzheimer's disease

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Abstract

BACKGROUND: All individuals with Down syndrome (DS) will develop full-blown Alzheimer´s disease (AD) pathology by age 40. Several genes encoded in chromosome 21, including dual-specificity tyrosine phosphorylation-regulated kinase 1A (*DYRK1A*), have been proven to contribute to the pathology. Phosphorylation of tau at

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threonine-212 (p-tau212) is very sensitive to DYRK1A phosphorylation and is increased in DSAD brain lysates. Here, we assessed the potential of this biomarker in DSAD and sporadic AD.

METHODS: Using single molecule array (Simoa) technology, we tested p-tau212 and p-tau181 ($n = 245$ for plasma, $n = 114$ matching cerebrospinal fluid [CSF] samples).

RESULTS: We have confirmed that the levels of plasma p-tau212 are increased in the DS population and sporadic AD cases, including prodromal and mild cognitive impairment states. Plasma p-tau212 started increasing approximately when people became amyloid positron emission tomography positive.

DISCUSSION: Plasma p-tau212 might have utility for theragnostics, monitoring therapy efficacy, and as a target engagement biomarker in clinical trials both in sporadic and DSAD.

KEYWORDS
Alzheimer´s disease, CSF biomarkers, DABNI, Down syndrome, *DYRK1A*, plasma biomarkers, p-tau212, Simoa, SPIN

Highlights

- Plasma p-tau212 is increased in the Down syndrome (DS) population.
- Plasma p-tau212 increases ≈15 years before the disease onset in DSAD.
- Plasma p-tau212 accurately differentiates between control and disease groups.
- Plasma p-tau212 accurately differentiates amyloid beta (Aβ)+ and Aβ− participants.

1 | BACKGROUND

A triplication of chromosome 21 causes Down syndrome (DS).[1] All individuals with DS develop full-blown Alzheimer's disease (AD) pathology by age 40,[2] and the lifetime risk of developing AD exceeds 90% in the seventh decade.[3] The estimated age at onset of AD dementia in this population is 53.8 years, decades before the occurrence of late-onset AD in the general population.[4] Understanding this strong DSAD relationship is important to accelerate diagnostics and treatment. This ultra-high risk is mainly due to the triplication of the amyloid precursor protein (*APP*) gene, which leads to the overproduction of amyloid beta (Aβ) peptides and increased Aβ plaque formation.[5] Although other genes encoded in chromosome 21, such as dual-specificity tyrosine phosphorylation-regulated kinase 1A (*DYRK1A*) and *RCAN1*, contribute to the pathology.[6–9] *DYRK1A* is a dose-sensitive gene, the overexpression of which contributes to DS cognitive dysfunction.[10] This protein phosphorylates different targets involved in AD development and progression, for instance, glycogen synthase kinase-3β (GSK-3β),[11] Presenilin-1 (PSEN1),[12] APP,[6] and tau.[13]

Diagnosing DSAD is challenging due to the association of DS with cognitive dysfunction.[14,15] Recent advances allow us to recognize ante-mortem AD pathology using blood-based biomarkers.[16–19] These reflect the disease almost as accurately as more expensive and less available cerebrospinal fluid (CSF) and imaging biomarkers.[20] Several plasma p-tau biomarkers have been found to reflect both Aβ and tau pathology.[21] Recently validated plasma p-tau212 has shown very high performance for detecting those pathologies and AD diagnosis.[22] That phosphorylation site might also have the strongest biological correlation with AD pathology in DS because threonine-212 is a primary target for DYRK1A in tau protein.[23] Intensified phosphorylation at Thr-212 induces tau aggregation, reduces tau binding to microtubules, and increases cell toxicity in studies in vitro.[24] Levels of p-tau212 are highly elevated in reference to AD and control participants in human DSAD brains.[25] In addition, a major tau phosphatase—protein phos-

phatase 1A (PP1A) is not dephosphorylating p-tau212 derived from AD brains,[26] suggesting that this epitope might be vulnerable to very subtle changes related to AD pathology. Knowing that direct biological association, we hypothesized that p-tau212 is an accurate tau species to reflect AD pathology in the DS population. To test this hypothesis, we used single molecule array (Simoa) immunoassays to measure plasma and CSF p-tau212 concentrations in asymptomatic DS (aDS), prodromal ADDS (pDS), and dementia ADDS (dDS) individuals, as well as in sporadic AD patients both in mild cognitive impairment (MCI) and dementia states, and we compared the results with a validated biomarker.

RESEARCH IN CONTEXT

1. **Systematic review**: A literature review was conducted using traditional search websites. The influence of genes encoded in chromosome 21 on tau phosphorylation at threonine-212 has been known for more than 20 years. These articles are appropriately cited. However, only recent technological advancements allowed us to measure levels of this biomarker in plasma and cerebrospinal fluid.
2. **Interpretation**: Our findings confirm that plasma p-tau212 levels are increased in the Down syndrome (DS) population and continue to increase with progression to Alzheimer's disease (AD). Moreover, this biomarker increases in parallel with amyloid–positron emission tomography and has excellent performance in discriminating amyloid positivity and clinical diagnosis.
3. **Future directions**: Plasma p-tau212 might facilitate clinical trials recruiting and find utility as a biomarker for diagnostic, theragnostic, monitoring, and screening purposes both in sporadic and DSAD. In addition, p-tau212 can find utility as a target engagement biomarker for *DYRK1A* modulators.

