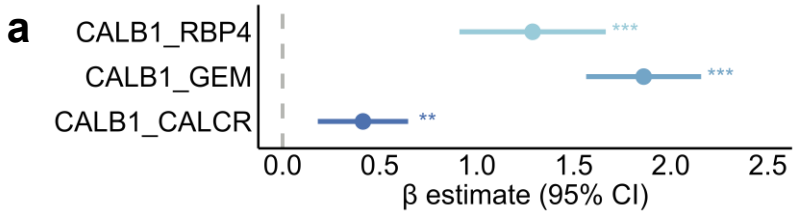

Fig.S1 Elevated NPTX2 expression in PD dopaminergic neurons. a Forest plots showed increased expression of NPTX2 in the single-cell RNA sequence in dopaminergic neurons of PD.

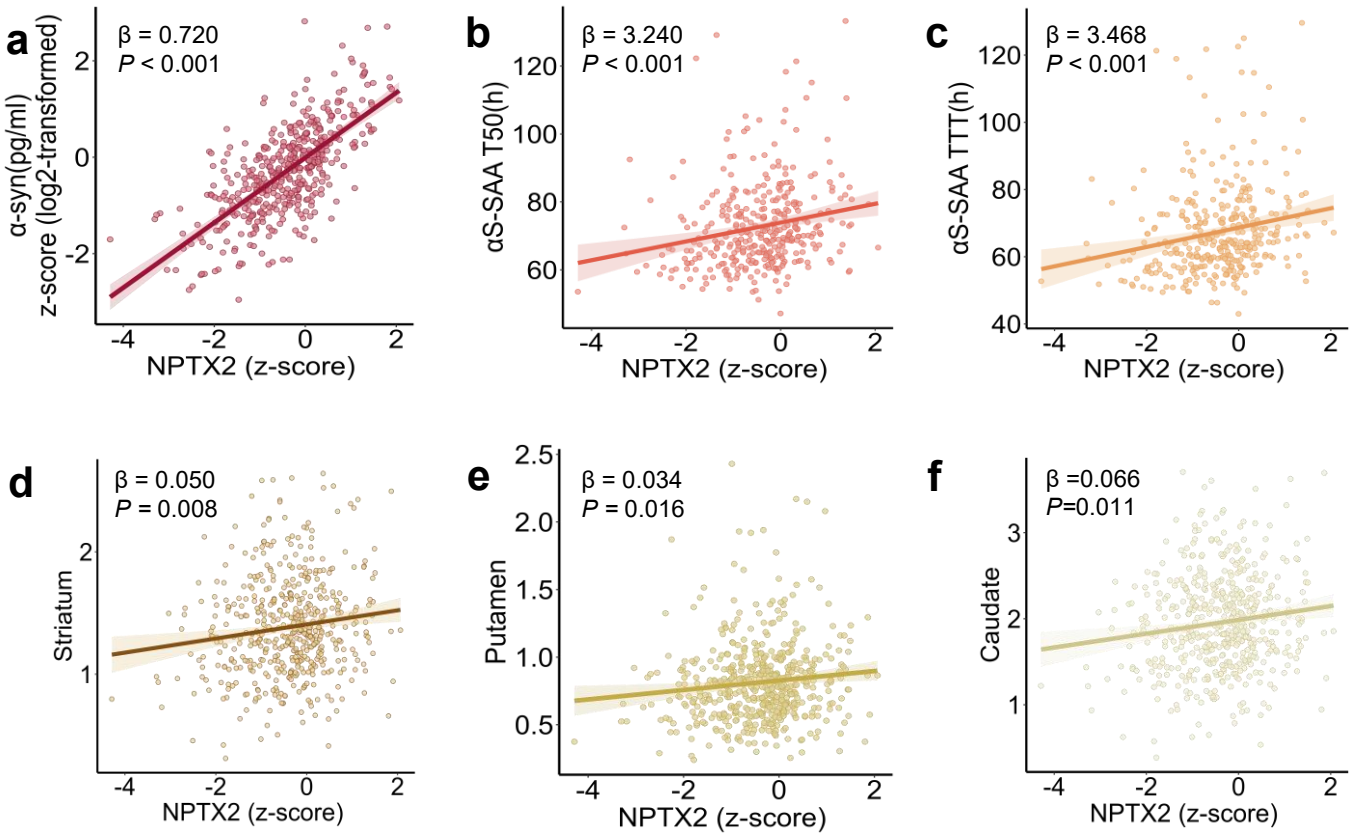

Fig.S2 The baseline relationship between CSF NPTX2 and α-synuclein, as well as the dopaminergic degeneration. a-f Scatterplots showing the correlation between NPTX2 and total a-syn amounts in CSF (**a**), the time to 50% max fluorescence (T50%) of α-syn SAA (**b**) , the time to threshold (TTT) of α-syn SAA (**c**), mean striatum binding ratio(**d**), mean putamen binding ratio(**e**), and mean caudate binding ratio(**f**) in patients with PD. Measurements were adjusted for