OBJECTIVE
To investigate whether excessive daytime sleepiness (EDS) is mediated by loss of dopaminergic function by using dopaminergic specific single photon emission computed tomography (SPECT) molecular imaging in early de novo PD patients with and without EDS.

BACKGROUND
EDS is one of the earliest and most debilitating non-motor symptoms of PD and often challenging to manage in the clinic. An amalgamation of dopaminergic denervation, nocturnal sleep disruption and dopaminergic medication is likely to be causative [1], though several studies have suggested that EDS may be a primary feature of PD, unrelated to dopaminergic therapies or nocturnal sleep disturbances. Preclinical investigations have demonstrated that dopamine depletion causes sleep disturbances [2], suggesting that dopamine may play a fundamental role in regulating the sleep-wake cycle, hence potentially underlie EDS pathogenesis.

METHODS
We performed a case-control study using the Parkinson’s Progression Markers Initiative database, where we assessed and compared semi-quantified [123]I-FP-CIT SPECT, and motor and non-motor features from two groups of 84 early de novo PD patients with and without EDS who were matched for age, gender, age of diagnosis, years of education and disease duration. We also explored clinical and imaging correlates of EDS and the predictive significance of these markers in the development of EDS in PD patients without EDS.

RESULTS
PD patients with EDS had worse non-motor (MDS-UPDRS-Part I, p<0.001; MDS-UPDRS-Part II, p=0.005), autonomic (SCOPA-AUT, p<0.001) and cognitive (MoCA, p<0.05) function, depression (GDS, p<0.001), and reduced caudate dopamine transporters ([123]I-FP-CIT, p<0.024) compared to PD patients without EDS. Lower caudate [123]I-FP-CIT values correlated with higher EDS scores (r²=0.037, p=0.013). Among patients without EDS, 47 PD patients (56%) developed EDS over a median follow-up of 36 months. Cox multivariate analysis including all clinical and imaging data available, revealed abnormal caudate [123]I-FP-CIT uptake (p=0.030) and disease duration (p=0.018) were predictors for the development of EDS.

CONCLUSION
Our findings demonstrate that the development of EDS in patients with PD is related to the advancing disease and dopaminergic deficits in the caudate. We show a loss of dopaminergic function in the caudate of PD patients with EDS compared to those without. Dopaminergic deficits in the caudate were associated with the severity of EDS in the PD-EDS group and with a two-fold increased risk (HR=1.94) of developing EDS over a period of 36 months in the PD non-EDS group. Cognitive impairment, autonomic dysfunction and depression were strongly associated with EDS. Our data provides novel insight that loss of caudate dopaminergic function is associated with EDS severity and susceptibility. Impairment of dopaminergic function within the caudate should be further investigated to confirm its role in regulating the sleep-wake cycle.

References