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PARKINSON'S DISEASE

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ABSTRACT

Sleep disturbances may signal presence of prodromal parkinsonism, including Parkinson's disease. Whether general sleep quality or duration in otherwise healthy individuals is related to the risk of parkinsonism remains unclear. We hypothesized that both worse self-reported sleep quality and duration, as well as a longitudinal deterioration in these measures, are associated with the risk of parkinsonism, including Parkinson's disease.

In the prospective population-based Rotterdam Study, we assessed sleep quality and duration with the Pittsburgh Sleep Quality Index in 7,726 persons (mean age 65 years, 57% women) between 2002-2008, and again in 5,450 persons between 2009-2014. Participants were followed until 2015 for a diagnosis of parkinsonism and Parkinson's disease. Outcomes were assessed using multiple modalities: interviews, physical examination, and continuous monitoring of pharmacy records and medical records of general practitioners. We used Cox regression to associate sleep, and changes in sleep over time, with incident parkinsonism and Parkinson's disease, adjusting for age, sex, education and smoking status.

Over 64,855 person-years in 13 years of follow-up (mean: 8.4 years), 75 participants developed parkinsonism, of whom 47 developed Parkinson's disease. We showed that within the first 2 years of follow-up, worse sleep quality (hazard ratio 2.38 per standard deviation increase (95% confidence interval 0.91-6.23)) and shorter sleep duration (hazard ratio 0.61 per standard deviation increase (0.31-1.21)) related to a higher risk of parkinsonism. Associations of worse sleep quality (hazard ratio 3.86 (1.19-12.47)) and shorter sleep duration (hazard ratio 0.48 (0.23-0.99)) with Parkinson's disease were more pronounced, and statistically significant, compared to parkinsonism. This increased risk disappeared with longer follow-up duration. Worsening of sleep quality (hazard ratio 1.76 per standard deviation increase (95% confidence interval 1.12-2.78)), as well as shortening of sleep duration (hazard ratio 1.72 per standard deviation decrease (1.08-2.72)), were related to Parkinson's disease risk in the subsequent 6 years. Therefore we argue that, in the general population, deterioration of sleep quality and duration are markers of the prodromal phase of parkinsonism, including Parkinson's disease.

INTRODUCTION

Parkinson's disease is primarily characterized by motor disturbances,[1] but also includes non-motor features. Sleep-wake disturbances are a common non-motor feature of Parkinson's disease[2-8] and related synucleinopathies.[9-11] Sleep-wake disturbances are also reported to precede a diagnosis of parkinsonism in prodromal Parkinson's disease.[12] Objectively measured increases in sleep fragmentation have also been related to increased Parkinson's disease pathology at brain autopsy in old individuals without Parkinson's disease.[13] Sleep-wake disturbances may be a risk factor for Parkinson's disease, or indicate presence of disease in a prodromal phase. [14,15]

Several sleep disorders have been reported to precede Parkinson's disease or related synucleinopathies,[12] including rapid eye movement (REM) sleep behavior disorder[1,16,17] and obstructive sleep apnea.[18-21] These seem to represent, however, only the 'tip of the iceberg' of various sleep-wake disturbances in prodromal Parkinson's disease.[22-27] Subclinical impairments in sleep, such as poor sleep quality and short sleep duration, are more common in the general population and may well capture aforementioned sleep-wake disturbances. These impairments are particularly important as they are often investigated and easily determinable aspects of sleep in any healthcare setting. To date, however, only few studies investigated if sleep duration reflects prodromal Parkinson's disease,[27,28] and none studied sleep quality. Furthermore, it is unknown if long-term changes in sleep duration and quality relate to subsequent risk of parkinsonism, including Parkinson's disease.

We studied the association of subjectively assessed sleep quality and duration with parkinsonism, including Parkinson's disease. We hypothesized that i) worse sleep quality, and shorter sleep duration, are associated with the risk of parkinsonism, including Parkinson's disease; and ii) deterioration in sleep quality and duration over time is associated with the subsequent risk of parkinsonism. We tested these hypotheses in a prospective, population-based study, using the Pittsburgh Sleep Quality Index to (repeatedly) measure sleep quality and duration, with up to 13 years of follow-up for incident parkinsonism.