2 | METHODS

2.1 | Study design and participants

We performed a cross-sectional cohort study of adults with DS and euploid individuals along the AD continuum in the Hospital of Sant Pau, Barcelona (Spain). Adults with DS in Barcelona were recruited from a population-based health plan designed to screen for symptomatic AD and dementia from other neurological disorders, which includes yearly neurological and neuropsychological assessments. Those subjects interested in research studies are included in the Down Alzheimer Barcelona Neuroimaging Initiative (DABNI) cohort. Participants in the DABNI cohort undergo a thorough neurological and neuropsychological assessment. This includes the Spanish version of the Cambridge Cognitive Examination for Older Adults with Down syndrome (CAMCOG-DS), which evaluates global cognition through tests covering orientation, language, memory, attention, praxis, abstract thinking, and perception. Consistent with prior studies, participants were clinically classified during a consensus meeting involving neurologists and neuropsychologists, who were blinded to biomarker data. They were categorized into the following groups: asymptomatic (or aDS), for those with no clinical or neuropsychological signs of AD-related cognitive decline; prodromal AD (or pDS), for those with cognitive decline attributable to AD without significant impairment of baseline daily activities; and AD dementia (dDS), for those whose cognitive decline interfered with daily functioning. The functional differentiation between pDS and dDS was determined using anamnesis, the Dementia Questionnaire for Persons with Mental Retardation, and the Cambridge Examination for Mental Disorders of Older People with DS and Others with Intellectual Disabilities. Furthermore, intellectual disability (ID) severity was stratified using the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), based on each individual's highest level of functioning achieved in their lifetime. categorized as mild, moderate, or severe/profound. Those subjects interested in research studies are included in the DABNI cohort.[14,15] Optional neuroimaging, plasma, CSF, and genetic biomarker assessments were eligible.[15,27,28] Plasma samples were collected, processed, aliquoted, and frozen at −80°C according to standardized procedures. In the subset of participants that donated CSF samples, the biofluid was acquired according to international consensus recommendations the same morning of the blood sampling, as described previously.[29] We also recruited euploid controls and sporadic AD patients from the Sant Pau Initiative on Neurodegeneration (SPIN cohort). For biological samples, the protocols of collection and analysis for the SPIN and DABNI cohorts are the same. The SPIN cohort is a comprehensive observational platform for studying neurodegenerative diseases, utilizing multiple biomarker types and an integrative research approach. Participants in SPIN consent to donate biofluids (blood and CSF) and undergo detailed neurological and neuropsychological evaluations. A subset also undergoes advanced imaging studies including 3T brain magnetic resonance imaging (MRI), video-polysomnography, and positron emission tomography (PET) imaging for [18F]-fluorodeoxyglucose, amyloid, or tau. Participants are followed for at least 4 years, with additional biofluid samples and imaging studies collected every 2 years. In this study, we included individuals with MCI due to AD (MCI-AD), AD dementia, and cognitively unimpaired controls. Diagnoses were based on internationally recognized clinical criteria, and controls demonstrated normal cognitive performance on standard neuropsychological evaluations. Cognitively normal (CN) controls in the SPIN cohort undergo a structured neurological assessment and a comprehensive neuropsychological battery. Inclusion criteria for controls were normal neuropsychological results for their age and education, a Clinical Dementia Rating (CDR) scale score of 0, and normal AD biomarkers in CSF. Further details on the inclusion and exclusion criteria for the SPIN cohort, as well as a comprehensive description of all procedures, have been described previously.[30]

2.2 | Biomarker measurements

Plasma samples were drawn into 10 mL ethylenediaminetetraacetic acid (EDTA) tubes, centrifuged at 4°C for 10 min, and subsequently stored at −80°C. CSF samples were collected in 10 mL polypropylene tubes (Sarstedt. #62.610.018) and transferred to the laboratory. There, samples were centrifuged, aliquoted, and stored at −80°C within 2 h of collection. Amyloid-PET imaging was conducted using either 18F-Florbetapir or 18F-Flutemetamol tracers, co-registered with each participant's MRI. PET images were intensity-scaled using the whole cerebellum as the reference region. The resulting images were aligned to the cortical ribbon's midpoint, visually inspected for errors, and smoothed with a 10 mm kernel. The images were then normalized to Montreal Neurological Institute (MNI) space, and standardized uptake value ratios (SUVRs) were calculated using target amyloid regions and the whole cerebellum regions as defined on the GAAIN website (www.gaain.org). Finally, SUVR values were converted to the Centiloid scale for consistency. The amyloid-PET cutoff was set at 24 units, as this was the value previously described to be more specific to AD changes.[31] The median time interval between PET and plasma/CSF collection was: 253 days (interquartile range [IQR]: 84–821). Aβ peptide (Aβ40, Aβ42) analyses were performed on the LUMIPULSE G600II, and the cutoff for positivity was 0.062 as determined in the previous publication.[32] All other plasma and CSF biomarker assays were performed on the Simoa HD-X platform at the University of Gothenburg. Concentrations of p-tau212 and p-tau181 were measured using published and validated in-house assays.[16,22] For p-tau181, the AT270 antibody (Invitrogen) was used as a capture antibody and was paired with an n-terminal antibody for detection (Tau12; BioLegend). For p-tau212, a sheep monoclonal antibody was used for capture paired with Tau12 as the detector. Coefficients of variation for three different internal quality controls for plasma were 5.3%–12% for within-plate variation and 6.4%–12% for between-plate variation. For CSF, these values were 10.8%–13.3% and 12.9%–15.5%, respectively.

2.3 | Statistical analysis

The diagnostic performance of the biomarkers was assessed through receiver-operating characteristic (ROC) curve analyses. Logistic regression models incorporating age, sex, and apolipoprotein E (*APOE*) ε4 status were used to evaluate the added diagnostic accuracy of biomarkers. Comparisons of the areas under the curve (AUCs) were performed using DeLong's test with corrections for multiple comparisons. Spearman correlation is used to examine correlations. Fold changes relative to median levels are calculated for their respective asymptomatic groups. Potential outliers were evaluated through visual inspection of the normalized data distributions, but no values required exclusion. Baseline characteristics across diagnostic groups were compared using age-adjusted analysis of covariance (ANCOVA) with age as a covariate, followed by Tukey's post hoc test with corrections for multiple comparisons.

To examine the temporal progression of plasma biomarker changes in individuals with DS, we applied a first-degree locally estimated scatterplot smoothing curve (LOESS) curve to data from adults with DS and age-matched controls independently. Estimated years to symptom onset (EYO) were calculated as the difference between each participant's age and the average age at symptom onset. For participants with DS, we used a mean age at symptom onset of 53.8 years, based on a prior study from the DABNI cohort.[33] The same reference age was applied for comparison in euploid controls. Biomarker data were log-transformed in those analyses that required a parametric approach (regression models, ANCOVA) and in LOESS visualization. We used natural logarithms (logarithms with base e). For ROC analysis and correlation assessments (Spearman), non-parametric methods were used, and therefore log-transformation was not required. CAMCOG-DS was not transformed as it was only included in the non-parametric correlation analyses. All significance tests were two-sided, and significance was set at $p < 0.05$.

