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Chapter 5:

The course of insomnia in Parkinson's disease

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ABSTRACT

Introduction. Insomnia is a debilitating symptom in Parkinson's disease (PD) that has been scarcely investigated in a longitudinal design. Knowledge of factors associated with occurrence of insomnia may provide clues for an increased understanding of underlying pathophysiology and facilitate early detection. The objective of this study is to examine the course and factors associated with longitudinal changes in insomnia severity in patients with PD. *Methods.* Analyses were performed in data of the SCOPA-PROPARK cohort, a 5-year longitudinal cohort study (2003-2011) of 421 PD patients who have been examined annually. Linear mixed models were used to identify factors associated with longitudinal changes in scores of the SCOPA-SLEEP-Nighttime sleep (NS) problems section. A generalized estimating equations (GEE) analysis was performed to determine which baseline variables were associated with the different aspects of insomnia (sleep initiation or maintenance difficulty). *Results*. Baseline SCOPA-SLEEP-NS scores were available for 412 patients, of whom 110 (27%) had insomnia (i.e. score ≥7). Of the remaining 302 patients, 99 (33%) developed insomnia at some point during follow-up. More severe depressive symptoms, motor fluctuations, higher dopamine agonist doses and sleep medication use were independently associated with higher SCOPA-SLEEP-NS scores over time. GEE analysis did not identify an unique set of determinants that affected specific aspects of insomnia. *Conclusion.* The presence of depressive symptoms, motor fluctuations and the use of higher doses of dopamine agonists are associated with more severe insomnia. Attention to these aspects could potentially contribute to a better management of insomnia symptoms in PD.

INTRODUCTION

Insomnia is a common sleep disorder in Parkinson's disease (PD) and affects up to 60% of patients according to earlier population-based prevalence studies.[1] The American Academy of Sleep Medicine defines insomnia as problems involving initiating sleep, maintaining sleep, early awakenings and poor overall sleep quality.[2] In PD, sleep fragmentation and early awakenings are the most common complaints, whereas initiation of sleep is often unimpaired.[3] Insomnia may be related to ageing, the progression of the disease or the use of drugs with a sleep-altering effect.[1-4] Insomnia has a great negative impact upon health-related quality of life[5,6] and is one of the most frequently reported non-motor symptoms in PD, with larger studies finding prevalence rates between 37 and 45%.[7,8] Remarkably, there are only a few longitudinal studies on insomnia in PD and information on its course and possible determinants is therefore scarce. To date only one large longitudinal study (n=231) has been performed,[1] which showed that insomnia often exhibits a fluctuating course and is associated with female gender, longer disease duration and coexistent depression. Cross-sectional studies on this topic showed that increased levels of anxiety and depression, impulsivity, excessive daytime sleepiness (EDS), fatigue, autonomic dysfunction and higher doses of dopaminergic medication are associated with insomnia in PD, whereas conflicting results emerged regarding disease severity.[3,4,9-12] However, cross-sectional studies provide limited information on the course and features that are longitudinally associated with insomnia. A thorough knowledge of factors that are associated with occurrence and severity of insomnia may provide clues for an enhanced understanding of the underlying pathophysiology, facilitate early detection and guide future intervention strategies. The aim of the current study was to use a prospective cohort design to determine the frequency, course, longitudinal associations and risk factors of insomnia in PD.

METHODS

Study design and participants

Since 2013, post-hoc analyses on the PROPARK cohort have been performed to determine the longitudinal course of several non-motor domains.[13] The original purpose of the PROPARK cohort study was to evaluate the longitudinal course of several motor and non-motor symptoms in PD. The cohort included 421 PD patients who have been examined annually and followed for up to five years (i.e., six assessments) on several motor and non-motor features; this makes this study very well-suited for the purpose of identifying factors associated with longitudinal changes in insomnia in PD.[14] Patients were recruited from neurology clinics of university and regional hospitals in the western part of The Netherlands and all fulfilled the United Kingdom Parkinson's disease Society Brain Bank criteria for idiopathic PD.[15] The majority of patients were evaluated at the Leiden University Medical Centre, but more severely affected patients were offered the possibility to be examined at their homes to minimize selective drop-out. In view of the fact that we aimed to obtain information on the full spectrum of the disease, a recruitment strategy based on age-at-onset (< or ≥50 years) and disease duration (< or ≥10 years) was applied. We intended to recruit at least 100 patients in each of the four strata.[14] The medical ethical committee of the Leiden University Medical Centre approved the PROPARK study and written informed consent was obtained from all patients.[14]

