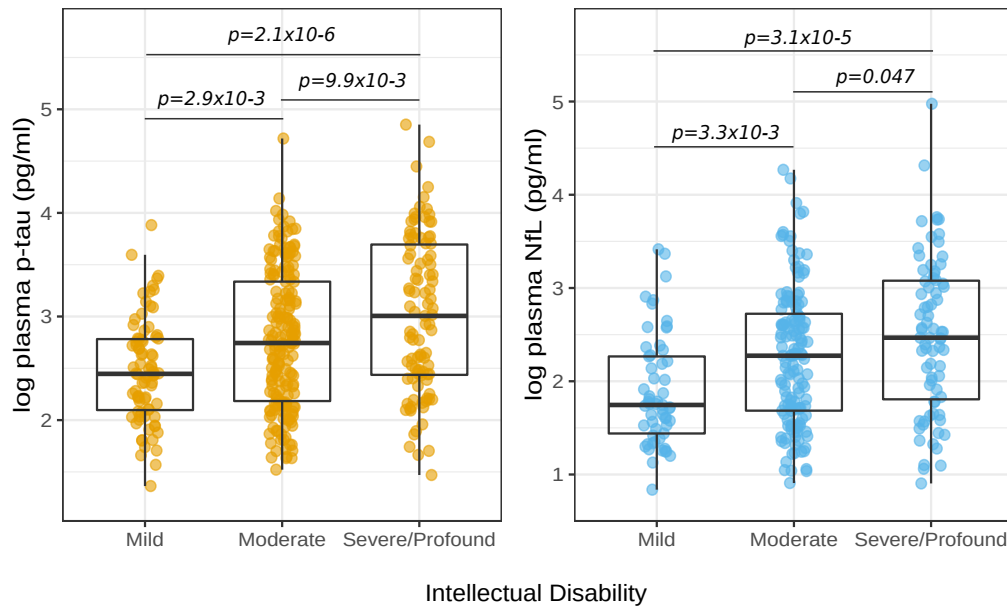


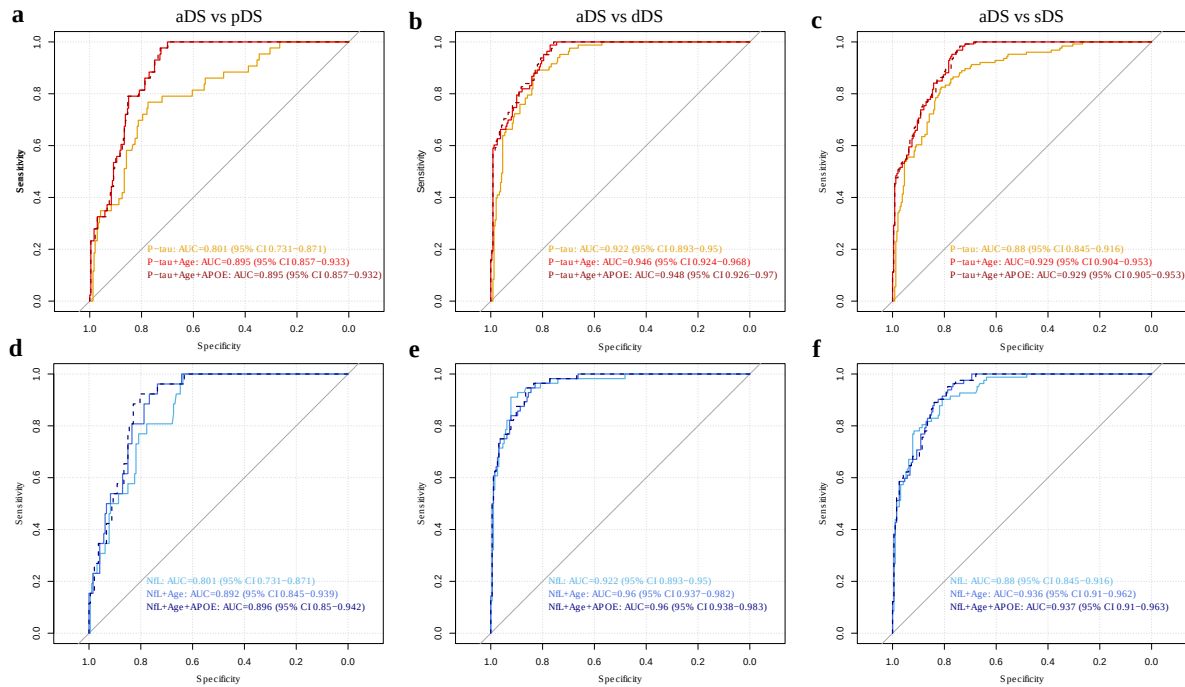
Supplementary Information

Supplementary Figure 1



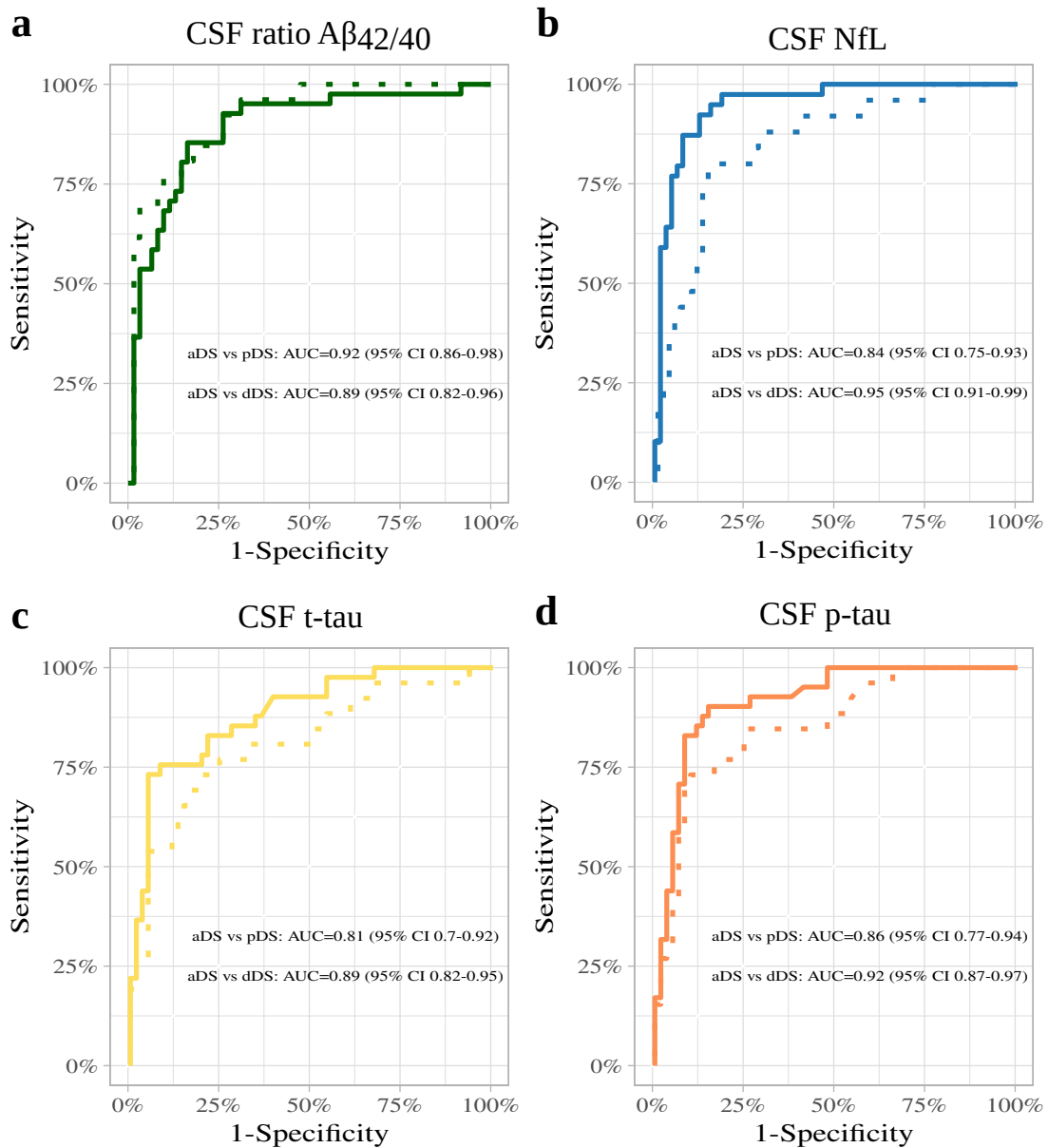
Plasma p-tau181 concentrations according to the degree of intellectual disability. a Concentrations of plasma p-tau plasma across mild ($n=80$), moderate ($n=187$) and severe/profound ($n=99$) intellectual disability. **b** Concentrations of plasma NfL across mild ($n=57$), moderate ($n=147$) and severe/profound ($n=75$) intellectual disability. The central black lines show the median values, regions above and below these lines show the upper and lower quartiles, respectively, and the whiskers extend from the IQR limits to the largest value no further than $1 \cdot 5 \times$ IQR. Two-sided Kruskal-Wallis with Dunn's test of multiple comparisons correcting by the Holm method was used to assess the differences between groups.