3 | RESULTS

3.1 | Cohort characteristics

We tested $n = 245$ plasma samples for p-tau212 and p-tau181. A subset of participants had amyloid PET data. Table 1 shows the demographics, cognitive, and plasma biomarkers across groups of all participants included in the analyses. One hundred fourteen participants (47%) had CSF biomarker measurements. Demographics for the CSF subset are shown in Table S1.

3.2 | Correlations with biomarkers and cognition

Plasma and CSF p-tau212 were highly correlated with each other within the cohort. We observed moderate correlation across sample types in all participants ($r = 0.712$ $p < 0.0001$) (Figure 1A). However, the strongest correlation of plasma p-tau212 with CSF p-tau212 was observed in the DS-only subgroup ($r = 0.867$, $p < 0.0001$) (Figure 1A). This improved CSF–plasma correlation in DS groups was not seen for p-tau181, which showed similar correlations in the whole cohort and subgroups ($r = 0.652$–0.681, $p < 0.0001$) (Figure 1B). Those results indicate that plasma p-tau212 measurements accurately reflect AD-related p-tau level changes in CSF in sporadic and DS groups.

Both biomarkers were correlated with a decrease in the CAMCOG-DS in plasma ($r = -.338$; $p = 0.001$ for p-tau212 and $r = -.328$ for p-tau181; $p = 0.002$) and in CSF ($r = -.686$; $p < 0.001$ for p-tau212 and $r = -.511$; $p < 0.001$ for p-tau181).

3.3 | Plasma p-tau212 levels are increased in asymptomatic Down syndrome

Mean plasma p-tau212 concentration was 2.4× times higher in the aDS group compared with CN people ($p < 0.001$), whereas plasma p-tau181 was not significantly changed ($p = 0.052$) (Table 1).

TABLE 1 Study participants.

	aDS	pDS	dDS	CN	MCI-AD	AD
n = Female/male	36/56 (39.1/60.9%)	5/3 (62.5/37.5%)	8/9 (47.1/52.9%)	31/15 (67.4/32.6%)	35/27 (56.5/43.5%)	12/8 (60/40%)
AGE, years, range	18–62	41–60	46–59	18–75	56–83	53–83
AGE, years, mean (SD)	42.2 (9.78)	51.5 (7.41)	51.8 (3.75)	50 (14.8)	72.3 (6.03)	70.5 (8.94)
AGE, years, median [IQR]	44 [35.8–49][b,c]	52 [46.2–57][a]	52 [49–55][a]	46.5 [39–63.8][e,f]	72 [68–76.8][d]	71 [64.8–77.5][d]
APOE4−/APOE4+	68/23 (74.7/25.3%)	7/1 (87.5/12.5%)	13/4 (76.5/23.5%)	39/7 (84.8/15.2%)	24/37 (39.3/60.7%)	10/10 (50/50%)
Plasma p-tau212, *n*	92	8	17	46	62	20
Plasma p-tau212, range	0.0435–1.69	0.666–2	0.404–2	0.0163–0.444	0.079–1.65	0.174–1.23
Plasma p-tau212, mean (SD)	0.404 (0.377)	1.11 (0.445)	0.929 (0.46)	0.166 (0.0856)	0.498 (0.28)	0.629 (0.29)
Plasma p-tau212, median [IQR]	0.245 [0.156–0.529][b,c]	0.926 [0.831–1.24][a]	0.764 [0.627–1.23][a]	0.151 [0.113–0.235][e,f]	0.427 [0.33–0.632][d]	0.65 [0.372–0.738][d]
Plasma p-tau181, range	3.34–47.8	17–50.1	13.5–42.9	3.95–41.6	4.97–53.7	11.4–37.8
Plasma p-tau181, mean (SD)	15.9 (10.9)	29 (11.8)	23.5 (8.18)	11.1 (7.03)	22.3 (11.5)	22.6 (7.01)
Plasma p-tau181, median [IQR]	11.7 [7.54–20.9]	24.7 [20.4–35.3]	21.6 [18.9–27.7]	9.02 [7.07–12.7][e,f]	19.3 [14.6–27.9][d]	22.5 [18.2–27.4][d]
Aβ+/Aβ−	5/12 (29.4/70.6%)	4/0 (100%)	8/0 (100%)	0/29 (0%)	51/0 (100%)	19/1 (95%)
Total CAMCOG-DS score, *n*	73	3	12	0	0	0
Total CAMCOG-DS score, range	25–102	6–56	32–77	-	-	-
Total CAMCOG-DS score, mean (SD)	70.7 (20)	37.7 (27.5)	49.8 (13)	-	-	-
Total CAMCOG-DS score, median [IQR]	74 [57–87]	51 [28.5–53.5][a]	52 [38.5–57.2][a]	-		-

Abbreviations: AD, Alzheimer's disease; aDS, asymptomatic Down syndrome; Aβ, amyloid beta; CAMCOG-DS, Cambridge Cognitive Examination for Older Adults with Down syndrome e; CN, cognitively normal; dDS, dementia Alzheimer's disease Down syndrome; IQR, interquartile range; MCI-AD, mild cognitive impairment due to Alzheimer's disease; pDS, prodromal Alzheimer's disease Down syndrome; SD, standard deviation.

[a]Significantly different from aDS.
[b]Significantly different from pDS.
[c]Significantly different from dDS.
[d]Significantly different from CN.
[e]Significantly different from MCI-AD.
[f]Significantly different from AD.