METHODS

The study was embedded in the Rotterdam Study, a large, prospective, population-based study in a suburban district in the city of Rotterdam, the Netherlands, details of which are described elsewhere.[29] The study was set up to investigate the frequency, risk factors and natural history of common chronic diseases in the elderly, including neurodegenerative diseases such as Parkinson's disease. The first cohort was initiated in

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1990 and included 7,983 persons aged ≥55 years, and was expanded with 3,011 persons aged ≥55 years in 2000, and 3,932 persons aged ≥45 years in 2006. Examination rounds consisted of a home interview and visits to our dedicated research center, including a wide range of questionnaires and physical measurements. Visits are repeated every 4-5 years. Measurements are kept similar across inclusion rounds and time. In between examination rounds, incident disease is assessed with continuous linkage of the study database and medical records of general practitioners, which also holds summaries from all specialist and inpatient care.

The Rotterdam Study has been approved by the Medical Ethics Committee of the Erasmus MC (registration number MEC 02.1015) and by the Dutch Ministry of Health, Welfare and Sport (Population Screening Act WBO, license number 1071272-159521-PG). The Rotterdam Study Personal Registration Data collection is filed with the Erasmus MC Data Protection Officer under registration number EMC1712001. This study is registered with the Netherlands National Trial Register and WHO International Clinical Trials Registry Platform under the shared catalogue number NTR6831. All participants provided written informed consent to participate in the study and to have their information obtained from treating physicians.

Study population

We included participants from all three inclusion rounds when a sleep questionnaire, the Pittsburgh Sleep Quality Index (PSQI), was first introduced. At this baseline visit (between 2002-2008), we included 7,726 individuals who had valid data on sleep quality or sleep duration, did not have prevalent parkinsonism or Parkinson's disease,[30] and were not cognitively impaired based on a Mini-mental state examination (MMSE) score > 25. We followed the remaining participants until the first of: onset of parkinsonism or Parkinson's disease, 1 January 2015, or death. Study follow-up for incident parkinsonism was nearly complete (64,855 person-years [98.1%]).[31]

For analyses of changes in sleep over time, we similarly included 5,450 individuals at the follow-up visit (between 2009-2014) and started follow-up time for parkinsonism and Parkinson's disease after this visit. See Supplementary Fig. 1 for a detailed flowchart of included participants for analyses at baseline and the follow-up visit.

Assessment of sleep

Subjective aspects of sleep were measured with a Dutch version of the PSQI, which assesses past month's average sleep quality. The PSQI[32] has a good test-retest reliability and validity in a non-clinical sample of older adults.[33] Answers can be categorized, scored and combined into seven component scores ranging from 0 (not problematic) to 3 (very problematic), labeled 'quality', 'latency', 'duration', 'efficiency', 'disturbances', 'sleep medication', and 'daytime dysfunction'. These scores are summed to provide the global

PSQI score (range: 0 – 21) of subjectively assessed sleep quality (hereafter: 'sleep quality'). Higher scores indicate poorer sleep, and scores > 5 indicate a 'poor' sleep quality.

For participants with more than one PSQI component missing, the global PSQI score was not calculated (n=156, 2%). To minimize loss of participants, we calculated weighted component scores for participants who missed one component score (n=1,099, 13%) by multiplying the six-component sum scores by 7/6. Most of these participants missed information on sleep disturbances (n=847) due to introducing a skip rule in PSQI items on disturbances (5a-5j[32]) in a subset of participants, to limit participant burden. If answers to items 5a-5b were both negative ('not in the last month'), items 5c-5j were skipped. Weighting scores minimized any effect of the skip rule on global PSQI scores, as in persons who answered items 5a-5b negatively, weighted scores were not different between those who followed the skip rule versus those who did not (data not shown). Analogously, at follow-up we did not calculate the global PSQI score for 484 (8%) due to missing more than one PSQI component at the follow-up visit (and excluded participants who missed global PSQI score at the baseline visit so that changes could not be calculated [n=203]). We weighted scores for 252 participants (5%) who mostly missed data on efficiency (n=190; see flowchart in Supplementary Fig. 1).

Assessment of parkinsonism and Parkinson's disease

A detailed description of parkinsonism and Parkinson's disease assessment methods used in this study has previously been published.[34] In short, we used four overlapping modalities to collect information on parkinsonism and Parkinson's disease: in-person interviews, examinations, use of antiparkinsonian medication, and continuous monitoring of medical records. Examinations included standardized screening assessments of parkinsonian signs (i.e. tremors, hypo- and bradykinesia, cogwheel rigidity, and postural reflex) by a trained research nurse during center visits. If one or more signs were present, individuals were subsequently invited for a structured physical examination by a trained research physician.