Supplementary Figure 2



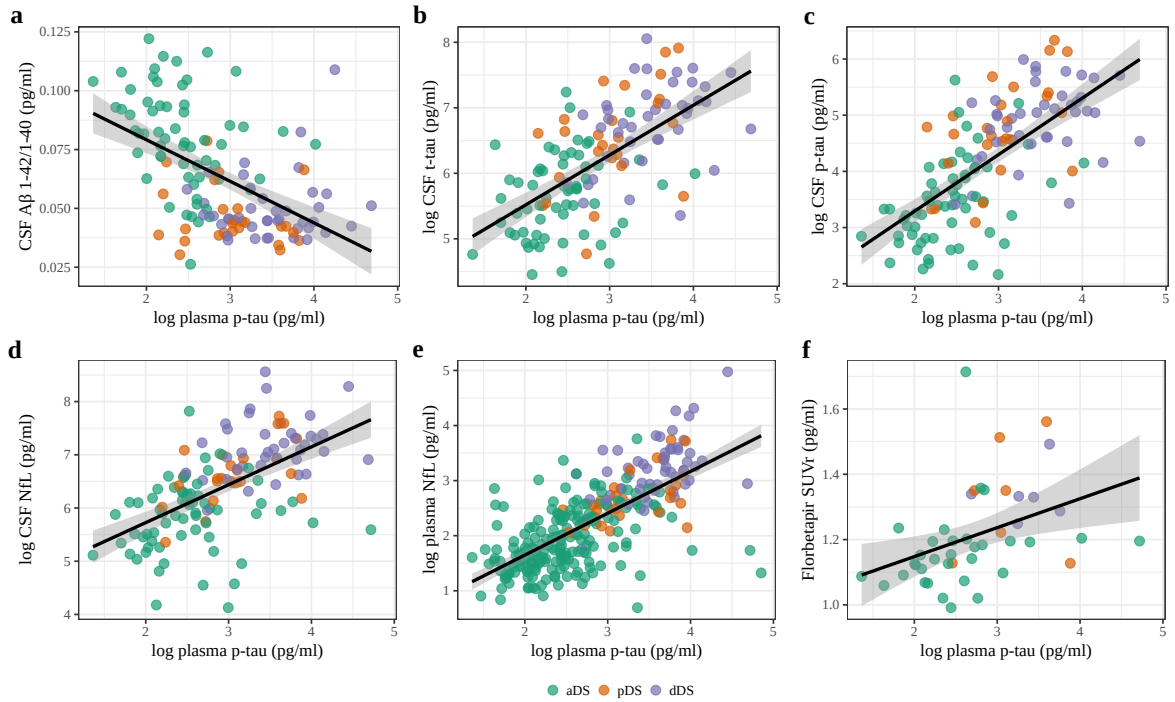
Diagnostic performance of p-tau and NFL, age, APOE genotype and their combination to detect AD in DS. a ROC curves for plasma p-tau to discriminate aDS and pDS. **b** aDS and dDS. **c** aDS and sDS. **d** ROC curves for plasma NFL to discriminate aDS and pDS. **e** aDS and dDS. **f** aDS and sDS. aDS: asymptomatic Down syndrome; pDS: prodromal Alzheimer's disease in Down syndrome; dDS: Alzheimer's disease dementia in Down syndrome; sDS: symptomatic Alzheimer's disease dementia in Down syndrome; AUC: area under the curve; CI: confidence interval.