age, sex, apolipoprotein E ε4 status, LEDD, baseline Hoehn-Yahr stage, and disease duration. Linear trend lines are shown, and the 95% confidence intervals are indicated by shading. h = hours; SAA, seed amplification assay.

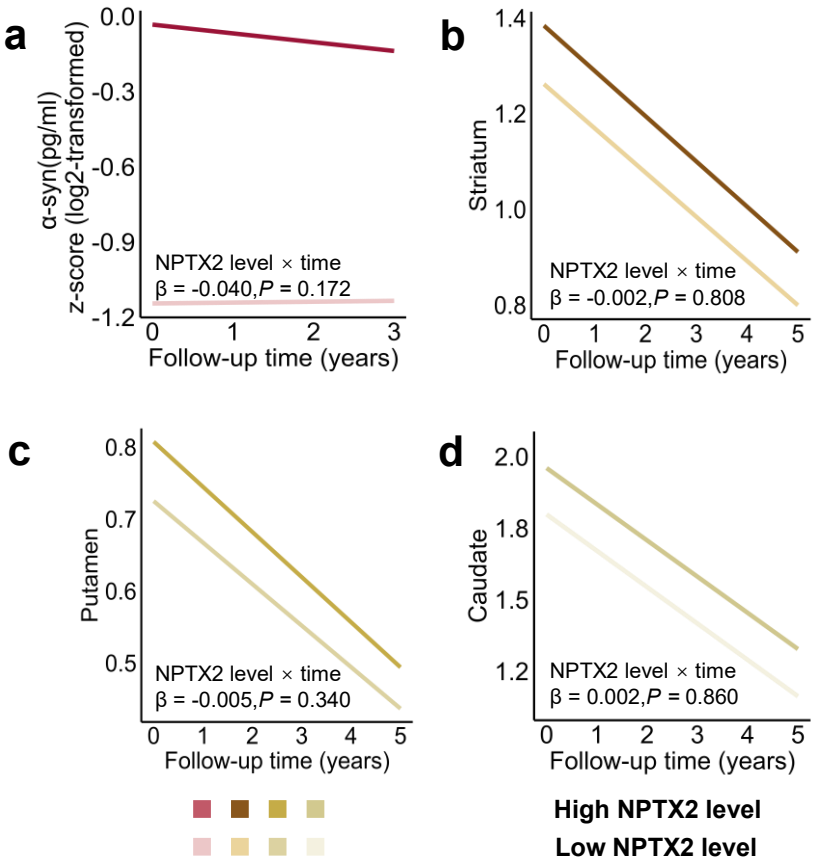

Fig.S3 The relationship between baseline CSF NPTX2 and longitudinal α-synuclein, as well as the dopaminergic degeneration. a-d LMMs were used to examine effects of baseline CSF NPTX2 levels with follow-up time on CSF longitudinal α-synuclein(**a**), mean striatum binding ratio(**b**), mean putamen binding ratio (**c**), and mean caudate binding ratio(**d**). Measurements were adjusted for age, sex, apolipoprotein E ε4 status, LEDD, baseline Hoehn-Yahr stage, and disease duration.