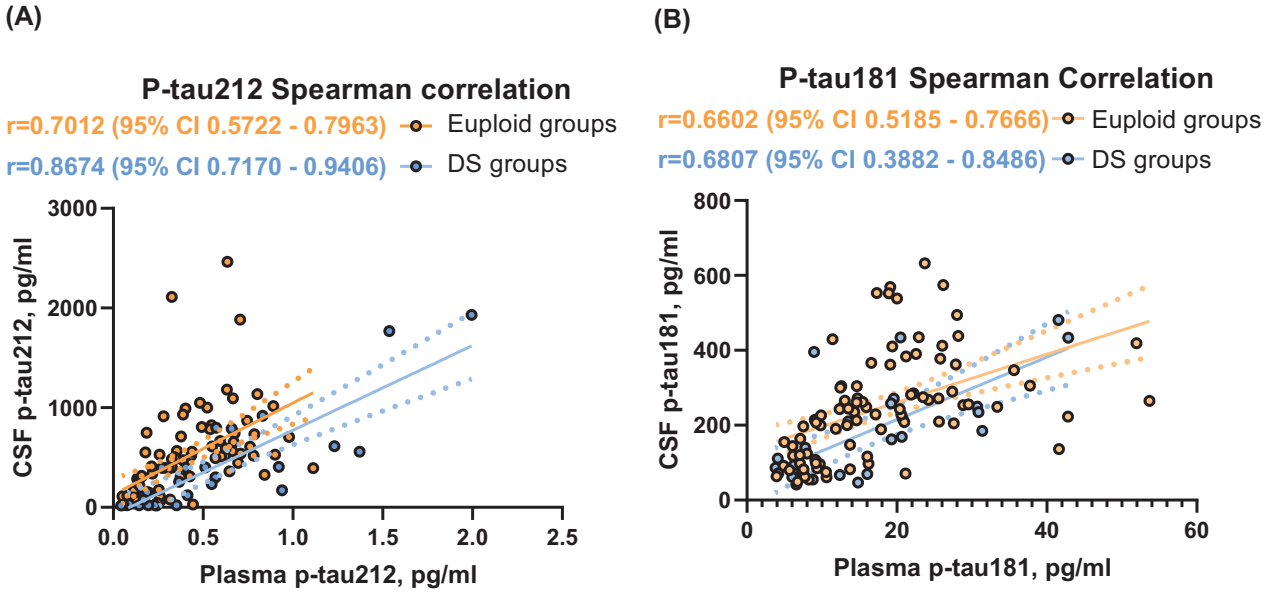

FIGURE 1 Spearman correlations for plasma and CSF p-tau212 and p-tau181. The figure shows correlations between plasma and CSF for (A) p-tau212 and (B) p-tau181 for euploid groups ($n = 88$; $p < 0.001$; $r = 0.701$ and $r = 0.660$, respectively) and DS groups ($n = 26$; $p < 0.001$; $r = 0.867$ and $r = 0.681$, respectively). The correlation between plasma and CSF measurements for all measurements ($n = 114$, $p < 0.001$) is 0.712 for p-tau212 and 0.652 for p-tau181. The fitted simple linear regression line is presented as a mean and standard error. DS, Down Syndrome; CSF, Cerebrospinal Fluid.

3.4 | Plasma and CSF p-tau212 increase along the AD continuum in DSAD and sporadic AD

Both in individuals with DS and euploid participants, p-tau212 levels were increased in symptomatic patients in comparison with asymptomatic individuals (Figure 2A). For pDS we observed a 3.4× ($p = 0.003$) mean fold increase in plasma and a 5.6× mean fold increase in CSF in reference to aDS. For dDS we observed a 2.9× ($p = 0.004$) mean fold increase in plasma and a 7.1× mean fold increase in CSF. For MCI-AD, compared with CN euploid people, we observed a 3.0× ($p < 0.001$) mean fold increase in plasma and a 7.8× mean fold increase in CSF. AD dementia patients had a 3.8× mean fold increase in plasma ($p < 0.001$) and a 9.1× mean fold increase in CSF. Concentrations of p-tau181 were also increased, but with a lower magnitude than p-tau212, and comparison between DS groups showed no significance (Figure 2B). Both biomarkers kept the pattern of greater increases in CSF than in plasma (Figure S1A,B).

3.5 | Plasma p-tau212 has greater diagnostic accuracy than p-tau181

ROC analysis was used to evaluate the diagnostic performance of plasma and CSF p-tau212 and p-tau181. AUCs were usually higher for biomarkers in CSF and for p-tau212 than for p-tau181. In our comparisons, we included Age+*APOEε4*+Sex, since they have been shown to influence diagnostic accuracy.[34] AUCs of Age+*APOEε4*+Sex were not significantly different from p-tau212 but were better than p-tau181. Both biomarkers had high accuracy to differentiate between CN and AD in plasma AUC = 0.96 (95% confidence interval [CI] 0.92–1) for p-tau212 and AUC = 0.89 (95% CI 0.84–0.95) for p-tau181 (Figure 3B). For differentiating between CN and MCI-AD (Figure 3A) or MCI-AD+AD (Figure 3C), p-tau212 had an accuracy of 0.91 (95% CI 0.85–0.97) and AUC = 0.93 (95% CI 0.88–0.97), respectively. That accuracy was significantly higher than p-tau181 (p = 0.026 for both comparisons). Plasma p-tau212 reached AUC = 0.91 (95% CI 0.86–0.97) to differentiate between aDS and dDS diagnosis (Figure 3D). When pDS and dDS participants were analyzed as a symptomatic group in reference to aDS, the diagnostic accuracy of p-tau212 reached AUC = 0.84 (95% CI 0.76–0.92), and AUC = 0.83 (95% CI = 0.75–0.91) for p-tau181. Combining both plasma biomarkers in the model to differentiate symptomatic from asymptomatic patients did not significantly improve the diagnostic accuracy of the biomarkers (Figure S2A–S2C). Detailed information about sensitivities, specificities, positive predictive values (PPVs), negative predictive values (NPVs), accuracy, and Youden indices is in Table S2.

3.6 | Plasma p-tau212 increases approximately parallel to amyloid PET positivity and has great accuracy in discriminating between Aβ+ and Aβ− participants

Both biomarkers had significant accuracy in discriminating between Aβ+ and Aβ− participants (Figure 4). Plasma p-tau212 had numerically higher accuracy than p-tau181 both for DS (AUC = 0.86, 95%