Supplementary Figure 3



Diagnostic performance of CSF biomarkers to detect AD in DS. **a** ROC curves for CSF $A\beta_{42/40}$ ratio to detect pDS and dDS from aDS. **b** ROC curves for CSF NfL to detect pDS and dDS from aDS. **c** ROC curves for CSF t-tau to detect pDS and dDS from aDS. **d** ROC curves for CSF p-tau181 to detect pDS and dDS from aDS. aDS: asymptomatic Down syndrome; pDS: prodromal Alzheimer's disease in Down syndrome; dDS: Alzheimer's disease dementia in Down syndrome; AUC: area under the curve; CI: confidence interval.

Supplementary Figure 4



Age-adjusted partial correlation between plasma p-tau181 and different biomarkers. **a** CSF ratio A β 42/40. **b** CSF t-tau. **c** CSF p-tau181. **d** CSF NfL. **e** Plasma NfL. **f** Florbetapir SUVr. The black lines indicate the fitted linear model and the shadowed ribbons show the 95% confidence level intervals.

Supplementary Table 1. Demographics, cognitive and biomarker data of participants with Down syndrome and controls with plasma p-tau181 and plasma NfL available (n=289).

| | Control 14 | aDS 193 | pDS 26 | dDS 56 |
|---|-------------------------|-------------------------|--------------------------|---------------------------|
| N | | | | |
| Age (years) (median [IQR]) | 44.41 [37.96, 51.58] | 37.96 [30.35, 45.24] | 51.22 [47.90, 55.62] | 53.62 [49.54, 56.72] |
| Gender = Male (%) | 5 (35.7) | 107 (55.4) | 14 (53.8) | 32 (57.1) |
| MMSE score (median [IQR]) | 30 [30, 30] | - | - | - |
| CAMCOG score (median [IQR]) | | 78.00 [65.00, 86.00] | 61.00 [43.25, 75.00] | 41.50 [29.50, 55.00] |
| Degree of disability (%) | | | | |
| Mild | | 52 (26.9) | 4 (15.4) | 1 (1.8) |
| Moderate | | 100 (51.8) | 10 (38.5) | 33 (58.9) |
| Severe/Profound | | 41 (21.2) | 12 (46.2) | 22 (39.3) |
| plasma p-tau181 (pg/ml) (median [IQR]) | 8.36 [6.82, 13.10] | 11.37 [8.07, 16.05] | 23.60 [19.18, 42.71] | 38.70 [28.22, 46.75] |
| plasma NfL (pg/ml) (median [IQR]) | 3.38 [2.89, 4.16] | 5.93 [4.43, 10.25] | 13.61 [11.50, 18.26] | 23.86 [17.33, 33.65] |
| CSF A β 42/A β 40 (median [IQR]) | 0.11 [0.10, 0.11] | 0.08 [0.06, 0.10] | 0.04 [0.04, 0.04] | 0.05 [0.04, 0.05] |
| CSF t-tau (pg/ml) (median [IQR]) | 197.00 [168.75, 284.50] | 275.00 [158.00, 464.00] | 886.00 [593.50, 1472.25] | 964.00 [671.00, 1541.75] |
| CSF p-tau (pg/ml) (median [IQR]) | 27.10 [21.88, 34.82] | 31.90 [17.20, 58.70] | 150.70 [97.95, 239.60] | 155.00 [94.45, 224.60] |
| CSF NfL (pg/ml) (median [IQR]) | 304.00 [216.00, 356.45] | 357.40 [212.78, 460.55] | 751.33 [663.44, 1076.89] | 1271.05 [924.52, 1631.50] |
| SUVr 18F-FBP (median [IQR]) | | 1.15 [1.09, 1.20] | 1.35 [1.17, 1.43] | 1.33 [1.30, 1.34] |
| SUVr 18F-FDG (median [IQR]) | | 1.34 [1.26, 1.40] | 1.10 [1.06, 1.15] | 0.78 [0.68, 0.90] |

Abbreviations: N= sample, IQR= interquartile range, ID=intellectual disability, CSF= cerebrospinal fluid, A β =Amyloid- β , NfL= Neurofilament light protein, FDG= 18-Fluorodeoxyglucose, SUVr=Standardized Uptake Value Ratio. aDS= asymptomatic Down syndrome, pDS= prodromal Alzheimer's disease Down syndrome, dDS= Alzheimer's disease dementia Down syndrome, Controls= euploid healthy controls.