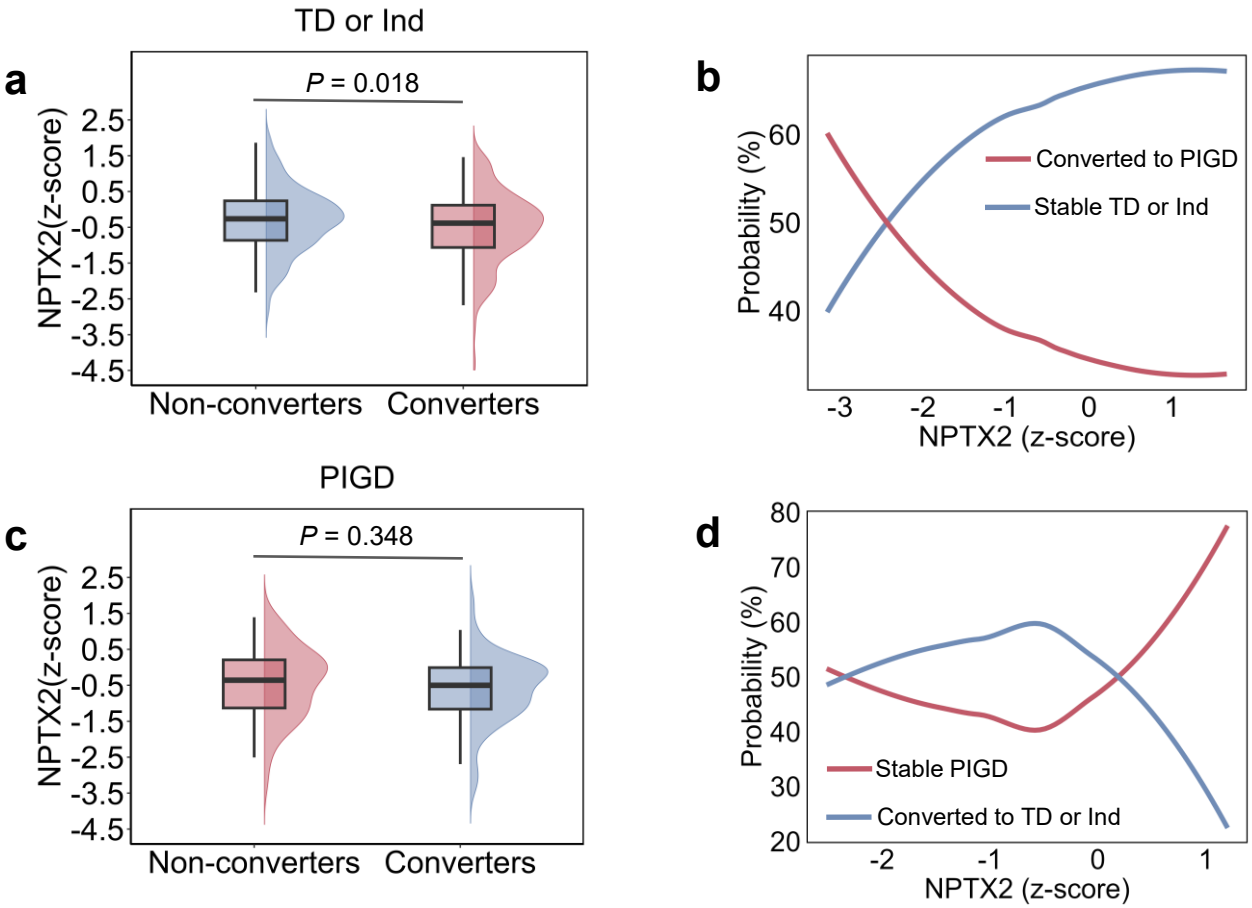

Fig.S4 Baseline CSF NPTX2 predict motor subtype conversion. a, c Baseline CSF NPTX2 was compared in non-converters and converters at baseline TD group (**a**) and PIGD group (**c**). Multivariate linear regression were used for group comparison. **b, d** Relationship between baseline CSF GFAP and the probability of TD (**b**) and PIGD (**d**) motor subtypes after correction for confounders. The confounders including age, sex, apolipoprotein E ε4 status, LEDD, baseline Hoehn-Yahr stage, and disease duration. NPTX2, Neuronal pentraxin II; TD, tremor dominant; Ind, indeterminate, PIGD, postural instability and gait disturbance.