Assessment of baseline variables

Baseline assessments were performed between 2003 and 2005. In the five subsequent annual visits, all patients received standardized assessments. The last assessments of individual patients were performed between 2008 and 2011. The assessments included an evaluation of demographic and clinical characteristics, family history of PD, and registration of antiparkinsonian medication. A levodopa dose equivalent (LDE) of daily levodopa and dopamine agonists dose was calculated for each patient at baseline. The total LDE is the sum of levodopa dosage equivalent (LDE-Dopa) and the dopamine agonist dosage equivalent (LDE-DA).[16] Diagnosis of PD and Hoehn & Yahr (H&Y) stages of the patients were ascertained at every assessment.[17] The following instruments were administered by qualified examiners: the SPES/SCOPA[18] (including sections on motor examination, activities of daily living and motor complications), the SCOPA-COG (cognitive function),[19] and the SCOPA-PC (psychiatric complications; items 1-5).[20] Over the years, there were in total five examiners, who all regularly attended retraining and recalibration sessions to prevent inter-rater variability. All patients were assessed during “on’’ and patients completed the following instruments themselves: the SCOPA-AUT (subscales gastrointestinal, urinary tract and cardiovascular),[21] the SCOPA-SLEEP (nighttime sleep problems [NS] and daytime

sleepiness [DS]),[22] and the Beck Depression Inventory (BDI).[23] For all instruments except the SCOPA-COG, higher scores reflect poorer functioning. Patients were classified according to motor subtype into those with and without postural-instability-and-gait difficulty (PIGD) by using a ratio of tremor score over PIGD score.[19] Patients with a ratio value <1.0 were classified as PIGD dominant, whereas those with values ≥1.0 were classified as non-PIGD dominant.[18,24]

Ascertainment of insomnia

Insomnia was assessed using the nighttime sleep (NS) section of the SCOPA-SLEEP questionnaire,[22] an instrument that was appraised as "recommended" by the Movement Disorder Society Sleep Scale Task Force (MDS-SSTF).[25] It consists of 5 items that evaluate problems with sleep initiation, sleep maintenance, early awakenings and subjective sleep quality. Patients were considered to suffer from insomnia if they scored ≥7.[22]

Statistical analysis

The objectives of the statistical analysis in this study were: 1) to examine which factors are associated with the presence of insomnia; 2) to evaluate which variables are associated with longitudinal variations in SCOPA-SLEEP-NS scores; and 3) to determine which specific aspects of insomnia are affected by the different baseline variables.

For objective 1 we evaluated which features were associated with insomnia in the baseline data of our population. Cross-sectional analyses were performed to assess differences at baseline between patients with and without insomnia using the appropriate tests.

For objective 2 a linear mixed models (LMM) analysis was performed using the data of all patients included in the follow-up. This method is suitable for identifying baseline variables that are associated with variation in SCOPA-SLEEP-NS scores over time. LMM takes into account that repeated measures in the same patient are correlated and a restricted maximum likelihood model with an autoregressive (heterogeneous) covariance structure type was used in all LMM analyses; this covariance structure takes into account that measurements performed closer in time are more strongly correlated than those that have been performed over longer intervals. Since heterogeneity between patients was expected in baseline levels and in change over time, random intercepts and slopes were used. Variables that have been found associated with insomnia in earlier studies were considered in the LMM. The H&Y stage was not included because it is partly determined by motor phenotype and the sumscore of motor impairment.

The relationship between variables that were associated with variation in SCOPA-SLEEP-NS scores over time were first analyzed including only one variable at a time (unadjusted model). Additionally, an adjusted model was performed that considered the main effects of

all significant baseline variables from the unadjusted model. The final model only included the variables that were significant from the adjusted model.
A generalized estimating equations (GEE) method was applied to determine if the same or different baseline variables determined the various characteristics of insomnia (i.e. the different items of the SCOPA-SLEEP-NS, e.g., difficulty initiating sleep, sleep maintenance or early awakenings) (objective 3). This method is suitable for identifying variables that are associated with variation in a binary outcome over time (here: the presence or absence of a particular insomnia symptom). Similar to the LMM procedure, an autoregressive (heterogeneous) covariance structure type was used. Scores on different items of each annual SCOPA-SLEEP-NS assessment were dichotomized, and patients were classified as impaired if they scored ≥1 on a specific item. Baseline variables that are significant from the unadjusted model were entered in the multivariate analysis. All analyses were performed with the Statistical Package for the Social Sciences (SPSS) version 21.0.

RESULTS

Of the 412 patients of whom a baseline SCOPA-SLEEP-NS score was available, 110 (27%) were classified as having insomnia at baseline (Figure 5.1). Of the remaining 302 patients who did not have insomnia at baseline, 99 (37%) developed this symptom in one or more of the subsequent assessments. Overall, 51% of the patients had insomnia at some point during follow-up, either at baseline or during follow-up. Insomnia was not a persistent symptom (Figure 5.1), although persistency increased with longer follow-up (33-46%). There was no trend towards an increase in insomnia over time at a group level (Supplement 5.1 Figure S5.1a). We also found that in comparison with patients without insomnia at baseline, patients with insomnia at baseline consistently had higher scores during the follow-up period, although a clear tendency towards lower scores can be observed over the course of follow-up, probably due to regression to the mean (Supplement 5.1 Figure S5.1b). Higher insomnia scores during follow-up were also found for patients with depression (BDI≥15) at baseline and patients classified as PIGD phenotype at baseline (Supplement 5.1 Figure S5.1c and S5.1d).