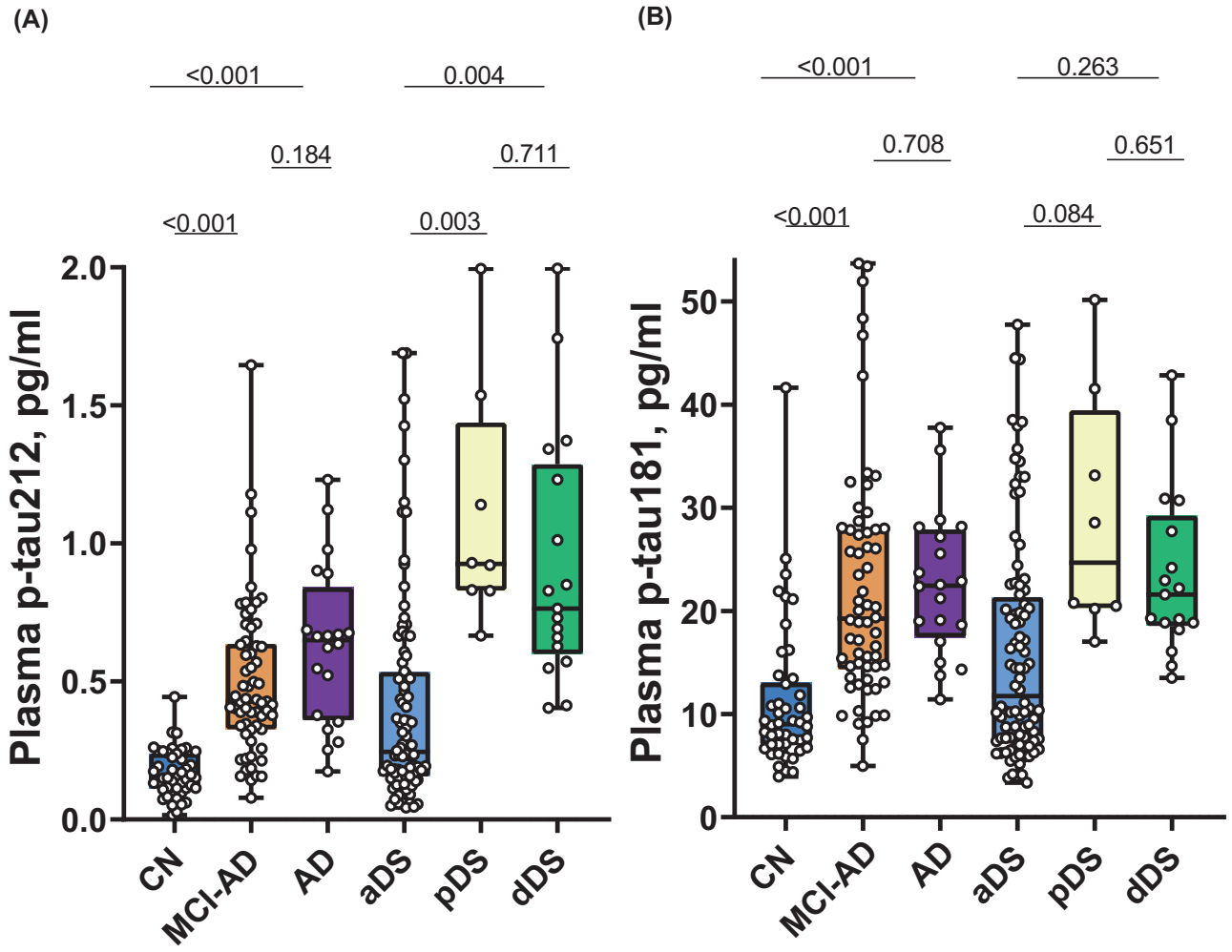

FIGURE 2 Plasma p-tau212 and p-tau181 levels in euploid and DS groups. Box plots represent median and IQR, and boundaries of the whiskers are minimum to maximum values for (A) plasma p-tau212 and (B) plasma p-tau181. Differences for euploid participants are calculated for mild cognitively impaired due to Alzheimer's disease (MCI-AD; $n = 62$) and Alzheimer's disease (AD; $n = 20$) in reference to cognitively normal (CN; $n = 46$) participants. Differences for prodromal Alzheimer's disease in DS (pDS; $n = 8$) and Alzheimer's disease dementia in DS (dDS; $n = 17$) are calculated in reference to asymptomatic (aDS; $n = 92$). Age-adjusted ANCOVA followed by Tukey post hoc test is used to calculate differences across groups. ANCOVA, analysis of covariance; CN, cognitively normal; DS, Down syndrome; IQR, interquartile range.

CI = 0.7–1) (Figure 4B) and euploid participants (AUC = 0.9, 0.83–0.96) (Figure 4C).

An early increase in plasma levels was observed many years before the onset of clinical AD symptoms in DS (Figure 5). For p-tau212, the increase started approximately when people became amyloid PET-positive, that is, in their late 30s, and ≈15 years before disease onset (Figure 5A). Increases in p-tau181 started ≈10 years before the estimated disease onset (Figure 5B).

4 | DISCUSSION

In this cross-sectional study, we show that p-tau212 serves as a biomarker to track AD-related changes in sporadic cases and DSAD. A very high correlation in p-tau212 is shown between plasma and CSF. The strongest correlation was observed for the DS population, where p-tau212 reached a greater correlation than for euploid participants. Correlation in euploid and DS groups of p-tau181 was similar, suggesting greater translation from CSF to plasma for p-tau212 in DS populations.

We observed elevated p-tau212 concentration in plasma and CSF in aDS compared with euploid CN. That elevation is greater than the p-tau181 elevation, which did not reach statistical significance. In addition, other reported biomarkers, such as p-tau217 glial fibrillary acidic protein (GFAP),[34,35] had lower increases. Therefore, the suggested predisposition of p-tau212 to be the main target for the DYRK1A kinase seems to be reflected in our study, indicating a better fit for the use of this biomarker, p-tau212 levels, in the DS population.