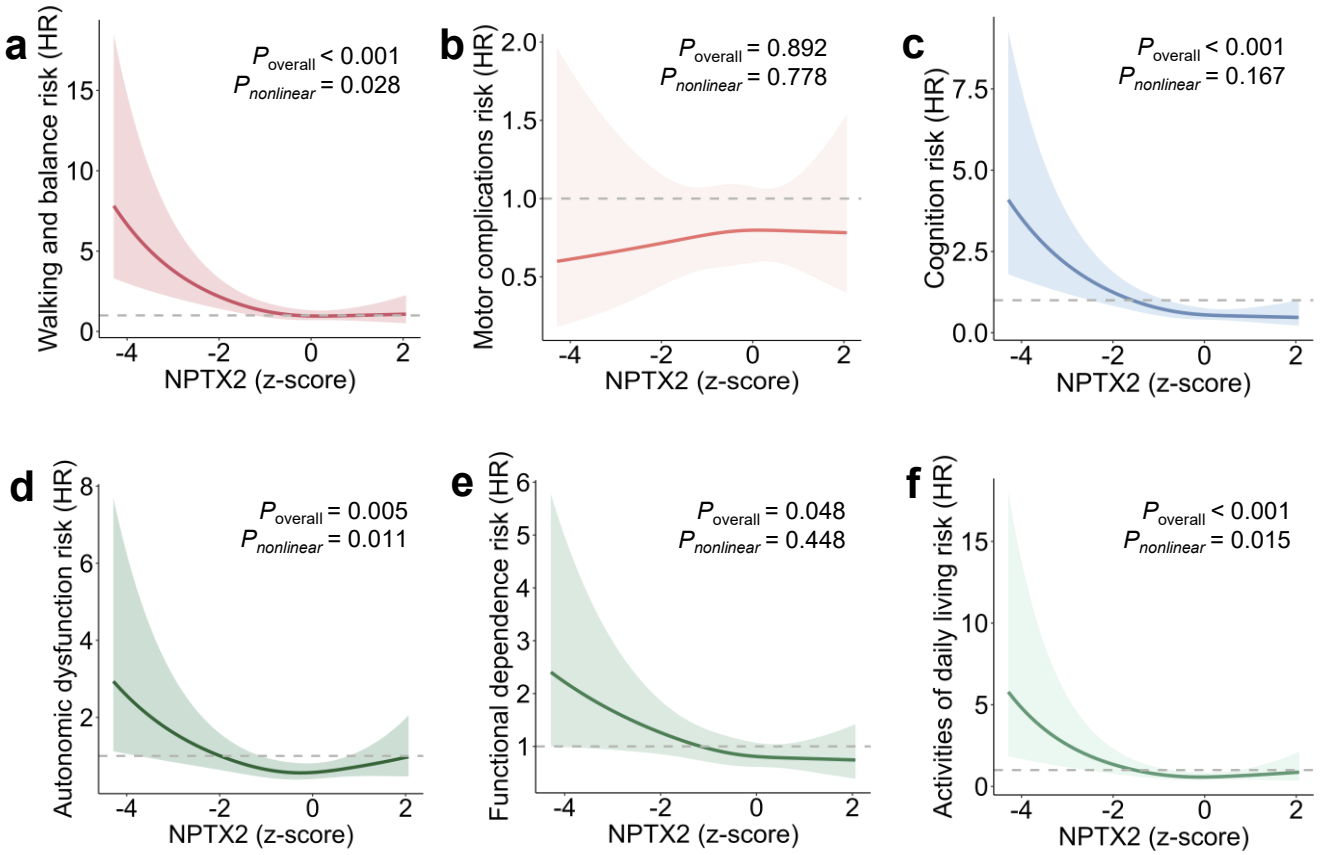

Fig.S5 CSF NPTX2 level were nonlinearly associated with progression milestones in PD

a-f Using Cox regression model with RCS to explore non-linear relationship between CSF NPTX2 levels and the milestones of Parkinson's Disease progression. Walking and balance(**a**); Motor complications(**b**); Cognition(**c**); Autonomic dysfunction(**d**); Functional dependence(**e**); Activities of daily living(**f**). The analyses were adjusted for age, sex, apolipoprotein E ε4 status, LEDD, baseline Hoehn-Yahr stage, and disease duration. In addition, in terms of cognition, the model also corrected Baseline MoCA score and education.