Variables associated with insomnia at baseline (cross-sectional analysis)

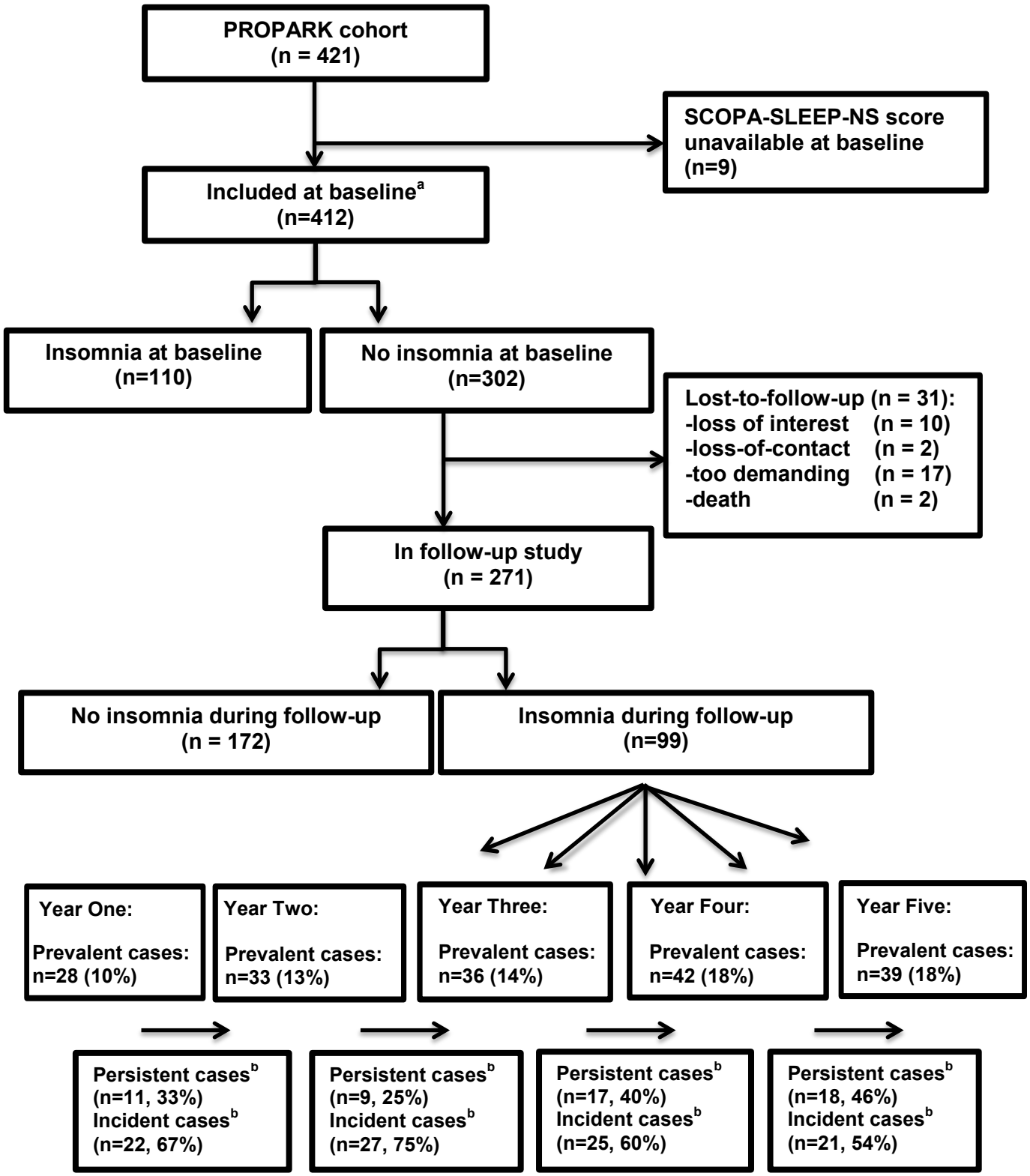
A larger proportion of patients with insomnia at baseline were female. In addition, patients with insomnia at baseline had a longer disease duration, higher H&Y stage, and higher levels of disability and autonomic dysfunction (Table 5.1). Patients with insomnia also had more severe motor complications (dyskinesias and motor fluctuations), depressive symptoms and EDS. They suffered more often from hallucinations and presented more often

with a PIGD phenotype. Regarding the use of medication, insomnia patients used more sleep medication and higher doses of antiparkinsonian medication.

Variables associated with longitudinal changes in SCOPA-SLEEP-NS score (LMM analysis)
The final model of the LMM analysis showed that higher BDI scores and more severe motor fluctuations at baseline were associated with higher SCOPA-SLEEP-NS scores over time (Table 5.2). Regarding medication, higher dopamine agonist doses and sleep medication use were also significantly related to higher SCOPA-SLEEP-NS scores.

Variables associated with specific characteristics of insomnia (GEE analysis)
The final model of the GEE analysis showed that depressive symptoms and motor fluctuations were associated with all items of insomnia (items 1-5, Table 5.3). Urinary tract symptoms only affected items 2, 3 and 5 (frequent awakenings, lying awake too long and subjective lack of sleep), cardiovascular symptoms affected items 1 and 3 (sleep initiation and lying awake too long), while female gender and EDS both only contributed to item 4 (early awakenings) and item 5 (subjective lack of sleep quality), respectively.
Regarding medication, items 2, 4 and 5 (frequent and early awakenings, subjective lack of sleep) were all associated with higher dopamine agonists doses, while items 1, 2 and 4 (sleep initiation, frequent and early awakenings) were associated with sleep medication use.
To verify the robustness of our findings, we repeated the analysis at a cut-off level of ≥2 (Supplement 5.1 Table 5.1). Again we found no specific set of variables that was uniquely associated with a particular aspect of insomnia. The BDI score was still associated with all aspects of insomnia, while at this cut-off the severity of motor fluctuations was associated with 3 aspects (instead of 5 at the lower cut-off), and use of sleep medication with 4 aspects (instead of 3 at the lower cut-off). Some disagreement was to be expected due to potential misclassification of certain patients.

