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Excessive daytime sleepiness increases dementia risk in cognitively unimpaired Parkinson's disease patients over 12 years

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Research Article

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Excessive daytime sleepiness increases dementia risk in cognitively unimpaired Parkinson's disease patients over 12 years.

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Running title: Excessive daytime sleepiness and cognitive decline in Parkinson's disease.

Abbreviations: PPMI = Parkinson's Precision Medicine Initiative; PD = Parkinson's Disease; CN = Cognitively Normal Older Adults; MCI = Mild Cognitive Impairment; EDS = Excessive Daytime Sleepiness; RBD = rapid eye movement (REM) sleep behavior disorder.

ABSTRACT

Background: Excessive daytime sleepiness (EDS) is a common non-motor symptom of Parkinson's disease (PD) that often precedes diagnosis. Although EDS has been proposed as a predictor of cognitive decline, evidence linking it to specific cognitive deficits remains inconsistent.

Objective: This study investigated whether EDS increases the risk of conversion from cognitively normal (PD-CN) to mild cognitive impairment (PD-MCI) or dementia (PDD) and whether it relates to executive function and processing speed decline.

Methods: We analyzed data from 1147 initially cognitively normal PD participants with and without MCI and 266 cognitively normal older adults (CN) across 12 years. EDS was measured using the Epworth Sleepiness Scale (ESS) and cognition was assessed with the MoCA, Trail Making Test A and B, verbal fluency test, Symbol Digit Modality Test and the Letter-Number Sequencing. Cox proportional hazards models assessed conversion risk across three transitions. Mixed-effect linear regressions with FDR correction examined associations between ESS and cognitive performance over time in PD and CN participants. All models controlled for demographics, medication, PD severity, sleep and neuropsychiatric symptoms.

Results: Higher ESS scores were associated with greater risk of PD-CN to PDD conversion and with declining processing speed over time. Greater REM sleep behavior disorder was associated with higher risk of PD-CN to PD-MCI conversion. No significant association emerged in CN participants after FDR correction.

Conclusion: In early PD, EDS was associated with faster cognitive decline and elevated dementia risk, suggesting it may serve as a clinically useful marker of cognitive vulnerability.

Keywords: Excessive daytime sleepiness, Executive functions, Parkinson's Disease, Mild Cognitive Impairment, Cognitively Normal Older Adults.

INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disease, characterized by a complex clinical picture of motor and non-motor symptoms (NMS)[1, 2]. NMS often precede motor diagnosis by years, contribute to the overall disease burden and significantly impact quality of life[3]. Among these, cognitive impairment in PD encompasses a spectrum from cognitively normal (PD-CN) to mild cognitive impairment (PD-MCI) to Parkinson's dementia (PDD), varying in severity, rate of progression and cognitive domains affected[4]. Approximately 80% of patients develop cognitive impairment over the course of the disease. The prevalence of PD-MCI is around 25.8%, while nearly 46% of patients develop dementia after 10 years of diagnosis[2, 5]. Over follow-up periods of 3 years or more, 29% of PD-CN convert to PD-MCI, 34% of patients with PD-MCI progress to PDD and 8% of PD-CN convert directly to PDD[6]. Importantly, not all patients follow a linear trajectory and around 21% revert from PD-MCI to PD-CN over a follow-up period of more than 3 years[6]. This variability highlights the need to distinguish patients at risk of cognitive decline from those who remain stable, to allow for better clinical prognosis and treatment planning. With such high prevalence of cognitive impairment in PD, identifying early predictors of cognitive decline is crucial, yet remains an unmet need[2].

NMS are increasingly recognized as key determinants of clinical and cognitive trajectory in PD[7]. Among these, excessive daytime sleepiness (EDS) is a common NMS whose specific contribution to cognitive decline remains unclear, especially in *de novo* participants. EDS is defined as the incapacity to remain awake and alert during major periods of wakefulness, resulting in periods of irresistible sleepiness or involuntary bouts of drowsiness or sleep[8]. It is one of the most common sleep disorders in PD with a prevalence of up to 50% and incidence increasing over time[9]. EDS can emerge at the prodromal stage of the disease, often preceding clinical diagnosis[3]. Furthermore, studies have shown a dissociation between the severity of EDS

and the quality of nocturnal sleep, suggesting that EDS may be an integral component of PD pathology[10]. Importantly, Goldman [11] showed that EDS predicted cognitive decline independently of nocturnal sleep disturbances and dopaminergic medication, further supporting the view that EDS reflects underlying neurodegeneration rather than being a secondary effect of sleep disruption or treatment. These findings have led to a growing interest in the investigation of the relationship between EDS and cognitive impairment in PD. Cross-sectional studies have reported that EDS is associated with decreased performance in global cognition, executive functions and processing speed[11, 12]. However, other cross-sectional and longitudinal investigations in *de novo*, untreated cohorts have not replicated these findings, with no differences observed in cognitive performance over a 3-year follow-up period[13-15]. A possible explanation for these results is the different methodology used between these studies (different neuropsychological assessment and EDS measures, small sample size) and the presence of uncontrolled confounding variables (age of onset, years of education, medication)[16]. Given these inconsistencies, further longitudinal investigation is needed to clarify whether and how EDS contributes to cognitive decline across the course of PD. Thus, this study aims to assess whether EDS increases the risk of conversion from PD-CN to PD-MCI or PDD and from PD-MCI to PDD in a large, longitudinal *de novo* cohort with up to 12 years of follow-up. Given that previous studies have identified global cognition, executive function and processing speed as cognitive domains potentially related with EDS, we examined the cross-sectional and longitudinal relationship between EDS and these domains.

MATERIALS AND METHODS

PARTICIPANTS

Participants with newly diagnosed, untreated PD and matched cognitively normal non-PD older adults (CN) were enrolled in the Parkinson's Precision Medicine Initiative (PPMI) database (https://ida.loni.usc.edu/). The PPMI is a longitudinal, multicenter study with up to 12 years of follow-up. Its overall objective is to identify markers of PD progression that could be used clinically to reduce the progression of Parkinson's-related disability.