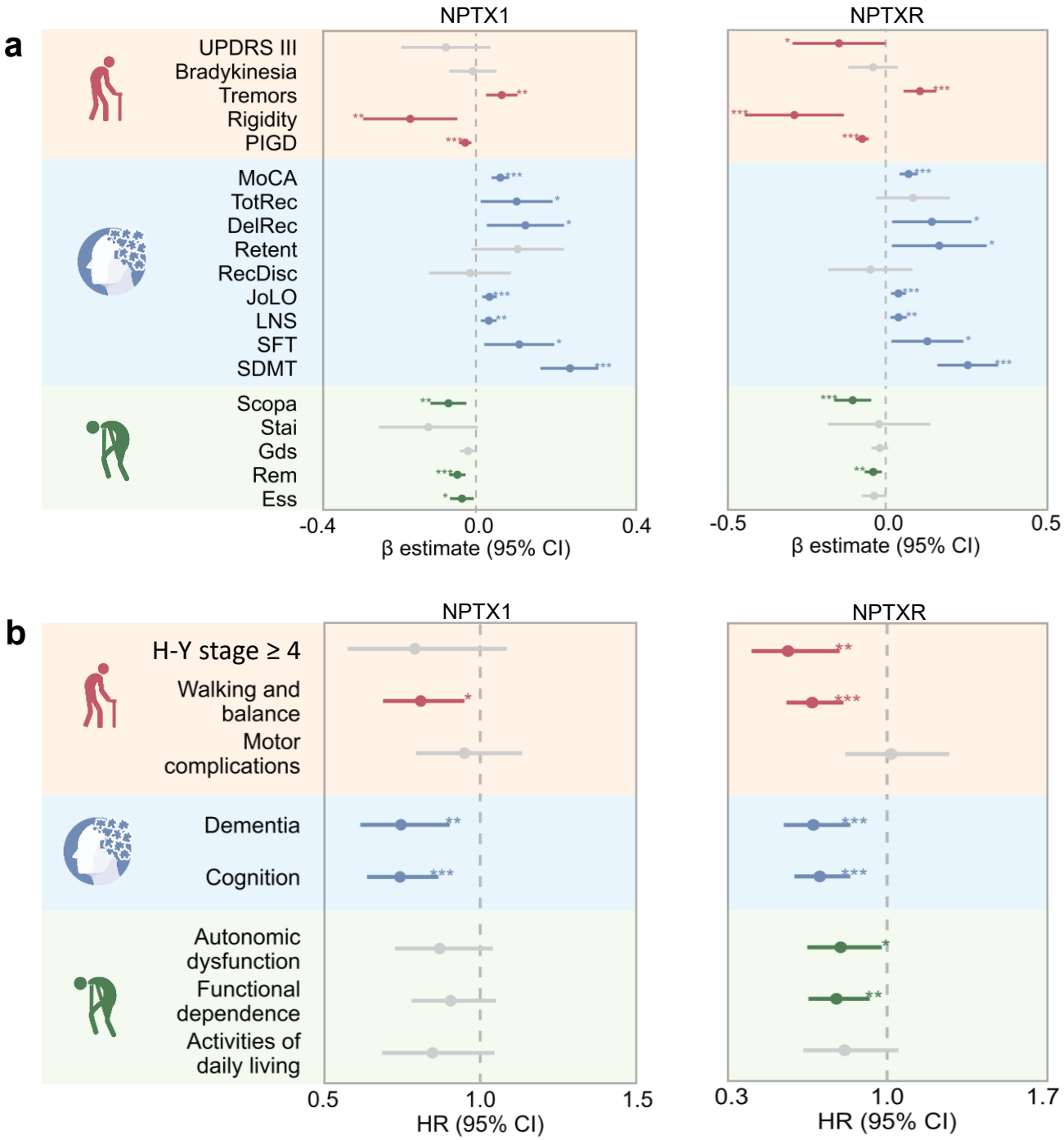

Fig.S6 Effects of NPTX1 and NPTXR on longitudinal symptoms in Parkinson's disease. a LMMs were used to examine effects of baseline CSF NPTX1 level and NPTXR level with follow-up time on longitudinal symptoms. **b** Cox proportional hazards models provided evidence of associations between CSF NPTX1 level and CSF NPTXR level and incident Hoehn-Yahr stage ≥4, incident dementia or the milestones of PD. LMM, linear mixed model; dementia, MoCA < 22; TotRec, HVLT Immediate/Total Recognition Index t-score; JoLO, the Benton Judgment of Line OrientRecall t-score; DelRec, HVLT Delayed Recall t-score; Retent, HVLT Retention t-score; RecDisc, HVLT Discrimination ation, LNS, the Letter Number Sequencing; SFT, the Semantic Fluency Test; SDMT, Symbol Digit Modalities Test; Scopa, SCOPA-AUT Total Score; Stai, State-Trait Anxiety Index (STAI) Total Score; H-Y stage, Hoehn-Yahr stage.