Levels of plasma p-tau212 were significantly higher across disease groups. Plasma p-tau212 reached significance levels to differentiate between the aDS versus pDS and aDS versus dDS groups, whereas p-tau181 failed to do it. However, we think that this might be a lim-

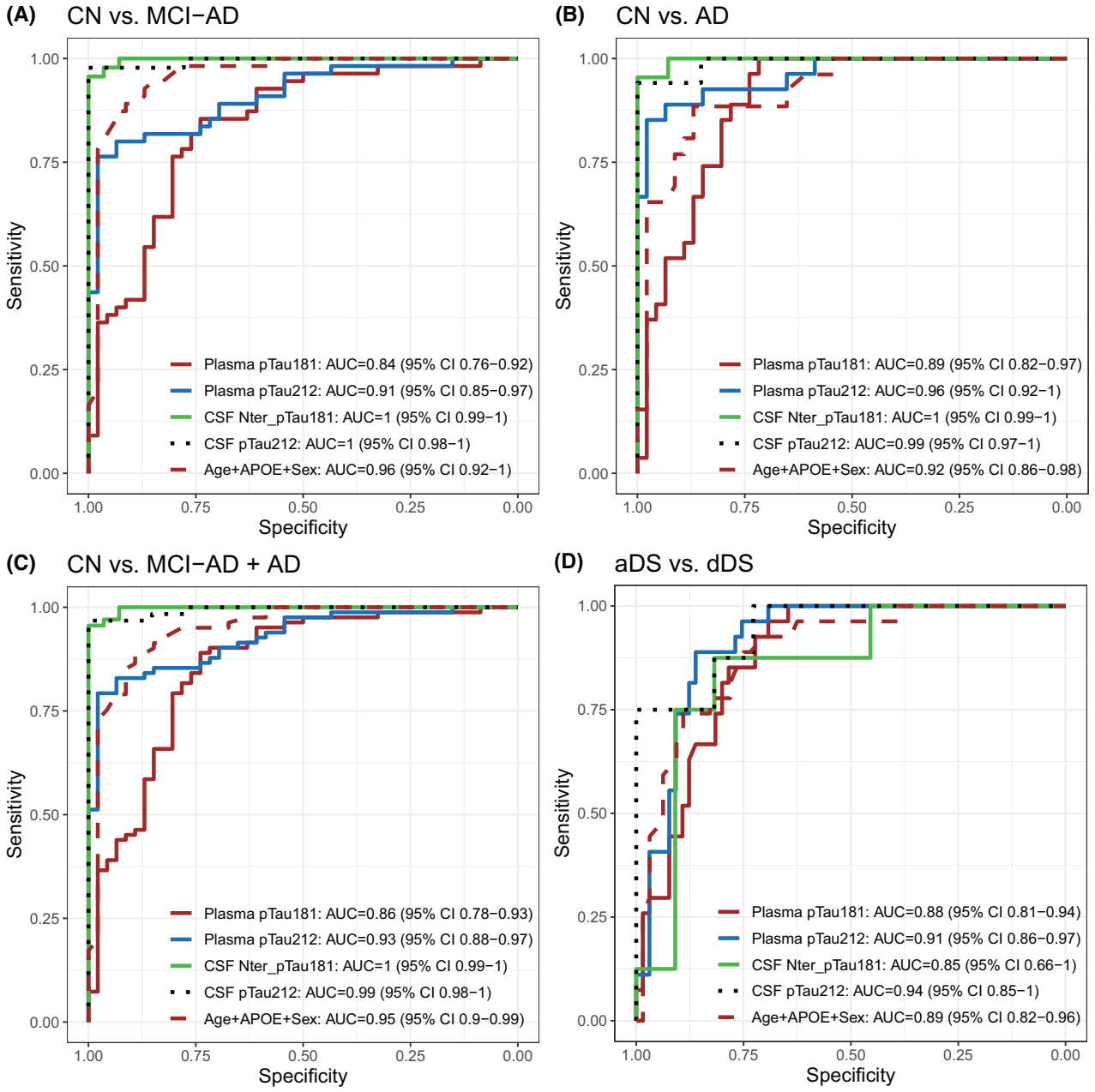

FIGURE 3 Diagnostic accuracy of plasma and CSF biomarkers to discriminate between sporadic and DSAD groups. P-tau212 and p-tau181 ROC curves to discriminate between sporadic and DSAD groups. Plasma p-tau181, plasma p-tau212, CSF p-tau181, CSF p-tau212, and Age+*APOEε4*+Sex are on each graph. (A) ROC curves for differentiating CN and mild cognitive impairment due toAlzheimer's disease (MCI-AD). (B) ROC curves for discriminating between CN and AD. (C) ROC curves for differentiating between CN and MCI-AD combined with the AD group. (D) ROC curves for discriminating between aDS and prodromal Alzheimer's disease Down syndrome (pDS) + dDS. AD, Alzheimer's disease; aDS, asymptomatic Down syndrome; CN, cognitively normal; dDS, dementia Alzheimer's disease Down syndrome; ROC, receiver-operating characteristic.

itation of the small sample size used in this cohort, since p-tau181 levels were shown previously to be significantly increased in pDS and aDS.[34,36] In MCI-AD and AD dementia groups, we observed significant increases for both biomarkers, concomitantly having fold changes higher for p-tau212, which confirms our previous findings.[22]

The excellent performance of the assay was confirmed in discriminating patients according to the diagnosis in both DS and euploid groups. In addition, p-tau212 has greater accuracy than p-tau181 in discriminating between MCI-AD and control groups, simultaneously reaching 0.96 AUC to differentiate CN from AD. Furthermore, plasma p-tau212 acquired very high AUC-ROC in discriminating between Aβ+ and Aβ− participants in both the euploid and DS groups. Combining p-tau181 and p-tau212 did not significantly improve the diagnostic accuracy of the p-tau212. In addition, the accuracy of plasma p-tau212