Figure 5.1: Flow Chart of follow-up for insomnia



[a] Data of these patients were used in the cross sectional analysis (objective 1), the Linear Mixed Models (LMM) analysis (objective 2) and the Generalized Estimating Equations (GEE) analysis (objective 3), n=412.

[b] Percentages of persistent insomnia for a particular year were calculated by dividing the number of patients with insomnia who also had insomnia in the previous year by the total number of patients with insomnia in that particular year. For example in year 2, a total number of 33 patents were classified as having insomnia, of which 11 also had been classified as having insomnia in year 1, resulting in a percentage of 33 (i.e. 11/33). So in other words, if a patient had insomnia in year one and year two, the patient counts as a case of persistent insomnia in year two. If a patient did not have insomnia in year one, but had insomnia in year two and three, he or she counted as a case of persistent insomnia in year three.

Table 5.1: Baseline data of patients with and without insomnia

	Total	With insomnia	Without insomnia	p-values
N	412	110	302	
Age, yr	61.1 (11.4)	61.0 (11.1)	61.2 (11.6)	.88
Sex, % female	35.8	44.7	31.2	.007[a,†]
Time of follow-up, yr	4.56 (1.13)	4.82 (0.81)	4.47 (1.22)	
Sleep medication, %	16.8	35.5	10.0	<0.001[a,f]
Education, yr	12.0 (4.1)	12.1 (4.2)	11.9 (4.1)	.54
Disease duration, yr	10.6 (6.5)	12.0 (6.3)	9.9 (6.6)	.002[f]
Age at onset, yr	50.5 (11.9)	49.1 (11.4)	51.3 (12.1)	.08
Hoehn & Yahr, stage	2 (2,3)	3 (2,4)	2 (2,3)	.02[b,†]
SPES/SCOPA Motor Impairments	13.3 (4.9)	13.8 (4.7)	13.1 (5.0)	.23
SPES/SCOPA Dyskinesias	0.9 (1.6)	1.4 (1.9)	0.7 (1.4)	.006[b,†]
SPES/SCOPA Motor Fluctuations	0.8 (1.3)	1.4 (1.5)	0.6 (1.1)	<.001[b,f]
SPES/SCOPA ADL	8.9 (3.6)	9.7 (3.5)	8.6 (3.5)	.006[f]
Motor phenotype, PIGD dominant, %	45.2	53.8	42.1	.04[a,f]
Beck Depression Inventory	10.2 (6.6)	13.7 (7.3)	8.4 (5.3)	<.001[†]
SCOPA-COG[c]	25.3 (6.7)	25.2 (6.7)	25.3 (6.7)	.79
SCOPA-SLEEP, NS[d]	4.5 (3.8)	9.7 (2.1)	2.6 (2.1)	<.001[†]
SCOPA-SLEEP, EDS[d]	4.9 (3.7)	5.6 (4.2)	4.5 (3.4)	.005[f]
SCOPA-AUT, GI score[e]	2.7 (2.2)	3.3 (2.3)	2.4 (2.1)	<.001[f]
SCOPA-AUT, UR score[e]	6.7 (4.0)	7.8 (3.9)	6.2 (4.0)	<.001[f]
SCOPA-AUT, CV score[e]	1.2 (1.2)	1.6 (1.4)	1.0 (1.0)	<.001[†]
Hallucinations, % with	16.9	23.1	13.8	.02[a,f]
Total LDE, mg/day	608 (463)	735 (449)	545 (458)	<.001[†]
LDE-Dopa, mg/day	379 (375)	471 (377)	334 (366)	<.001[f]
LDE-DA dose, mg/day	231 (226)	263 (227)	214 (224)	.04[f]

Variables are expressed as means (standard deviations), except for gender (percentages), motor subtype (percentages), Hoehn and Yahr stage (median ((interquartile range)). All differences are calculated with the independent-samples t-tests, except for
[a] Chi-square test and [b] Mann-Whitney U test.
[c] SCOPA-COG: cognitive function, higher scores reflect better functioning.
[d] SCOPA-SLEEP, NS score: nighttime sleep, insomnia DS score: daytime sleepiness
[e] SCOPA-AUT: sumscore autonomic functioning including items from the sections on gastrointestinal (GI), cardiovascular (CV) and urinary tract (UR).
[f] Significant variables

Abbreviations: ADL, activities of daily living; PIGD, postural instability gait difficulty; LDE, Levodopa dosage equivalent; DA, dopamine agonists.