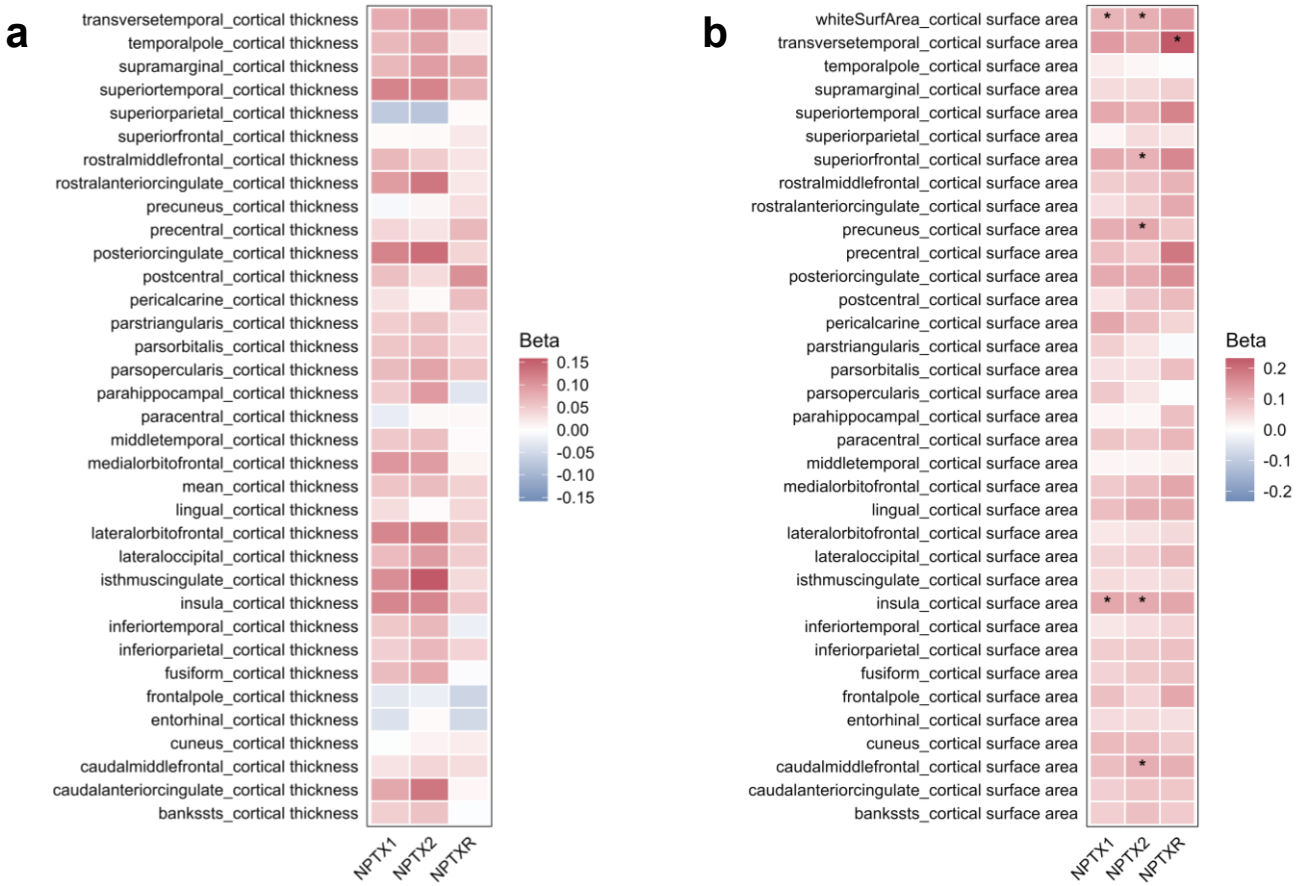

Fig.S7 The baseline relationship between CSF NPTX2 and brain cortical thickness and cortical surface area. a Heatmap showing baseline associations between CSF NPTXs and brain cortical thickness. **b** Heatmap showing baseline associations between CSF NPTXs and brain cortical surface area. The analyses were adjusted for age, sex, apolipoprotein E ε4 status, LEDD, baseline Hoehn-Yahr stage, disease duration, signal-to-noise ratio. For the cortical surface area, the model additionally adjusted for intracranial volume. Significant associations were determined with FDR-adjusted *P* value < 0.05. (*FDR-adjusted P value < 0.05, ** FDR-adjusted P value < 0.01, and *** FDR-adjusted P value < 0.001)