We originally extracted the data of 1891 participants at baseline, specifically: 1558 PD participants with and without cognitive impairments and 333 CN (Figure 1). At baseline, all participants with PD were required to be older than 30 years and (1) have a diagnosis of PD for two years or less at screening visit, (2) not expected to require PD medication within at least 6 months from baseline, (3) have at least two of bradykinesia, rigidity and resting tremor or have either an asymmetric resting tremor or asymmetric bradykinesia and (4) have had a dopamine transporter deficit on the ^{123}I Ioflupane dopamine transporter (DatScan®) imaging (ie DAT positive). The exclusion criteria for the study are as follows: (1) presence of an atypical parkinsonian syndrome, (2) other neurological, medical, or psychiatric conditions, (3) diagnosis of dementia, (4) use of medication for PD (e.g., Levodopa), and (5) inability to undergo a lumbar puncture [17].

CN participants were required to be older than 30 years and have confirmed eligibility based on screening SPECT imaging (i.e. DAT negative). They were matched by age, sex and education and must not have (1) a first degree relative with PD, (2) a current or active clinically significant neurological disorder, (3) a previous MRI scan showing evidence of a clinically significant neurological disorder or (4) any other medical or psychiatric condition or lab abnormality.

All participants had their cognitive status assessed by the site researcher or a qualified clinician appointed by the researcher. Based on information obtained from the participant or a relative, the researcher's clinical judgment and the result from cognitive testing across four domains (processing speed-attention, semantic fluency, memory and visuospatial function), participants were categorized as having normal cognition, MCI or dementia ("COGSTATE" PPMI variable). Normal cognition refers to individuals with intact cognitive functioning and typical cognitive abilities. MCI was determined based on the following factors: (1) impairment in at least one cognitive domain, (2) decline from pre-morbid function and (3) lack of significant impact of cognitive impairment on daily function. Dementia was determined based on: (1) impairment in more than one cognitive domain, (2) decline from pre-morbid function and (3) significant impact of cognitive impairment on daily function.

ETHICAL APPROVAL

All data are available on the PPMI websites upon demand (https://www.ppmi-info.org/access-data-specimens/download-data). PPMI is a large multicenter study and each site independently received ethics approval of the protocol. All subjects gave written informed consent in accordance with the Declaration of Helsinki. Ethics committee approval and individual patient consents were received by the corresponding registration sites according to PPMI rules (https://www.ppmi-info.org/study-design/research-documents-and-sops). This study was approved by *the Comité d'éthique de la recherche vieillissement-neuroimagerie* (CER VN 19-20-06). All participants provided written informed consent.

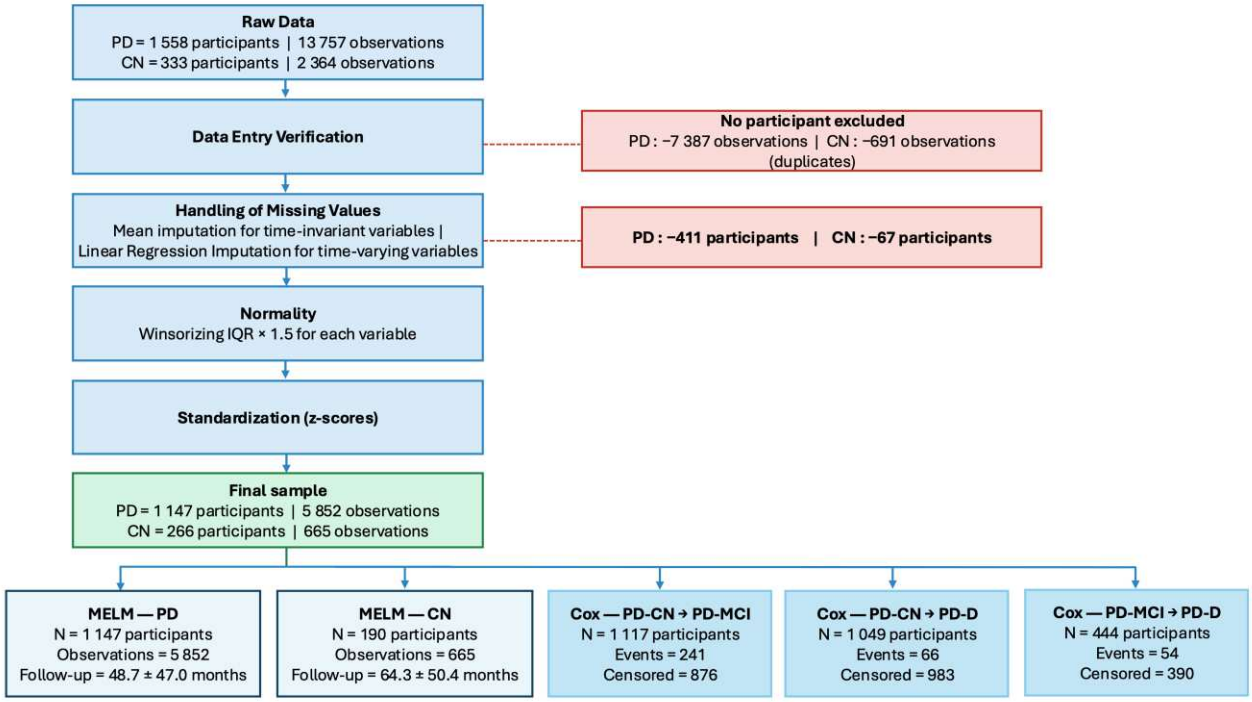


Fig. 1. Sample selection flow chart. Legend: IQR = interquartile range; MELM = Mixed Effect Linear Regression; Cox = Cox Regression Model.