Table 5.2: Factors associated with higher SCOPA-SLEEP NS scores over time

	Unadjusted Model[a]		Adjusted Model[b]		Final Model[c]	
Variable	**B (95%CI)**	**P**	**B (95%CI)**	**P**	**B (95%CI)**	**P**
Age	0.01 (-0.04-0.01)	.40				
Female gender	0.45 (-1.04-0.14)	.13				
Disease duration, yr	0.06 (0.01-0.10)	.009[g]	-0.03 (-0.08-0.02)	.26		
SPES/SCOPA – Motor Impairment	0.01 (-0.05-0.07)	.78				
SPES/SCOPA – ADL	0.13 (0.05-0.21)	.002[g]	-0.09 (-0.19-0.02)	.10		
SPES/SCOPA – Dyskinesia	0.12 (-0.05-0.30)	.17				
SPES/SCOPA – Motor Fluctuations	0.65 (0.43-0.88)	<.001[g]	0.45 (0.19-0.70)	.001[g]	0.41 (0.19-0.63)	<.001[g]
PIGD dominant phenotype	0.72 (0.12-1.32)	.002[g]	-0.25 (-0.86-0.37)	.44		
SCOPA-COG score[d]	0.01 (-0.05-0.04)	.80				
Presence of hallucinations	0.73 (-0.04-1.50)	.06				
SCOPA-SLEEP-DS score[e]	0.15 (0.07-0.22)	<.001[g]	0.09 (0.01-0.17)	.04[g]	0.07 (-0.01-0.14)	.07
BDI score	0.20 (0.16-0.24)	<.001[g]	0.16 (0.11-0.21)	<.001[g]	0.16 (0.11-0.20)	<.001[g]
SCOPA-AUT[f] GI score	0.16 (0.03-0.29)	.02[g]	-0.10 (-0.24-0.05)	.18		
SCOPA-AUT[f] CV score	0.47 (0.23-0.71)	<.001[g]	0.19 (-0.06-0.45)	.14		
SCOPA-AUT[f] UR score	0.16 (0.09-0.23)	<.001[g]	0.07 (-0.01-0.15)	.07		
Daily levodopa dose, p/100mg	0.11 (0.03-0.18)	.007[g]	0.03 (-0.06-0.12)	.49		
Daily DA dose, p/100 mg	0.22 (0.10-0.35)	<.001[g]	0.17 (0.04-0.30)	.01[g]	0.13 (0.01-0.25)	.03[g]
Use of sleep medication	2.33 (1.60-3.05)	<.001[g]	1.63 (0.87-2.39)	<.001[g]	1.59 (0.89-2.30)	<.001[g]

Estimates are presented as B with 95% confidence intervals (CI), where a positive value is associated with a positive relationship between the baseline variable and SCOPA-SLEEP NS scores.
Abbreviations: ADL, activities of daily living; PIGD, postural instability gait difficulty; BDI, Beck depression inventory; DA, dopamine agonists.
[a] *The unadjusted model between NSP scores and the baseline variables were analyzed including one covariate at a time.*
[b] *The adjusted model includes only the significant variables (p<.05) from the unadjusted model.*
[c] *The final model includes only the significant variables (p<.05) from the adjusted model.*
[d] *SCOPA-COG: cognitive function, higher scores reflect better functioning.*
[e] *SCOPA-SLEEP, DS: daytime sleepiness.*
[f] *SCOPA-AUT: sumscore autonomic functioning including items from the sections on gastrointestinal (GI), cardiovascular (CV) and urinary tract (UR).*
[g] *significant values*

Table 5.3: Variables associated with specific aspects of insomnia (GEE analysis)

Domain/Factor	OR	95% CI	P
1.Difficulty falling asleep			
SPES/SCOPA – Motor Fluctuations	1.15	1.00-1.32	.05
BDI score	1.03	1.00-1.06	.03
Use of sleep medication	1.97	1.21-3.20	.006
SCOPA-AUT – Cardiovascular	1.23	1.04-1.45	.01
2.Been awake too often			
SPES/SCOPA – Motor Fluctuations	1.36	1.11-1.67	.004
BDI score	1.07	1.03-1.11	.001
Use of sleep medication	1.88	1.08-3.29	.03
Daily DA dose, p/100 mg	1.14	1.04-1.25	.004
SCOPA-AUT – Urinary Tract	1.09	1.04-1.10	.001
3. Lying awake too long			
SPES/SCOPA – Motor Fluctuations	1.31	1.10-1.57	.003
BDI score	1.07	1.03-1.11	<.001
SCOPA-AUT – Urinary Tract	1.07	1.02-1.12	.008
SCOPA-AUT – Cardiovascular	1.23	1.04-1.46	.02
4. Waking too early			
SPES/SCOPA – Motor Fluctuations	1.20	1.03-1.40	.02
BDI score	1.05	1.01-1.09	.007
Use of sleep medication	1.76	1.06-2.93	.03
Daily DA dose, p/100 mg	1.13	1.05-1.23	.002
Female Gender	1.55	1.09-2.22	.03
5. Had too little sleep			
SPES/SCOPA – Motor Fluctuations	1.20	1.02-1.21	.03
BDI score	1.07	1.03-1.12	<.001
SCOPA-SLEEP-DS score[a]	1.08	1.03-1.14	.003
Daily DA dose, p/100 mg	1.12	1.03-1.23	.009
SCOPA-AUT – Urinary Tract	1.08	1.02-1.13	.007

For every aspect of insomnia (i.e., items in the SCOPA-SLEEP-NS) only variables are reported that were independently and significantly associated with changes in that aspect over time. All variables are expressed as odds ratio (OR) with 95% confidence interval (CI) , where a value >1 indicates that a higher score of that variable is associated with a higher risk to develop that specific aspect of insomnia.