Parkinsonism was defined by presence of hypo- or bradykinesia in combination with ≥1 cardinal sign (resting tremor, rigidity or postural imbalance) observed by any physician, or a clinical diagnosis of parkinsonism by a neurologist or geriatrician (if motor examination details were unavailable). Within those individuals, we diagnosed Parkinson's disease in presence of a clinical Parkinson's disease diagnosis by a neurologist or geriatrician, or a documented positive response to dopaminergic treatment in persons who did not have evidence for a secondary cause (e.g. preexistent dementia diagnosis, use of anti-dopaminergic drugs, cerebrovascular disease). We classified individuals with 'unspecified parkinsonism' if they had multiple possible causes or lacked a clear underlying cause of parkinsonism.

Potential confounders and effect-modifiers

Analyses were adjusted for potential confounders measured at baseline, selected based on relevant publications[1,22,35]: age, sex, education and smoking history. Educational attainment was assessed by interview and categorized as primary, secondary/lower vocational, intermediate vocational, and higher vocational or university. Smoking habits were assessed by interview and categorized as never, former or current smoking. We also examined potential effect-modification by depressive symptoms and anxiety disorders. Depressive symptoms were assessed with the validated Dutch version[36] of the Centre for Epidemiological Studies Depression Scale.[37] Presence of an anxiety disorder was assessed by an adapted version of the Munich Composite International Diagnostic Interview.[38]

Statistical analysis

A detailed explanation of our statistical methods is provided in the Supplementary Text. In short, we first used Cox proportional hazards regression models to associate both sleep quality and duration at baseline with both incident parkinsonism and Parkinson's disease. As we found that the Cox model assumption of proportionality was violated in some analyses, we also examined how aforementioned associations changed over follow-up time by performing analyses in incremental epochs of follow-up time from baseline (extending follow-up time e.g. baseline to 2 years, baseline to 4 years, etc.)[39], or using a stratified Cox model to obtain period-specific hazards (e.g. baseline to 2 years, 2 to 4 years, etc.). We furthermore looked at the effect of other PSQI components separately. As sensitivity analyses, we restricted analyses to persons without comorbid depression and anxiety. We also investigated potential effect-modification by age, sex, and presence versus absence of any of four parkinsonian signs. Second, we related changes in sleep quality and duration between the baseline and the follow-up visit with incident parkinsonism and Parkinson's disease after the follow-up visit.

Variables were standardized and, when right-skewed, log-transformed before standardization. Missing values on covariates were imputed using five multiple imputations.

RESULTS

Characteristics of the study sample at baseline are summarized in Table 1. Median global PSQI score was 3, and 2,115 participants (27%) scored over 5 indicating poor sleep quality. Global PSQI score and sleep duration were moderately correlated (Spearman's r = -0.69; P<0.01)). During 13.0 years of follow-up (mean 8.4 years), we observed 75 incident parkinsonism cases, of which 47 (63%) with Parkinson's disease (Supplementary Table 1).

Table 1. Characteristics of study population at baseline

Characteristic (unit)	Total sample	Incident PS	No incident PS
	N = 7,726	N = 75	N = 7,651
Age at baseline (years)	65.4 ± 10.3	71.6 ± 8.4	65.4 ± 10.3
Female	4,396 (57%)	33 (44%)	4,365 (57%)
Educational level			
Primary education	708 (9%)	8 (11%)	700 (9%)
Lower/intermediate or lower vocational	3,088 (40%)	29 (39%)	3,060 (40%)
Higher or intermediate vocational	2,371 (31%)	24 (32%)	2,347 (31%)
Higher vocational or university	1,559 (20%)	14 (19%)	1,545 (20%)
Smoking status			
Never	3,416 (44%)	34 (45%)	3,383 (44%)
Former	3,549 (46%)	33 (44%)	3,516 (46%)
Current	761 (10%)	8 (11%)	753 (10%)
Cognitive functioning (MMSE score)	28 (27-29)	28 (27-29)	28 (27-29)
Depressive symptoms (CES-D score)	3 (1-8)	4 (1-8)	3 (1-8)
Presence of any anxiety disorder	588 (8%)	8 (11%)	580 (8%)
Presence of any parkinsonian signs	807 (10%)	16 (21%)	792 (10%)
Sleep quality (global PSQI score)	3 (2-6)	3 (1-6)	3 (2-6)
Missing	46 (1%)	0 (0%)	46 (1%)
Sleep duration (hours)	6.8 ± 1.2	7.1 ± 1.3	6.8 ± 1.2

Characteristics of study population at baseline. Values are expressed as frequency (%) for categorical variables and mean ± standard deviation or median (interquartile range) for continuous variables, unless specified otherwise. Includes imputed values for covariates.