CLINICAL ASSESSMENT

Each participant underwent cognitive assessments at baseline and annually during the follow-up period. To assess participants' executive functioning, all tests measuring cognitive flexibility, working memory and processing speed were considered. Cognitive flexibility was assessed using the Trail Making Test B (TMT-B) and phonemic verbal fluency test (FAS). The Letter-Number Sequencing (LNS) measures the ability to mentally manipulate verbal information (working memory). The Trail Making Test A (TMT-A) and the Symbol Digit Modalities Test (SDMT) measure processing speed. Although processing speed is not classified as an executive function, related tests were included, as reduced processing speed can significantly impact working memory and cognitive flexibility[18]. In addition, the Montreal Cognitive Assessment (MoCA) was used to provide a measure of global cognition [19, 20].

EDS was assessed using the Epworth Sleepiness Scale (ESS; Johns [21]). The ESS is a self-administered questionnaire with 8 questions. Participants are asked to rate on a 4-point

scale their usual likelihood of falling asleep while engaged in eight different activities, which are chosen to reflect the ability to facilitate the onset of sleep in most individuals. A score from 0 to 3 is assigned to each question, giving a total score ranging from 0 to 24.

Other demographic variables include sex, years of education, age at baseline and age of PD symptom onset. Neuropsychiatric symptoms of anxiety and depression were assessed using the State and Trait Anxiety Inventory (STAI) and the 15-item Geriatric Depression scale (GDS-15)[22, 23]. Additionally, we extracted data from the Rapid eye movement behavior disorder (RBD) questionnaire (RBDSQ) for REM sleep behavior disorder and quantified motor symptom severity with the Unified Parkinson's Disease Rating Scale Part III (UPDRS-III)[24, 25].

Medication Data Management

To account for dopaminergic medication use as the disease progressed, the Levodopa equivalent daily dose (LEDD) was considered[26]. LEDD values were extracted from the PPMI database and conversion factors were based on Tomlinson, Stowe [27]. The total change in LEDD over time was calculated using an R script provided in the PPMI user guide[28]. Since medication start and end dates were recorded by month, the PPMI protocol assumed that each medication was taken for the entire month. We then calculated the average LEDD over the period of interest by aligning the medication start date with the date of the corresponding clinical visit. This approach ensured that, at each time point, a LEDD value was available for all PD participants receiving dopaminergic treatment. It is important to note, however, that not all PD participants were taking dopaminergic medication and all baseline participants were medication-free.

STATISTICAL ANALYSIS

Participants with missing data on the primary measures of interest were excluded from the analysis (PD = 411; CN = 67). For the remaining participants, missing data were handled using two approaches based on variable type. Time-varying measures were imputed using within-subject linear regression across visits, which allows to account for individual trajectories

over time rather than assuming a single fixed value. Time-invariant variables were imputed using the sample mean[29]. Normality was assessed using the skewness and kurtosis statistics and the Shapiro-Wilk test. Variables showing non-normal distributions underwent Winsorizing, with values exceeding 1.5 times the interquartile range capped to reduce the influence of outliers. Finally, all variables of interest were standardized using z-scores. The final sample used for analyses included 1147 PD and 266 CN participants.

Statistical analyses were performed on the open-source web application Jupyter Notebook (version 6.4.11) using scripts written in Python language (3.9.12). Descriptive analyses verified the similarity of the groups in terms of age, years of education, MoCA scores, ESS scores, UPDRS-III scores (motor assessment) and sex distribution (respectively mean comparisons by t-test and contingency Chi^2 analysis).

Cox proportional hazards analyses were conducted in the PD group only, as they assessed conversion between PD-related cognitive stages. Three Cox proportional hazards regression models were performed to assess the risk of conversion associated with ESS score : (1) from PD-CN to PD-MCI, (2) from PD-CN to PD-dementia (PD-D) and (3) from PD-MCI to PD-D. Time was measured in months from baseline and diagnosis of MCI or dementia was considered as the outcome event. For participants who did not develop MCI or dementia, their last available visit was used as the censoring point, while for those who converted, the visit at which MCI or dementia was diagnosed was used. For all models, age, sex, years of education, LEDD, UPDRS-III scores, RBD scores and neuropsychiatric symptoms of depression and anxiety were used as covariates. This analysis was performed using the lifelines.CoxPHFitter package (version 0.27.4). Figures were generated using MatPlotlib (version 3.5.1).

To examine the relationship between ESS score and executive functions, mixed effects linear models (MELM) were applied using Python's statsmodels library (version 0.13.2). Models were estimated separately in the PD and CN groups, allowing us to assess whether

associations observed in PD were specific to the disease or also present in CN. MELM are an extension of simple linear models that account for both fixed and random effects[30]. These models account for non-independent observations, such as in longitudinal data, and assume that random effects are normally distributed. MELM are robust for handling complex longitudinal data with repeated observations and data from various clinical sites[31]. Additionally, this type of analysis provides better management of missing data that may occur in longitudinal studies. Thus, we conducted MELM for each cognitive variable (each measure of executive function). For the PD group, participants were treated as random factors, while age at baseline, age of symptoms onset, sex, years of education, time, LEDD, time-LEDD interaction, ESS (specific variable), neuropsychiatric symptoms and time-ESS interaction were included as fixed factors. For the CN group, the same model structure was used but excluded PD-specific variables. Each regression model was estimated according to the following form, with bracketed terms included in the PD models only:

Dependent variables ~ age at baseline + [age of symptoms onset] + sex + education + depression + anxiety + RBD + UPDRS-III + [LEDD] + [LEDDxTime] + Time + ESS + ESSxTime + random intercept + random slope.

We applied a False Discovery Rate (FDR) correction to the Cox regression models and the MELM, to correct for multiple comparison resulting from the multiple dependent variables, fixed factors of interest and repeated measures. It was applied using the Python library statmodels, specifically the function stats.multitest.fdrcorrection with the Benjamini/Hochberg method and a family-wise error rate (FEW) threshold of 0.05.

RESULTS

Demographic characteristics

Descriptive analyses showed that groups were similar according to sex and age. The PD group had lower mean years of education, lower mean MoCA score and greater UPDRS-III scores, compared to the CN group (Table 1). Finally, PD participants had significantly higher ESS scores than CN.

Table 1. Demographic characteristics and mean ESS score at baseline.