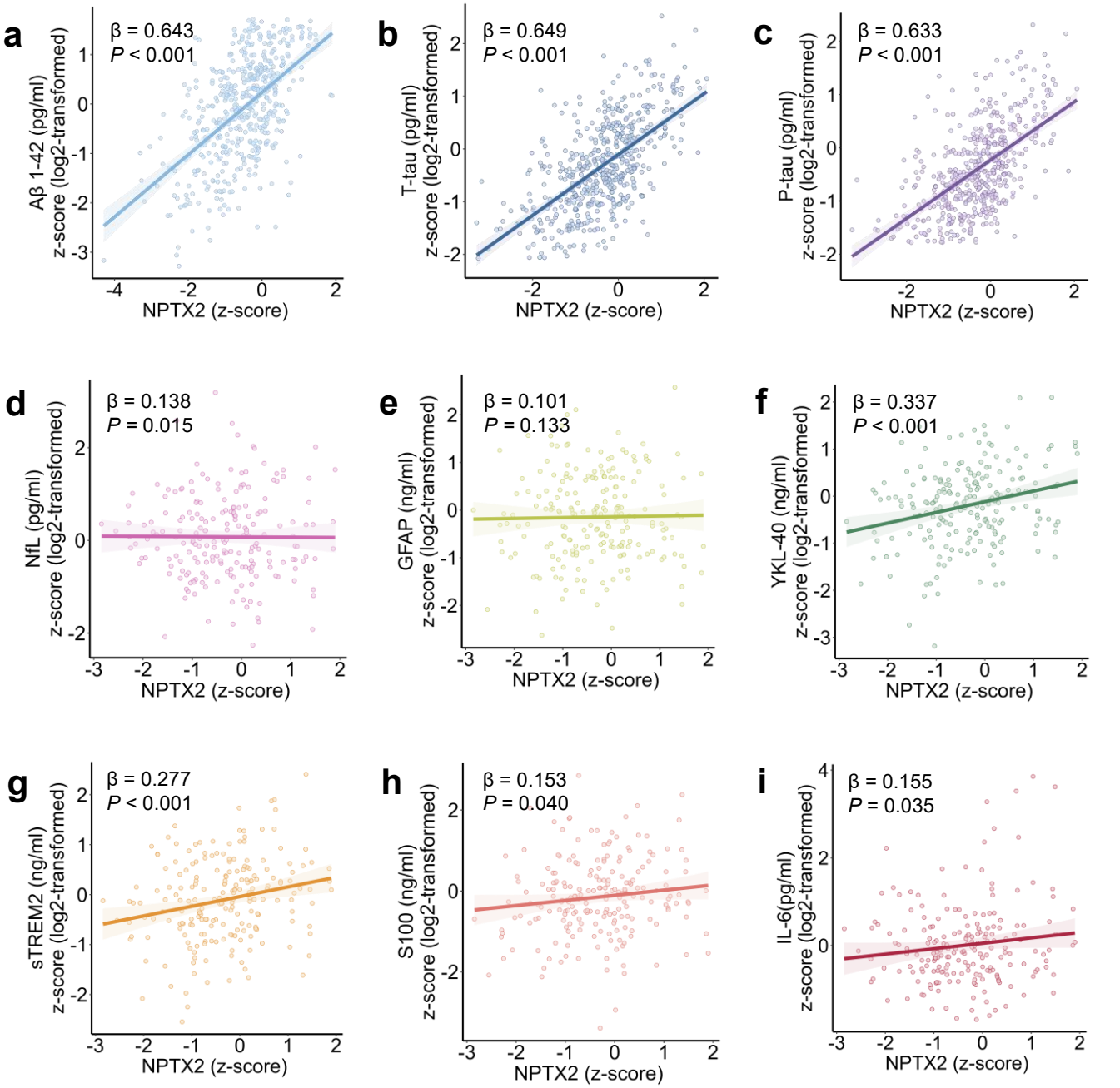

Fig.S8 The baseline relationship between CSF NPTX2 and CSF biomarkers. a-i Scatterplots showing the correlation between NPTX2 and $A\beta_{1\text{-}42}$(**a**), T-tau(**b**), P-tau(**c**), NfL(**d**), GFAP(**e**), YKL-40(**f**), sTREM2(**g**), S100(**h**), IL-6(**i**) in patients with PD. Measurements were adjusted for age, sex, apolipoprotein E ε4 status, LEDD, baseline Hoehn-Yahr stage, disease duration, baseline MoCA scores and education. Linear trend lines are shown, and the 95% confidence intervals are indicated by shading. $A\beta_{1\text{-}42}$, Amyloid-beta (1-42); T-tau, total tau; P-tau, tau