Abbreviations: BDI, Beck depression inventory; DA, dopamine agonists.
[a] *SCOPA-SLEEP, DS: daytime sleepiness.*

DISCUSSION

In this study we examined cross-sectional and longitudinal associations of insomnia in a hospital-based cohort of 421 PD patients who have been followed over a mean follow-up time of 4.56 years. Our study is the largest longitudinal study on this subject so far. Of the patients enrolled in the study, 51% had insomnia at some point, and 37% of those who did not have insomnia at baseline developed this symptom during follow-up. These rates are comparatively lower than those of an earlier population-based longitudinal study,[1] which may be due to differences in study settings (population-based versus hospital-based) and population characteristics (more female patients in the Norwegian study [50.1 versus 35.8%]). In addition, this study used a different questionnaire with different response options, and although similar aspects of insomnia were evaluated, broader criteria for insomnia were applied: i.e., patients were classified as having insomnia if they reported sleeping problems during the night or used sleeping pills due to sleeping problems and had experienced these symptoms for at least 1 month, while our patients were only classified as having insomnia if the applied cut-off score was attained.

With longer follow-up, the proportion of patients with insomnia increased slightly and insomnia became more persistent, indicating the importance of monitoring this symptom, particularly in patients who are at risk.

Among patients with PD, insomnia is a frequent symptom and past studies reported a significant reduction of total sleep time even in untreated PD patients with mild disease, as compared to healthy age-matched controls.[26] The causes of insomnia in PD are multifactorial, including the underlying degeneration of sleep regulatory centers, comorbidity, or the sleep-altering effect of antiparkinsonian drugs.[1,3,4] In addition, neuropsychiatric symptoms, nocturia, dyskinesias, pain or dystonia[27] as well as intrinsic circadian rhythm dysregulation[28] could significantly contribute to sleep disruption in PD patients.

Our cross-sectional analysis showed that, similar to the findings of another longitudinal study,[1] insomnia was associated with longer disease duration and occurred more often in females.

The analysis of changes in overall insomnia severity over time (i.e. with the SCOPA-SLEEP-NS score as dependent variable) confirmed that depressive symptoms and the dosage of dopamine agonists - variables that had previously been identified only in cross-sectional studies[4,5] - were associated with higher scores over time. Previous studies in PD showed that insomnia and depression frequently co-exist.[1,3,5,7] It is important to realize that insomnia is a characteristic of depression, and that therefore the two features are inherently related.[29] In one study in PD, insomnia remained related to depressive symptoms, even when subjects who qualified for the criteria of depression were excluded.[3] Hitherto, the direction of the relation between insomnia and depression has remained a chicken and egg dilemma

because of the cross-sectional design of most previous studies.[3,5,7] Our results suggest that depressive symptoms precede insomnia in PD, and consistently more severe insomnia was reported during follow-up by patients with more depressive symptoms at baseline. This indicates that adequate management of depression may not only improve the patient's mood, but the possibility exists that this also has an ameliorating effect on insomnia. However, it must be noted that the reverse relationship is also found in PD, as we observed in an earlier study.[30] We can therefore safely conclude that there is a bi-directional longitudinal relationship between the two symptoms, i.e. depressive symptoms may precede insomnia, whereas insomnia symptoms may in turn contribute to the development of depression in PD.

The finding that higher dopamine agonist doses are associated with insomnia in PD is in line with an earlier study.[4] However, this issue is controversial and it must be noted that while certain dopamine agonists may worsen insomnia, others have shown to improve sleep quality in PD.[31] In addition, timing of dopamine agonists is also an important aspect in treating insomnia.[4] Dopamine agonists could have an impact on sleep in PD in different ways. Firstly, treatment with dopaminergic therapy increases the patients risk to develop hallucinations, which in turn could cause nocturnal sleep disturbances.[7] This is supported by the finding that patients with insomnia and hallucinations at baseline also had higher dopamine agonist doses than those with insomnia, but without hallucinations (mean (SD) dopamine agonists dosage (p/100mg) of 3.88 (2.45) vs 2.36 (1.97), p=0.001). Secondly, dopamine plays an important role in sleep-wake regulation.[4] Further, dopamine agonists have biphasic effects on sleep-wakefulness and this effect has been attributed to D2 receptor stimulation; at low doses they reduce wakefulness and enhance sleep, whereas high doses induce opposite effects.[31]

We found that a higher levodopa dose was associated with more insomnia in the unadjusted – but not the adjusted - LMM analysis (Table 5.2). This indicates that the presence of other variables may confound this association and may in part explain the contradictory results observed in some previous studies, with some reporting a positive[32,33] and others reporting a negative[34] association. Lastly, motor fluctuations were found associated with more severe insomnia symptoms over time and this complication of levodopa treatment usually increases in prevalence and severity as PD progresses. Several effective strategies to target motor fluctuations are now available[35] and these approaches may potentially have a beneficial influence on insomnia in PD.