Variables	CN (N = 266)	PD (N= 1147)	Chi-square /T	p
Female, n (%) **Male, n (%)**	100 (37.6%) 166 (62.4%)	447 (39.0%) 700 (61.0%)	5.19	0.27
Age (years)	61.6 ± 11.31	62.3 ± 9.73	1.47	0.14
Education (years)	16.3 ± 2.96	16.01 ± 3.40	2.37	**0.018**
Mean MoCA Score	27.85 ± 1.49	26.66 ± 2.65	10.79	**<.001**
UPDRS3 mean score	1.35 ± 2.16	21.63 ± 10.47	61.84	**<.001**
Epworth sleepiness scale (ESS)	5.27 ± 3.34	5.60 ± 3.90	2.43	**0.015**

Legend. CN = Cognitively Normal older adults; PD = Parkinson's Disease; UPDRS3 = Unified Parkinson's Disease Rating Scale - III; p = p-values.

Risk factors for conversion to MCI and Dementia in PD only

The first Cox regression model assessed the risk of conversion from PD-CN to PD-MCI. Over the follow-up period, 241 participants out of 1117 converted to MCI. Older age was associated with a 85% increased risk of conversion per standard deviation increase (HR = 1.85, 95%CI: 1.60-2.15, p <.005, p_{fdr} <.005). Greater RBD symptoms were also associated with a higher risk of conversion, with a 16% increase per standard deviation (HR = 1.16, 95%CI: 1.04-1.30, p =0.01, p_{fdr} = 0.02), as were higher anxiety levels on the STAI, corresponding to a 36%

increased risk (HR = 1.36, 95%CI: 1.19-1.55, p <.005, p_{fdr} <.005). In contrast, higher LEDD was associated with a 19% reduced risk of conversion to PD-MCI (HR = 0.81, 95%CI: 0.74-0.88, p<.005, p_{fdr} <.005).

The second model examined the risk of conversion from PD-CN to PDD over the 12 years of follow-up. During this period, 66 participants out of 1049 developed dementia. Older age conferred the strongest risk, with a 151% increase per standard deviation (HR = 2.51, 95% CI = 1.85-3.41, p <.005, p_{fdr} <.005). Higher anxiety on the STAI was associated with a 50% increased risk (HR = 1.50, 95%CI: 1.17-1.92, p <.005, p_{fdr} = 0.004) and greater EDS on the ESS, with a 41% increased risk of conversion to dementia (HR =1.41, 95% CI = 1.16-1.71, p <.005, p_{fdr} = 0.003). More severe motor symptoms were associated with a 29% increased risk (HR = 1.29, 95%CI: 1.08-1.55, p = 0.01, p_{fdr} = 0.01). and elevated depressive symptoms on the GDS-15 with a 28% increased risk of conversion (HR = 1.28, 95%CI: 1.03-1.59, p = 0.03, p_{fdr} = 0.048).

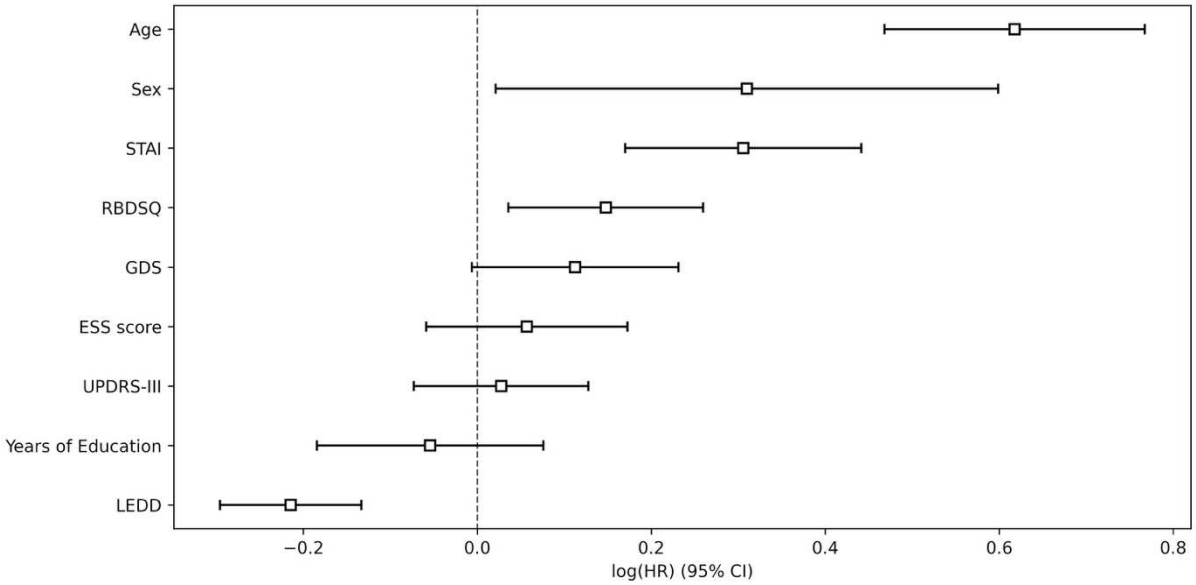
Finally, the third model assessed the risk of conversion from PD-MCI to PDD. Over the follow-up period, 54 participants with PD-MCI progressed to dementia. In this model, only older age remained significantly associated with conversion to dementia, corresponding with a 99% increased risk per standard deviation (HR = 1.99, 95% CI = 1.39-2.85, p <.005, p_{fdr} = 0.002). The full results of the three proportional hazards models are respectively reported in Table 2, 3 and 4 as well as Figure 2, 3 and 4.

Table 2. Risk of conversion from PD-CN to PD-MCI using Cox proportional hazards regression.