Abbreviations: CES-D=Center for Epidemiological Studies – Depression Scale; MMSE=Mini-mental state examination; N=sample size; PS=parkinsonism; PSQI=Pittsburgh Sleep Quality Index

Sleep quality was not associated with the risk of parkinsonism (hazard ratio [HR] per standard deviation [SD] increase in global PSQI score: 0.95 (95% confidence interval (CI) 0.76-1.20)) or Parkinson's disease (HR per SD increase 0.87 (95% CI 0.65-1.16)). We observed similar estimates when analyzing categorized poor (versus good) sleep quality: HR 0.97 (95% CI 0.57-1.66) for parkinsonism, and HR 0.79 (95% CI 0.39-1.59) for Parkinson's disease (Supplementary Table 2).

Longer sleep duration was not associated with the risk of parkinsonism (HR per SD increase 1.21, 95% CI 0.95-1.54) and PD (HR 1.24, 95% CI 0.92-1.69). After categorizing sleep duration, we did not observe a significant increase in risk with increasing categories of sleep duration (Supplementary Table 2).

In aforementioned analyses for Parkinson's disease risk, but not for parkinsonism, the proportionality assumption for both sleep quality and duration was significantly violated.

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We found that worse sleep quality related to an increased risk of parkinsonism (HR 2.38, 95% CI 0.91-6.23) in the first 2 years of follow-up, which disappeared when increasing follow-up time from baseline (Fig. 1A). In these 2 years, associations were more pronounced, and statistically significant, for Parkinson's disease (HR 3.86, 95% CI 1.19-12.47) compared to parkinsonism. Results for sleep duration were analogous (Fig. 1B): short sleep duration was associated with an increased risk of parkinsonism (HR 0.61, 95% CI 0.31-1.21) and Parkinson's disease (HR 0.48, 95% CI 0.23-0.99). Additionally, analysis of period-specific hazard ratios using a stratified Cox model suggested that associations of worse sleep quality, and shorter sleep duration, with an increased risk of parkinsonism and Parkinson's disease are confined to the first 2 years of follow-up (Supplementary Fig. 2).

Most PSQI components showed a similar pattern of associations with cumulative increasing follow-up duration, except for sleep medication (Fig. 2A-F). We observed noteworthy changes in effect sizes from short to long follow-up for sleep efficiency, and to a lesser extent for sleep quality, latency and daytime dysfunction (Fig. 2A-C; Fig. 2F; Supplementary Table 3). Also, for daytime dysfunction, the direction of hazard ratio estimates changed over increasing epochs of follow-up (Supplementary Table 3).

We further restricted the sample to persons without clinically relevant depressive symptoms and without any anxiety disorder, leaving 6,605 individuals of which 61 cases of parkinsonism, including 39 cases with Parkinson's disease. Associations over cumulatively increasing follow-up duration were similar to the total sample (Supplementary Fig. 3). For the association of sleep duration with Parkinson's disease, all hazard ratios shifted to higher values. As a result, longer sleep duration was now associated with increased Parkinson's disease risk in the overall follow-up (HR 1.47, 95% CI 1.02-2.11), for which proportionality was not violated.

Analyses stratified at median age did not reach statistical significance. We observed hazard ratio estimates suggesting associations of worse sleep quality with a lower risk of parkinsonism and Parkinson's disease in younger persons, while hazard ratios in older persons were close to the null. Similarly, estimates also suggested associations of longer sleep duration with a higher risk of both outcomes in younger persons. Case numbers in separate strata were small. Also, there were no significant interactions between age and sleep quality or duration on the risk of either outcome (Supplementary Table 4).

We observed a similar relation between sleep quality and duration and disease risk in persons without parkinsonian signs at baseline. Statistically testing these interactions on a multiplicative scale showed significant interactions of sleep quality with presence of parkinsonian signs on the risk of both parkinsonism and Parkinson's disease (Supplementary Table 4).