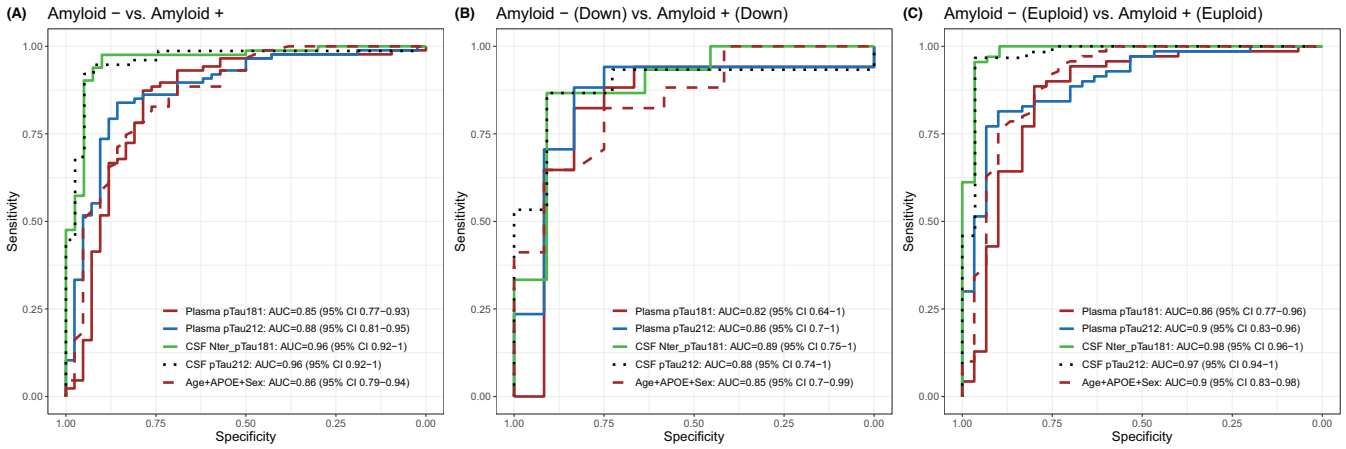

FIGURE 4 Diagnostic accuracy of plasma and CSF biomarkers to discriminate between Aβ+ and Aβ− participants. P-tau212 and p-tau181 ROC curves to discriminate between amyloid positive (Aβ+) and amyloid negative (Aβ−) participants in sporadic and DSAD groups. Plasma p-tau181, plasma p-tau212, CSF p-tau181, CSF p-tau212, and Age+*APOEε4*+Sex are on each graph. (A) ROC curves for differentiating Aβ+ ($n = 70$) from Aβ− ($n = 30$) in the whole cohort. (B) ROC curves for discriminating Aβ+ ($n = 17$) and Aβ− ($n = 12$) in the DS groups. (C) ROC curves for differentiating between Aβ+ ($n = 53$) and Aβ− ($n = 18$) in the euploid group. ROC, receiver-operating characteristic; Aβ, amyloid beta; CSF, Cerebrospinal Fluid; DSAD, Down Syndrome Alzheimer´s disease.

was not different from the CSF accuracy, supporting the high between-matrix translation of p-tau212 and providing additional reasoning for use of plasma p-tau212 to recruit participants for clinical trials.

Plasma p-tau212 starts increasing in the 30s, approximately when people start being positive in amyloid PET scans, and although we cannot be sure if the difference between increases of both biomarkers is statistically significant, p-tau212 visually starts increasing ≈5 years before we observe an increase in p-tau181. In addition, the biomarker increased further as AD progressed toward symptomatic stages. Therefore, p-tau212 could be useful for monitoring the progression of aDS to prodromal AD. Moreover, the onset of the increase comes with the appearance of neurofibrillary tangles (NFTs) and Aβ plaques in the brain.[4,37]

This is (to our best knowledge) the first study to measure p-tau212 in CSF and plasma as a biomarker for DSAD; however, the potential involvement of p-tau212 in this population and its association with DYRK1A activity was published more than 20 years ago.[13] The kinase is perceived as a target in DS and neurodegenerative diseases.[8,38] Its under- or overexpression leads to different clinical phenotypes, including cognitive impairment.[38] Because DYRK1A is a dose-sensitive protein in which downregulation or upregulation has a critical role, DYRK1A inhibitors have already been widely explored in clinical trials and have been proven to improve cognitive function in DS people.[10,39,40] It is important to note that p-tau212 has already been used successfully to test the efficacy of the DYRK1A inhibitor in cell models.[41] The use of the chosen inhibitor was further shown to reverse the up-regulation of p-tau212 in hippocampal tissue and temporal cortex in mouse models.[41] Our novel plasma p-tau212 immunoassay provides a simple-to-implement and cost-effective opportunity to monitor the efficacy of DYRK1A inhibitors or, in the future—enhancers, not allowing the activity of this kinase to be reduced or increased to levels that could cause more harm than good. The utility of p-tau212 as target engagement biomarker for DYRK1A modulators will be explored in our future research.

The major strength of this study is the confirmation that p-tau212 is increased in the DS population, and levels of this biomarker increase with progression to AD dementia. In our analyses we did not find any potential differences attributable to sex. P-tau212 reaches very high accuracy for differentiating between control and disease groups and Aβ+ and Aβ− participants. The high correlation between plasma and CSF p-tau212 also supports a very high translation of the results from CSF to plasma. DeLong tests between DS groups did not show significantly better performance of CSF p-tau212 compared with plasma p-tau212, providing further evidence that plasma measurements can be used for clinical evaluation of AD pathophysiological processes occurring in patients with suspected disease. Advantages would also be reflected in the economy, availability, and perception of the test, since lumbar punctures or PET scans are costly, require resources, and might be perceived as frightening.[20] Next, plasma p-tau212 increased approximately when people are starting to be amyloid PET positive and 5 years before p-tau181, indicating the benefits in disease monitoring.

This study has a few limitations. First is a slightly low representation of prodromal-DS participants, which prohibits us from making better AUC-ROC analyses in that group. Ideally, longitudinal measurements of p-tau212 in the DS population would tell us more about the trajectories of this biomarker. The second limitation is that p-tau217 measurements are unavailable at the moment; however, direct comparison between biomarkers was not a purpose of the experiments presented in this article. Still, p-tau181 is the most commercialized and fully automated immunoassay, with great utility in AD.

In conclusion, we have confirmed that levels of plasma p-tau212 are increased in the DS population and sporadic AD cases, including prodromal and MCI states. High accuracy in discriminating amyloid-