Variables	Exp(Coef)	95% CI of hazard ration		p-value	p_{fdr}
		Lower 95%	Upper 95%		
Age	1.85	1.60	2.15	**<.005**	**<.005**
Sex	1.36	1.02	1.82	0.04	0.06
Years of Education	0.95	0.83	1.08	0.41	0.47
ESS score	1.06	0.94	1.19	0.33	0.43
RBD score	1.16	1.04	1.30	**0.01**	**0.022**
LEDD	0.81	0.74	0.88	**<.005**	**<.005**
Motor score (UPDRS-III)	1.03	0.93	1.14	0.59	0.59
Depression score (GDS-15)	1.12	0.99	1.26	0.06	0.095
Anxiety score (STAI)	1.36	1.19	1.55	**<.005**	**<.005**

Legend. Exp(coef), exponential regression coefficient indicating increased (<1) or decrease (>1) risk for each additional point of the variable of interest; ESS, Epworth Sleepiness Scale; RBD, REM sleep behavior disorder; LEDD, Levodopa Equivalent Daily Dose. p_{fdr} = FDR corrected p-values. Bold font indicates p-values <0.05.

Fig 2. Hazard ratios for predictors of conversion from PD-CN to PD-MCI. All predictors are expressed as z-scores.



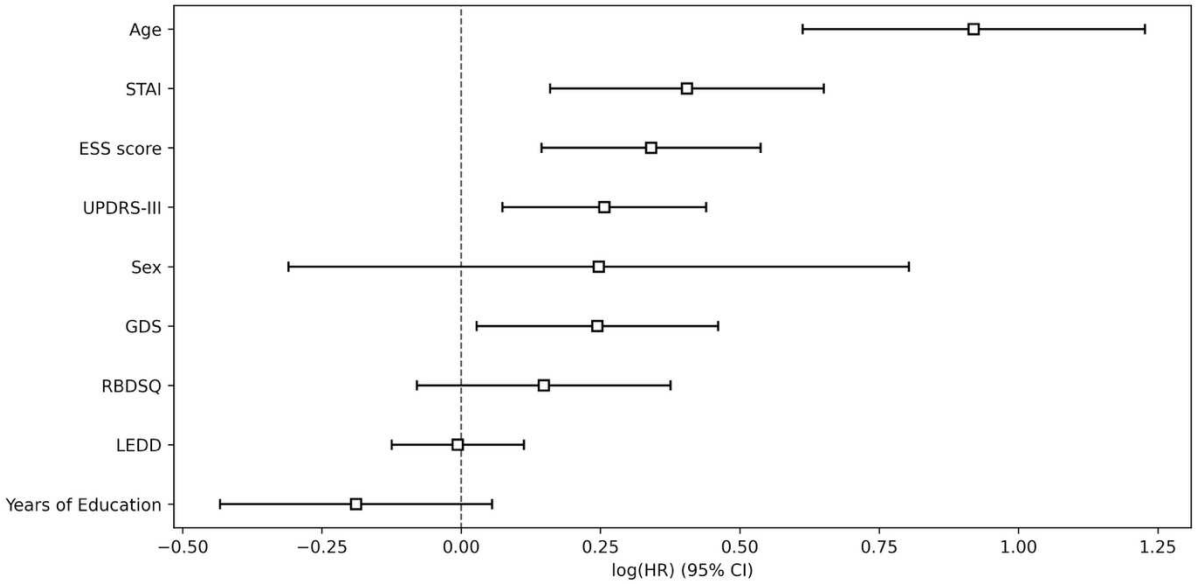
Legend. STAI, State-Trait Anxiety Inventory; RBDSQ, REM sleep behavior disorder screening questionnaire; GDS, Geriatric Depression Scale; ESS, Epworth Sleepiness Scale; UPDRS-III, Unified Parkinson's Disease Rating Scale part III; LEDD, Levodopa Equivalent Daily Dose.

Table 3. Risk of conversion from PD-CN to PDD using Cox proportional hazards regression.

Variables	Exp(Coef)	95% CI of hazard ration		p-value	p_{fdr}
		Lower 95%	Upper 95%		
Age	2.51	1.85	3.41	**<.005**	**<.005**
Sex	1.28	0.73	2.23	0.39	0.43
Years of Education	0.83	0.65	1.06	0.13	0.19
ESS score	1.41	1.16	1.71	**<.005**	**0.003**
RBD score	1.16	0.92	1.46	0.20	0.26
LEDD	0.99	0.88	1.12	0.92	0.92
Motor score (UPDRS-III)	1.29	1.08	1.55	**0.0059**	**0.013**
Depression score (GDS-15)	1.28	1.03	1.59	**0.03**	0.048
Anxiety score (STAI)	1.50	1.17	1.92	**<.005**	**0.0037**

Legend. Exp(coef), exponential regression coefficient indicating increased (<1) or decrease (>1) risk for each additional point of the variable of interest; ESS, Epworth Sleepiness Scale; RBD, REM sleep behavior disorder; LEDD, Levodopa Equivalent Daily Dose. p_{fdr} = FDR corrected p-values. Bold font indicates p-values <0.05.

Fig 3. Hazard ratios for predictors of conversion from PD-CN to PDD. All predictors are expressed as z-scores.