Characteristics of the study population at the follow-up visit are provided in Supplementary Table 5. Changes in sleep between the baseline and follow-up visit were
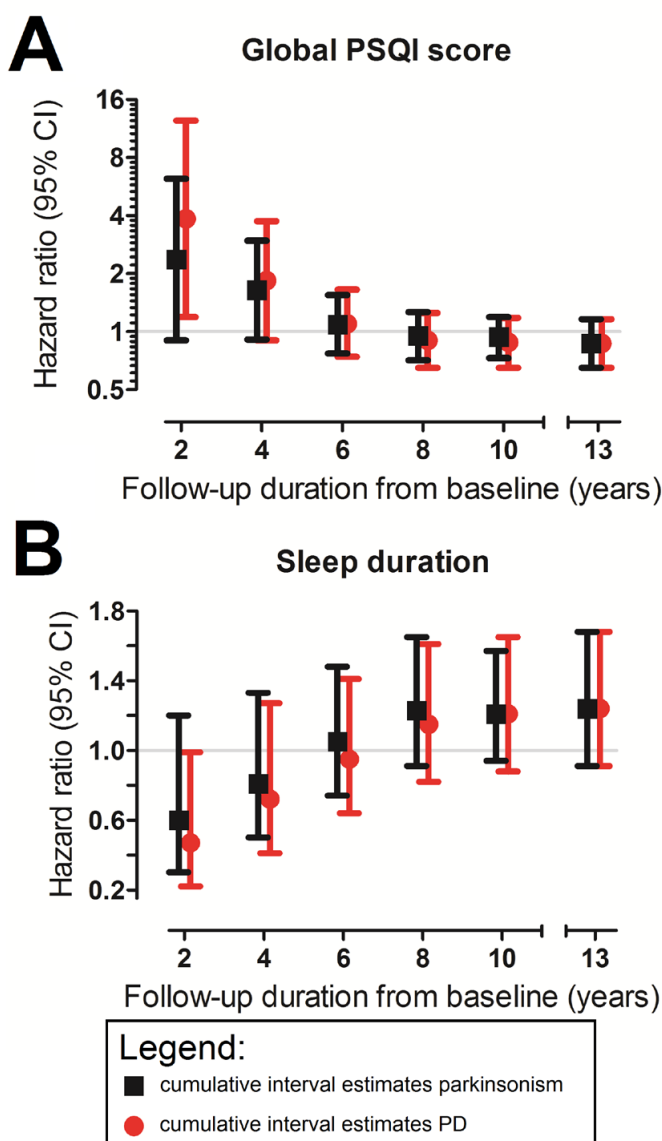
Figure 1. Associations of sleep quality and duration with risk of parkinsonism and Parkinson's disease, per cumulatively increasing duration of follow-up

The associations of (A) sleep quality and (B) sleep duration with incident parkinsonism and Parkinson's disease are shown for cumulatively increasing follow-up duration within the study timeframe. Hazard ratio estimates were obtained from multivariate Firth's penalized Cox regression models by censoring all participants still at risk at year 2, 4, 6, 8 and 10 after baseline, and after the total follow-up of 13 years. Hazard ratio estimates were adjusted for age at baseline, sex, educational level and smoking status, are expressed per standard deviation increase of (A) worse sleep quality, or (B) longer sleep duration, and are plotted at a (A) logarithmic (base 2) scale and (B) a linear scale. Abbreviations: CI=Confidence Interval; PD=Parkinson's disease; PSQI=Pittsburgh Sleep Quality Index