phosphorylated at the threonine181 position (p-tau181); GFAP, Glial fibrillary acid protein; YKL-40, Chitinase-3-like Protein 1; sTREM2, Soluble triggering receptor expressed on myeloid cells 2; S100, S100 calcium binding protein B; IL-6, Interleukin 6.

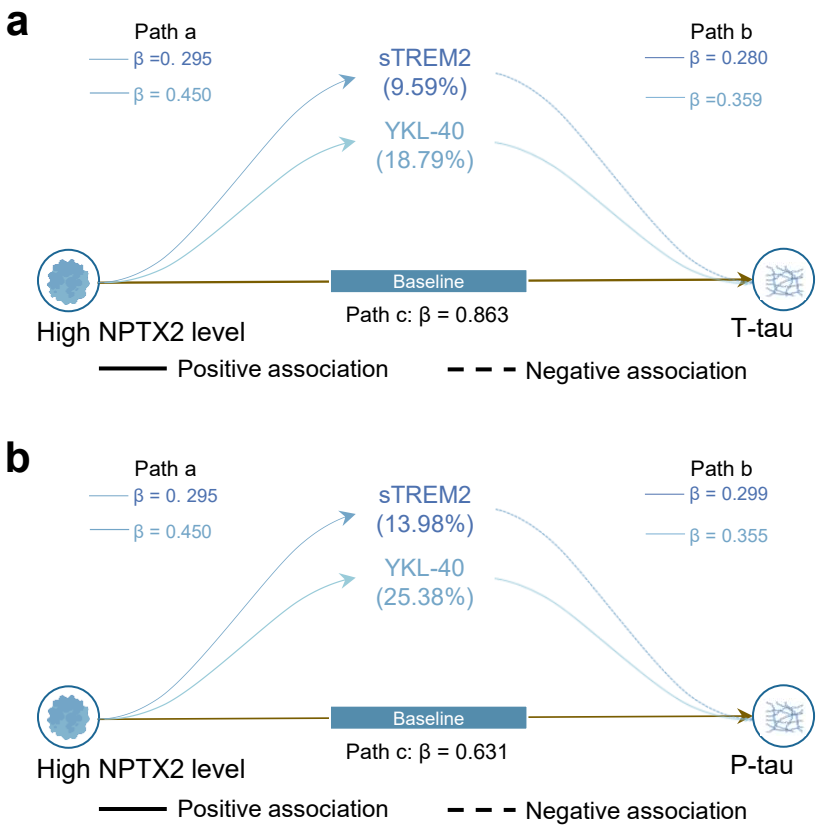

Fig.S9 Mediation of the association between CSF NPTX2 and tau pathology by sTREM2 and YKL-40. a, b sTREM2 and YKL-40 significantly mediated the association between CSF NPTX2 level and T-tau(**a**) and P-tau (**b**). Model were adjusted for age, sex, apolipoprotein E ε4 status, LEDD, baseline Hoehn-Yahr stage, disease duration, baseline MoCA scores and education.