Because the various aspects of insomnia may be differentially affected by PD – for example, sleep initiation is usually preserved whereas sleep maintenance is typically affected -, we evaluated if different sets of variables were associated with the separate insomnia items. These analyses revealed that, in line with our results from the LMM, more severe depressive

symptoms and motor fluctuations were longitudinally associated with all aspects of insomnia; although the odds ratios for motor fluctuations are higher, one should bear in mind that the metrics of the two scales are different: the SPES/SCOPA – Motor Fluctuations subscale has a range from 0-6, where the BDI has a range from 0-63. A higher dose of dopamine agonists was found to be associated with early and frequent awakenings and subjective lack of sleep, but not with sleep initiation or lying awake too long. This implies that dopamine agonists selectively affect sleep maintenance and not sleep initiation. Interestingly, urinary tract symptoms were associated with three out of five items (frequent awakenings, lying awake too long and subjective lack of sleep) and cardiovascular symptoms with two (sleep initiation and lying awake too long), even though both symptoms did not emerge as significant findings in our overall LMM analysis. In addition, our cross-sectional analysis also showed that patients with insomnia reported more urinary tract symptoms at baseline. Therefore, these patients could, for instance, benefit from desmopressin acetate, which may reduce the number of voidings at night and consequently disrupt nocturnal sleep less frequently.[36] Various (pharmacological and non-pharmacological) strategies to manage nocturia exist. [36] For more resistant forms of nocturia, a referral to an urologist for additional evaluation might be necessary.[37] The relation between cardiovascular symptoms and insomnia is less straightforward; however, there are indications that involvement of the vagal system -, which is an essential part of the cardiac autonomic network - and the locus coeruleus are affected in the course of the disease.[38] Interestingly, the locus coeruleus also plays a role in sleep/wake regulation, and damage to this structure could therefore contribute to sleep disruption in PD patients.[39] Findings of one earlier study suggested that sleep disturbances and cardiac autonomic dysfunction might together be a marker for disease severity in PD.[40] Collectively, the findings suggest that involvement of both anatomical structures may play a role in the development of sleep disturbances in PD. EDS only contributed to the item subjective lack of sleep, which is to be expected since frequent falling asleep during the day could contribute to less sleep at night and therefore a subjective lack of sleep.

Collectively our GEE analysis does not provide clues for an unique set of determinants for specific aspects of insomnia, but does give more insight that certain variables may play a pertinent role in particular aspects of insomnia.

At baseline, 69 patients used sleep medication, of whom 56 (81%) were on benzodiazepines. Since we had no information on the efficacy of drugs used to treat insomnia (e.g. benzodiazepines), we evaluated if the use of these drugs confounded the presence of insomnia. This seemed not to be the case since patients on medication for sleep disorders had significantly higher SCOPA-SLEEP-NS scores than patients without sleep medication (mean (SD) score: 7.25 (4.13) vs 3.96 (3.45), $p<0.001$) and sleep medication demonstrated a positive relationship in the LMM and the GEE. These results may suggest

that the potential effect of sleeping drugs on insomnia is limited, rendering a confounding influence on the results unlikely (i.e. under- rather than overestimation).

The strengths of this study are the prospective design, the broad clinical characterization, the limited loss to follow-up and the size of the cohort. Limitations involve the fact that certain patient-specific baseline variables, such as fatigue, sleep-disordered breathing and symptoms of impulse-control disorder, which have been reported as risk factors,[8,9] were not included. Another point worth considering is that our cohort is hospital-based and this may have resulted in some over- or underestimation of certain associations, but it seems unlikely that this has resulted in significant distortions of our conclusions. Finally, assessments were performed on an annual basis, while the time frame of the SCOPA-SLEEP-NS concerns the past month, which may not be fully representative of the entire past year.

In conclusion, insomnia is an important problem in PD, occurring in more than half of patients with this disorder. The presence of depressive symptoms, motor fluctuations and the use of higher doses of dopamine agonists are associated with more severe insomnia. Attention to these aspects could potentially contribute to a better management of insomnia symptoms in PD.

SUPPLEMENT 5.1

Figure S5.1: Course of mean SCOPA-SLEEP-NS scores for patients included at baseline (N=412)