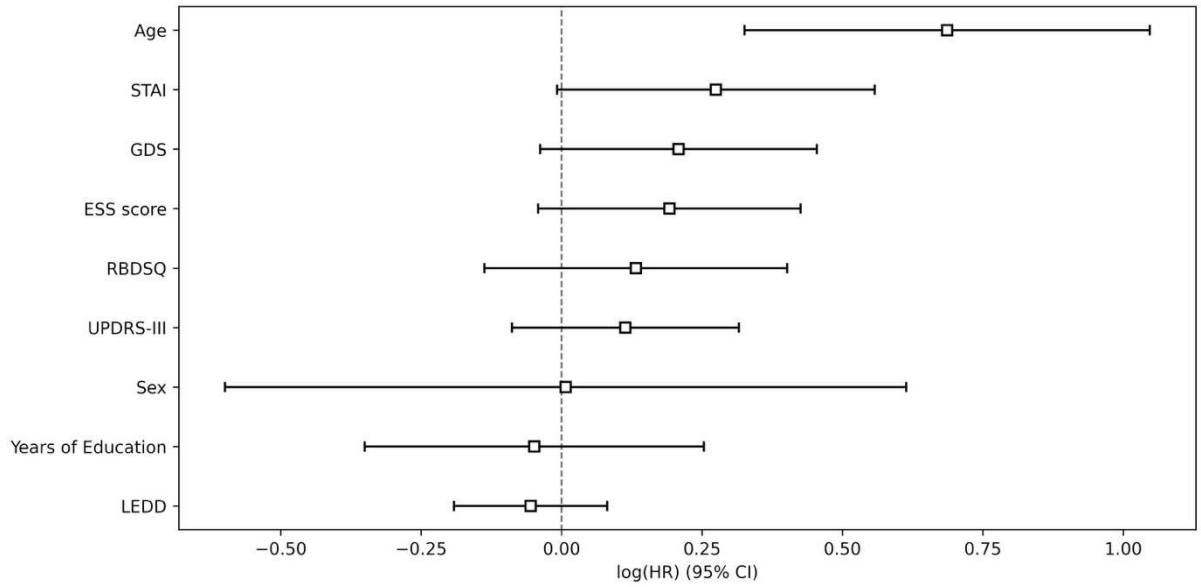
Legend. STAI, State-Trait Anxiety Inventory; RBDSQ, REM sleep behavior disorder screening questionnaire; GDS, Geriatric Depression Scale; ESS, Epworth Sleepiness Scale; UPDRS-III, Unified Parkinson's Disease Rating Scale part III; LEDD, Levodopa Equivalent Daily Dose.

Table 4. Risk of conversion from PD-MCI to PDD using Cox proportional hazards regression.

Variables	Exp(Coef)	95% CI of hazard ration		p-value	p_{fdr}
		Lower 95%	Upper 95%		
Age	1.99	1.39	2.85	**<.005**	**0.002**
Sex	1.01	0.55	1.85	0.98	0.98
Years of Education	0.95	0.70	1.29	0.75	0.85
ESS score	1.21	0.96	1.53	0.11	0.24
RBD score	1.14	0.87	1.49	0.34	0.51
LEDD	0.95	0.83	1.08	0.43	0.55
Motor score (UPDRS3)	1.12	0.92	1.37	0.27	0.49
Depression score (GDS-15)	1.23	0.96	1.58	0.10	0.24
Anxiety score (STAI)	1.32	0.99	1.75	0.06	0.24

Legend. Exp(coef), exponential regression coefficient indicating increased (<1) or decrease (>1) risk for each additional point of the variable of interest; ESS, Epworth Sleepiness Scale; RBD, REM sleep behavior disorder; LEDD, Levodopa Equivalent Daily Dose.

Fig 4. Hazard ratios for predictors of conversion from PD-MCI to PDD. All predictors are expressed as z-scores.



Legend. STAI, State-Trait Anxiety Inventory; RBDSQ, REM sleep behavior disorder screening questionnaire; GDS, Geriatric Depression Scale; ESS, Epworth Sleepiness Scale; UPDRS-III, Unified Parkinson's Disease Rating Scale part III; LEDD, Levodopa Equivalent Daily Dose.

Cognitive trajectories related to EDS (in PD and CN)

After controlling for age at visit, age at symptom onset, sex, years of education, neuropsychiatric symptoms (depression and anxiety), motor symptoms, LEDD and RBD scores, higher ESS scores were longitudinally associated with lower MoCA performance in the PD group (β = -0.0014, p = 0.024), although this association did not survive FDR correction (p_{fdr} = 0.06). Higher ESS scores were also longitudinally associated with lower SDMT performance in the PD group (β = -0.001, p = 0.004, p_{fdr} = 0.011). Results are shown in Table 5 and Figure 5.

In the CN group, higher ESS scores were unexpectedly longitudinally associated with higher SDMT (β = 0.001, p = 0.021) and verbal fluency performances (β = 0.002, p = 0.028). However, neither association remained significant after FDR correction (p_{fdr} = 0.11). Results are shown in Table 5.

Table 5. Effect of time, excessive daytime sleepiness and their interaction on cognitive performance.

		CN						PD					
Dependent	**Fixed factors**	**coef.**	**Std. Err.**	**[0.025]**	**[0.975]**	**p-value**	**p_fdr**	**coef.**	**Std. Err.**	**[0.025]**	**[0.975]**	**p-value**	**p_fdr**
MoCA	Time	-0.001	0.001	-0.003	0.001	0.35	0.72	-0.002	0.001	-0.004	0.001	**0.004**	**0.011**
	ESS	-0.021	0.052	-0.123	0.081	0.68	0.72	-0.014	0.016	-0.046	0.017	0.37	0.58
	Time*ESS	-0.0004	0.001	-0.002	0.001	0.68	0.72	-0.0014	0.00043	-0.001	0.00009	**0.024**	0.06
LNS	Time	-0.003	0.001	-0.004	-0.002	**<.005**	**<.005**	-0.005	0.001	-0.006	-0.004	**<.005**	**<.005**
	ESS	-0.027	0.036	-0.097	0.044	0.46	0.72	-0.026	0.015	-0.056	0.004	0.084	0.19
	Time*ESS	0.0005	0.001	-0.001	0.001	0.35	0.72	-0.0004	0.00027	-0.001	0.00014	0.15	0.27
SDMT	Time	-0.002	0.0005	-0.003	-0.001	**0.001**	**<.005**	-0.005	0.001	-0.007	-0.004	**<.005**	**<.005**
	ESS	0.015	0.030	-0.074	0.043	0.61	0.72	0.0002	0.014	-0.026	0.027	0.99	0.99
	Time*ESS	0.001	0.0004	-0.00006	0.002	**0.021**	0.11	-0.001	0.00024	-0.001	-0.00023	**0.004**	**0.011**
Verbal Fluency	Time	-0.001	0.001	-0.002	0.003	0.54	0.72	0.001	0.001	-0.001	0.002	0.50	0.65
	ESS	-0.20	0.10	-0.39	0.002	0.052	0.16	-0.058	0.036	-0.13	0.013	0.11	0.22
	Time*ESS	0.002	0.001	0.0002	0.004	**0.028**	0.11	-0.0001	0.00043	-0.001	0.001	0.82	0.87
TMT-A	Time	0.001	0.001	-0.001	0.003	0.48	0.72	0.004	0.001	0.002	0.005	**<.005**	**<.005**
	ESS	-0.082	0.11	-0.30	-0.13	0.45	0.72	0.030	0.035	-0.038	0.098	0.39	0.58
	Time*ESS	0.001	0.001	-0.002	0.003	0.56	0.72	0.0002	0.0005	-0.001	0.001	0.70	0.78
TMT-B	Time	0.003	0.001	0.0003	0.005	**0.030**	0.11	0.005	0.001	0.004	0.007	**<.005**	**<.005**
	ESS	-0.014	0.10	-0.21	0.19	0.89	0.88	0.017	0.036	-0.054	0.089	0.64	0.76
	Time*ESS	0.001	0.001	-0.002	0.003	0.64	0.72	0.0004	0.0005	-0.001	0.001	0.47	0.65