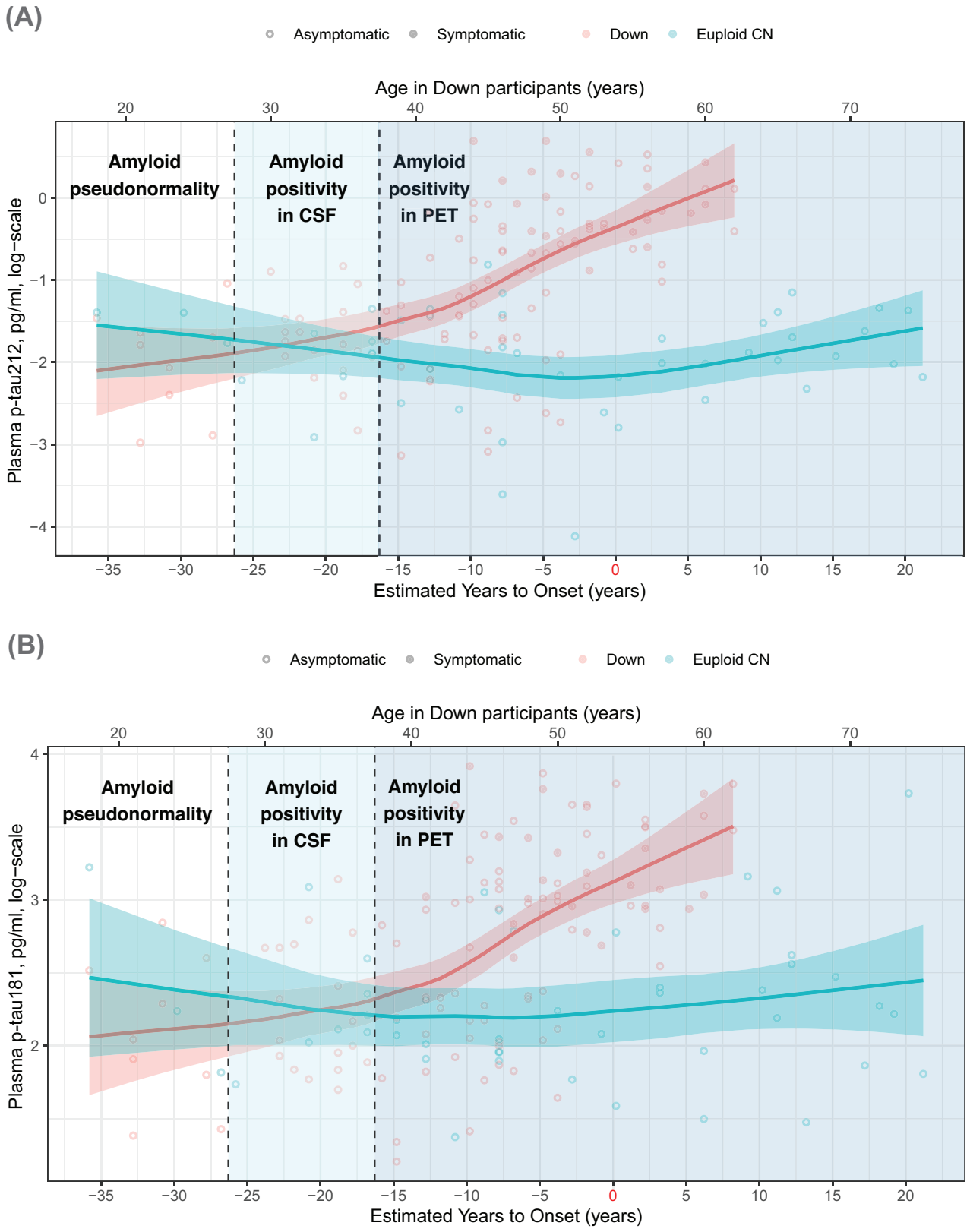

FIGURE 5 Age-related plasma p-tau212 and p-tau181 changes in Down syndrome and euploid controls. Open circles represent asymptomatic and filled circles represent symptomatic participants. Down syndrome population is represented in red and cognitively normal euploid people are represented in blue. Horizontal lines depict each group's fitted LOESS model, and fainted bands display confidence intervals. The vertical red line represents the estimated years to symptom onset, which is 53.8 for Down syndrome participants and was used as reference in euploid controls for comparison purposes. LOESS, locally estimated scatterplot smoothing; CSF, Cerebrospinal Fluid; PET, Possitron Emission Tomography, CN, Cognitively Normal.

positive from amyloid-negative people and an increase in parallel to amyloid-PET positivity give the promise of evaluating ongoing pathophysiological AD processes many years before disease onset in individuals with DS. This will also facilitate participant recrutation for clinical trials. This is a cost-effective application that provides a higher chance of receiving appropriate therapy. Plasma p-tau212 will also find high utility in theragnostics, for monitoring therapy efficacy, and as a target engagement biomarker in clinical trials both in sporadic and DSAD.

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CONFLICT OF INTEREST STATEMENT

M.T. and P.H. are employees of Bioventix Plc. H.Z. has served on scientific advisory boards and/or as a consultant for Abbvie, Acumen, Alector, Alzinova, ALZPath, Amylyx, Annexon, Apellis, Artery Therapeutics, AZTherapies, Cognito Therapeutics, CogRx, Denali, Eisai, LabCorp, Merry Life, Nervgen, Novo Nordisk, Optoceutics, Passage Bio, Pinteon Therapeutics, Prothena, Red Abbey Labs, reMYND, Roche, Samumed, Siemens Healthineers, Triplet Therapeutics, and Wave; has given lectures in symposia sponsored by Alzecure, Biogen, Cellectricon, Fujirebio, Lilly, Novo Nordisk, and Roche; and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program (outside submitted work). K.B. has served as a consultant or on advisory boards for Abcam, Axon, BioArctic, Biogen, JOMDD/Shimadzu. Julius Clinical, Lilly, MagQu, Novartis, Ono Pharma, Pharmatrophix, Prothena, Roche Diagnostics, and Siemens Healthineers. H.Z. and K.B. are co-founders of Brain Biomarker Solutions in Gothenburg AB, a GU Ventures-based platform company at the University of Gothenburg. D.A. participated in advisory boards from Fujirebio-Europe, Roche Diagnostics, Grifols S.A., and Lilly, and received speaker honoraria from Fujirebio-Europe, Roche Diagnostics, Nutricia, Krka Farmacéutica S.L., Zambon S.A.U. and Esteve Pharmaceuticals S.A. D.A. and J.F. declare a filed patent application (licensed to Adx, EPI8382175). J.F. reported receiving personal fees for service on advisory boards, adjudication committees or speaker honoraria from AC Immune, Adamed, Alzheon, Biogen, Eisai, Esteve, Eisai, Fujirebio, Ionis, Laboratorios Carnot, Lilly, Life Molecular Imaging, Lundbeck, Perha, and Roche, and, outside the submitted work. The other authors declare no competing interest. Author disclosures are available in the Supporting Information.

ETHICS STATEMENT

Study procedures were approved by the Sant Pau Ethics Committee (IIBSP-NGF-2018-36 and IIBSP-DOW-2014-30), following the standards for medical research in humans, as recommended in the Declaration of Helsinki. All participants or their legally authorized representative gave written informed consent before enrollment.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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