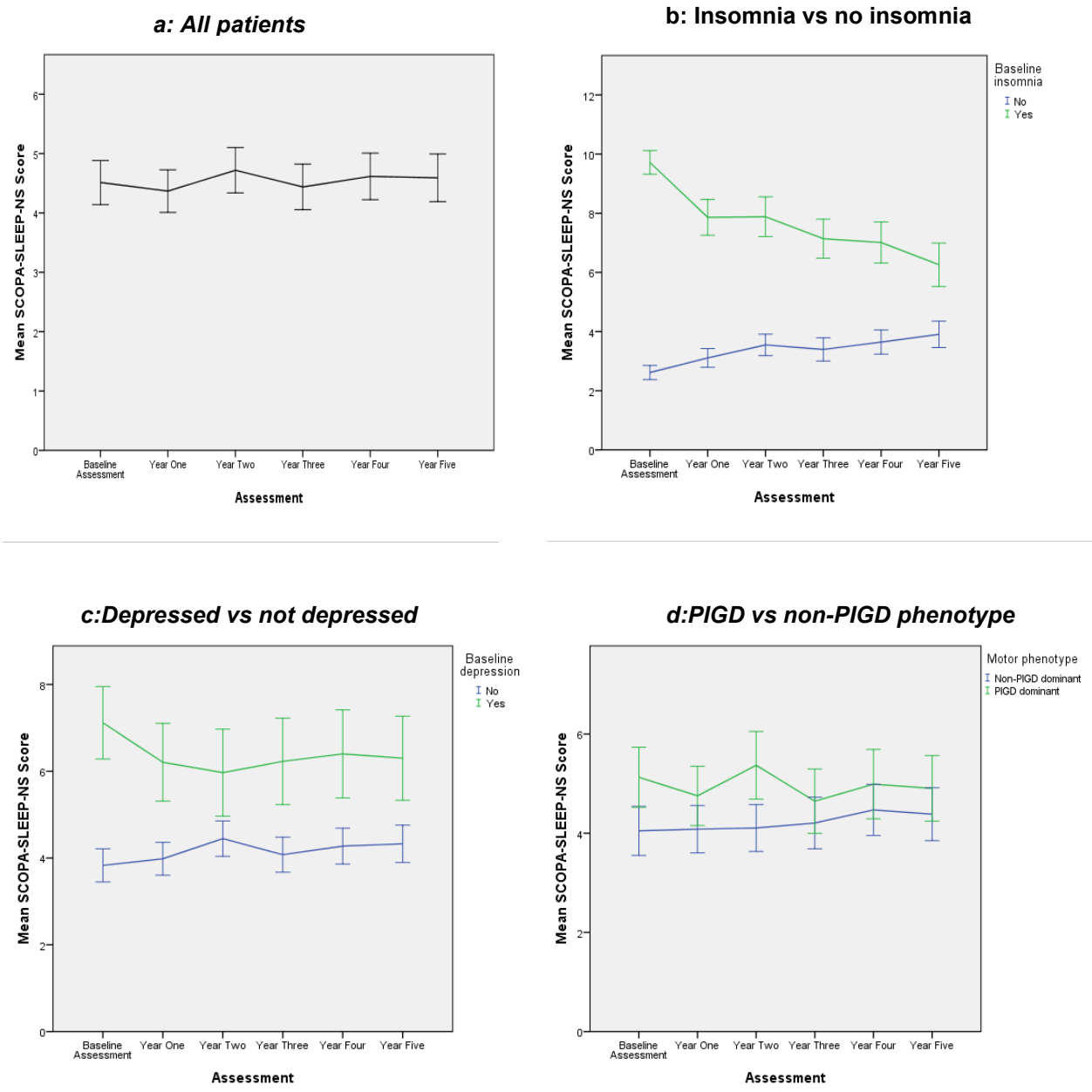


Figure 1a: *Mean SCOPA-SLEEP-NS score over time for all patients included at baseline.*
Figure 1b: *Mean SCOPA-SLEEP-NS scores over time for patients with insomnia (SCOPA-SLEEP-NS≥7)vs no insomnia at baseline.*
Figure 1c: *Mean SCOPA-SLEEP-NS scores over time for depressed (BDI≥15) vs non- depressed patients at baseline*
Figure 1d: *Mean SCOPA-SLEEP-NS scores over time for patients with PIGD-dominant vs non-PIGD-dominant motor phenotype*

Error bars are displayed as +/- 2SE (95%CI)
Abbreviations: PIGD: postural-instability-and-gait difficulty

Table S5.1: Variables associated with specific aspects of insomnia (GEE analysis; cutoff ≥2)

Domain/Factor	OR	95% CI	P
1.Difficulty falling asleep			
BDI score	1.06	1.02-1.09	<.001
Use of sleep medication	3.33	1.97-5.63	<.001
SPES/SCOPA – Motor Fluctuations	1.02	0.76-1.37	.91
2.Been awake too often			
SPES/SCOPA – Motor Fluctuations	1.22	1.05-1.42	.009
BDI score	1.07	1.04-1.10	<.001
Use of sleep medication	1.78	1.12-2.83	.02
Daily DA dose, p/100 mg	1.13	1.04-1.21	.002
SCOPA-AUT – Urinary Tract	1.05	1.00-1.10	.04
SCOPA-SLEEP-DS score[a]	1.06	1.01-1.11	.02
3. Lying awake too long			
SPES/SCOPA – Motor Fluctuations	1.17	1.00-1.36	.05
BDI score	1.06	1.03-1.09	<.001
Use of sleep medication	2.06	1.28-3.31	.003
SCOPA-SLEEP-DS score[a]	1.05	1.00-1.11	.05
4. Waking too early			
SPES/SCOPA – Motor Fluctuations	1.18	1.00-1.38	.05
BDI score	1.11	1.07-1.15	<.001
Use of sleep medication	1.69	1.09-2.62	.02
Daily DA dose, p/100 mg	1.11	1.02-1.20	.01
5. Had too little sleep			
SPES/SCOPA – Motor Fluctuations	1.10	0.95-1.27	.23
BDI score	1.09	1.06-1.13	<.001
Daily DA dose, p/100 mg	1.09	1.00-1.18	.05
SCOPA-SLEEP-DS score[a]	1.06	1.00-1.12	.05

For every aspect of insomnia (i.e., items in the SCOPA-SLEEP-NS) only variables are reported that were independently and significantly associated with changes in that aspect over time.
A patient is classified as impaired on a certain aspect, if a score of ≥2 is obtained.
All variables are expressed as odds ratio (OR) with 95% confidence interval (CI) , where a value >1 indicates that a higher score of that variable is associated with a higher risk to develop that specific aspect of insomnia.
Abbreviations: BDI, Beck depression inventory; DA, dopamine agonists.
[a] *SCOPA-SLEEP, DS: daytime sleepiness.*

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