Legend. Dependent, Dependent variables; MoCA, Montreal Cognitive Assessment; LNS, Letter Number Sequencing; SDMT, Symbol Digit Modalities Test; TMT-A, Trail Making Test A; TMT-B, Trail Making Test-B; ESS, Epworth Sleepiness Scale score; Models are adjusted for age at baseline, age of symptoms onset, sex, education, depression, anxiety, REM sleep behavior disorder, motor score and levodopa equivalent dose. Coefficient are expressed in standard deviation units (z-scores). Bold font indicates p-values <0.05.

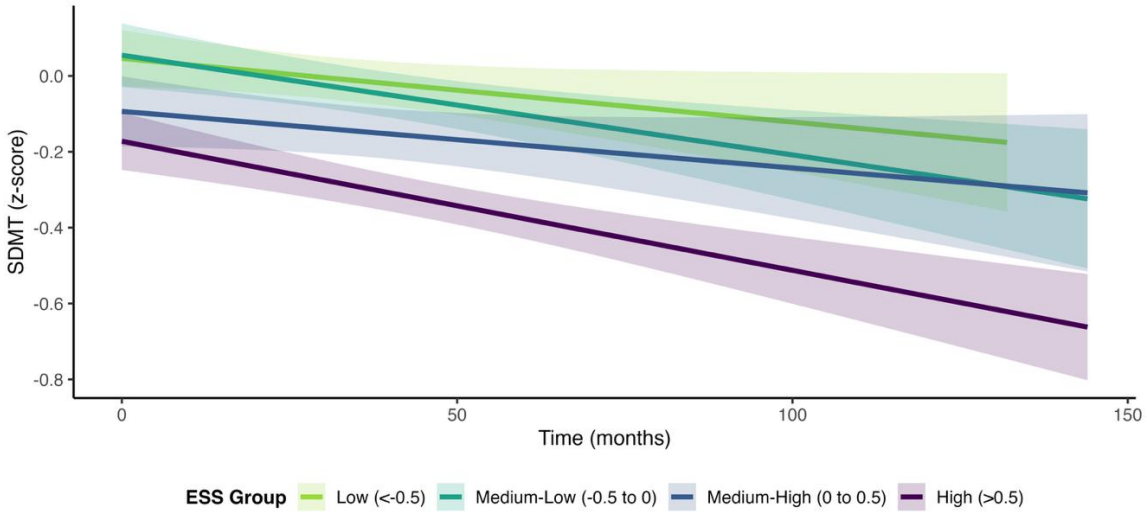


Fig. 5. SDMT score trajectories over time by ESS group. ESS groups are in quartiles, with low quartiles indicating higher ESS scores.

DISCUSSION

In this study, we investigated whether EDS predicts cognitive stage transition in PD (from PD-CN to PD-MCI or PDD and from PD-MCI to PDD). We also examined its cross-sectional and longitudinal associations with global cognition, executive function and processing speed. To our knowledge, this is the first study to assess the predictive role of EDS across distinct cognitive stages, using a large *de novo* PD cohort with up to 12 years of follow-up and addressing key methodological limitations of prior work.

Higher EDS was independently associated with an increased risk of conversion from PD-CN to PDD. Older age, higher motor symptom severity, anxiety and depression also predicted conversion, consistent with previously identified risk factors for PDD[32]. Notably, RBD and LEDD did not emerge as significant variables in this model, which is in line with prior observations by Goldman [11]. However, this contrasts with findings from Anang, Gagnon [33] who identified RBD as a strong predictor of dementia in a cohort with an average disease duration of 10 years, polysomnography-confirmed RBD and a high prevalence of baseline RBD among dementia converters. Differences in cohort characteristics and disease stage may

therefore partly explain the different findings, as our sample consisted of patients at an earlier disease stage. In this context, EDS emerged as a significant predictor of conversion while RBD did not, suggesting that EDS may become a more salient marker of dementia risk earlier in the disease course, whereas RBD predictive value for dementia may emerge later with longer disease duration. More broadly, EDS has been linked to the development of dementia in cognitively healthy older adults[34, 35]. In PD, participants with EDS at baseline showed greater cognitive impairment and demonstrated faster progression to dementia over a 4-year follow-up period compared to those without EDS[36]. Taken together, these findings suggest that EDS may be a marker of a more aggressive trajectory, possibly reflecting neurodegeneration of sleep-wake promoting nuclei that also overlap with circuits implicated in PDD[37]. Given that EDS can be easily assessed in clinical settings, it may represent a practical early marker to identify PD-CN patients at risk of cognitive decline.

We also found that age, RBD and anxiety were independently associated with a higher risk of conversion from PD-CN to PD-MCI. These results are consistent with previous cross-sectional studies linking RBD to PD-MCI[38-40]. Longitudinally, Boot [41] found that RBD predicted MCI but not dementia in CN participants, over 3.8 years of follow-up. Similarly, in *de novo* PD participants, RBD and age independently predicted cognitive impairment on the MoCA over 5 years[42]. Furthermore, anxiety at baseline, but not depression, predicted MCI in PD at 3 years[43]. The distinction between anxiety and depression is noteworthy, as it might reflect distinct neurobiological processes with different implications for cognition[44]. Together, these findings indicate that age, RBD and anxiety may capture early neurodegenerative changes that precede and predispose to cognitive decline in PD.

Interestingly, we also found that LEDD was associated with a decreased risk of conversion to PD-MCI. Some prior studies have suggested that LEDD might have a neuroprotective effect on cognitive impairments at early stages[45, 46]. Alternatively, since

participants were drug naïve at baseline, those who converted to MCI earlier in their follow-up had less LEDD exposure by the time of conversion, making it difficult to determine whether LEDD is truly protective or simply reflects a shorter exposure in early converters. Future studies should use time-varying LEDD in their analysis to clarify this finding.

Together, our findings raise the possibility that RBD and EDS reflect distinct neural mechanisms and temporal stages of neurodegeneration in PD. In fact, in early PD, RBD is thought to reflect brainstem α-synuclein pathology in pontine nuclei[47], while EDS may indicate broader neurodegeneration of sleep-wake promoting nuclei[37]. This distinction aligns with our observation that RBD predicted earlier cognitive decline toward MCI, while EDS predicted conversion to dementia, suggesting that these sleep disturbances may reflect sequential stages of pathological spread. It should be noted that these interpretations remain speculative and future neuroimaging studies will be needed to determine whether RBD and EDS truly mark distinct neurodegenerative pathway or successive stages of the same process.

Age was the only predictor of conversion from PD-MCI to PDD, in line with prior findings[48]. This may suggest that once cognitive decline started, progression might be driven by accumulating pathology, rather than clinical markers.

Finally, in PD but not in CN, we found EDS to be associated with worse global cognition and processing speed over time, while controlling for key confounding variables as recommended by Jester, Lee [16]. This extends previous findings linking EDS to cognitive decline in PD by demonstrating this relationship longitudinally in a large *de novo* cohort[12, 49-51]. While two cross-sectional studies reported deficits in processing speed associated with EDS in *de novo* and newly diagnosed participants[52, 53], others did not find any association[13-15]. Our extended follow-up period may account for this discrepancy, as EDS-related cognitive deficits may emerge gradually with accumulating neurodegeneration, making them difficult to detect in

cross-sectional assessments or shorter longitudinal designs. Taken together, our results suggest that EDS may serve as an early, clinically accessible marker of cognitive impairment in PD.

STRENGTHS AND LIMITATIONS

Our study has several notable strengths. The use of a longitudinal design with a 12-year follow-up period allowed us to capture the gradual emergence of EDS related cognitive decline, which shorter studies may have missed. Our analyses drew on a well-characterized, multi-site cohort with standardized cognitive assessments, enhancing the reliability of our findings. Furthermore, by focusing on *de novo* PD individuals, we were able to examine EDS as an early marker of cognitive decline, prior to the potential confounding effects of long-term dopaminergic treatment. Finally, we controlled for multiple covariates in our models, providing a more precise picture of the independent contribution of EDS to cognitive outcomes.

A few limitations should be acknowledged. First, EDS was assessed using the ESS, a subjective questionnaire that may diverge from objective measures of daytime sleepiness such as the MSLT or actigraphy. However, ESS scores at baseline have been shown to be the main risk factor for developing EDS[54]. This suggests the ESS captures a meaningful and progressive process rather than merely reflecting situational sleepiness. Second, the number of conversions from PD-CN to PDD and from PD-MCI to PDD was relatively small, which should be considered when interpreting the results. Finally, although we controlled for multiple covariates, we did not account for all sleep disturbances. In particular, EDS can be secondary to obstructive sleep apnea and future studies should include this variable in their models [55]. Further work is also needed to better characterize how EDS interacts with other sleep disturbances and neuropsychiatric symptoms over the course of PD progression and to determine whether EDS represents an independent predictor of cognitive decline or a marker of broader underlying neurodegenerative processes. Integrating neuroimaging and other brain

biomarkers may help clarify the neural mechanisms linking EDS to dementia risk in PD. It should also be noted that our results in CN are limited by the fact that a very little number of participants developed MCI (N=28) or dementia (N=2).

CONCLUSION & IMPLICATION OF THE CURRENT STUDY

With this study, we revealed that EDS is a key symptom for predicting PDD and the decline of processing speed while RBD is a key predictor of PD-MCI in *de novo* participants across a 12-year follow-up period. These findings underscore that EDS may help identify patients at risk for rapid progression to dementia, allowing early interventions. Thus, ESS screening should be integrated in cognitive monitoring protocols for PD. Furthermore, combined screening of sleep disturbances and neuropsychiatric symptoms could improve predictive accuracy for different cognitive outcomes.

DECLARATIONS

Ethics approval and consent to participate

PPMI is a large multicenter study and each site independently received ethics approval of the protocol. Ethics committee approval was received by the corresponding registration sites according to PPMI rules (https://www.ppmi-info.org/study-design/research-documents-and-sops). This study was approved by *the Comité d'éthique de la recherche vieillissement-neuroimagerie* (CER VN 19-20-06).

All subjects gave written informed consent in accordance with the Declaration of Helsinki. Individual patient consents were received by the corresponding registration sites according to PPMI rules (https://www.ppmi-info.org/study-design/research-documents-and-sops).

Consent for publication

Not applicable.

Availability of data and materials

Data used in the preparation of this article were obtained from the Parkinson's Precision Medicine Initiative (PPMI) database (www.ppmi-info.org/access-data-specimens/download-data), RRID:SCR_006431. For up-to-date information on the study, visit www.ppmi-info.org.

Competing interests

The authors declare that they have no competing interests.

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Authors 'contributions

Research conception and design were carried out by OM, LR and LME. LME analyzed the data and drafted the manuscript. OM supervised the study. All authors contributed to the interpretation of the data, the revision of the manuscript and approved the final version.

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