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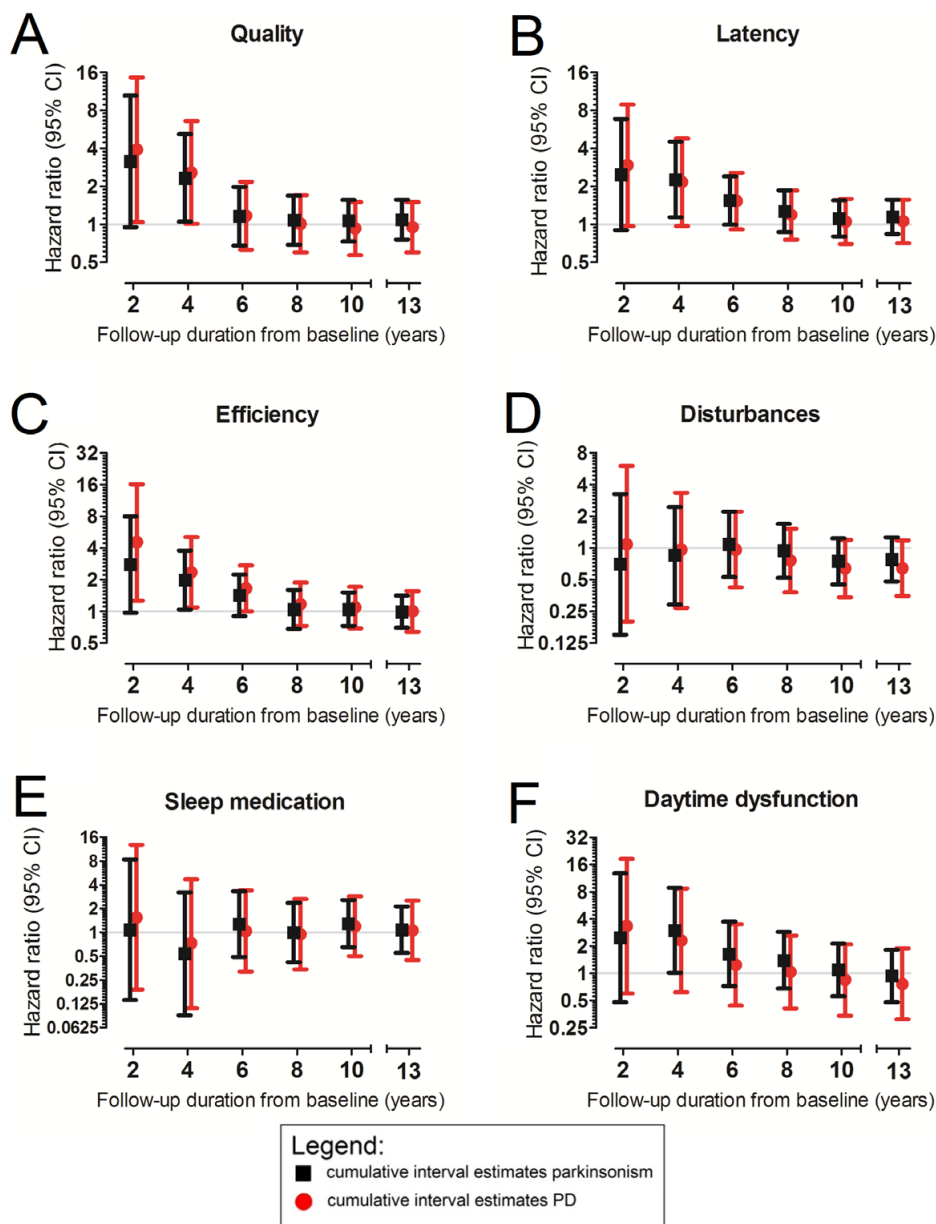
Figure 2. Associations of Pittsburgh Sleep Quality Index component scores with risk of parkinsonism and Parkinson's disease, per cumulatively increasing duration of follow-up

The associations of the PSQI components (A) quality, (B) latency, (C) efficiency, (D) disturbances, (E) sleep medication, and (F) daytime dysfunction with incident parkinsonism and Parkinson's disease are shown for cumulatively increasing follow-up duration within the study timeframe. Hazard ratio estimates were obtained from multivariate Firth's penalized Cox regression models by censoring all participants still at risk at year 2, 4, 6, 8 and 10 after baseline, and after the total follow-up of 13 years. Estimates are adjusted for age at baseline, sex, educational level, and smoking status, are expressed per category increase in component

score, and are plotted at different logarithmic (base 2) scales per component. For parkinsonism analyses, we included following numbers of participants: (A) 7716, (B) 7718, (C) 7473, (D) 6840, (E) 7725, (F) 7689 (samples were 5 to 7 participants smaller for analyses on Parkinson's disease). To ensure sufficient (>10%) observations in each category, we combined scores 2 and 3 for components quality, latency and efficiency, and scores 1, 2 and 3 for components disturbances, medication and daytime dysfunction.

Abbreviations: CI=Confidence interval; HR=Hazard ratio; N=Sample size; PD=Parkinson's disease; PSQI=Pittsburgh Sleep Quality Index

measured over 10.9 years (on average 6.0 years) in all participants. In the subsequent 6.0 years (average follow-up: 2.9) after the follow-up visit, we observed 25 incident parkinsonism cases, of which 17 with Parkinson's disease.

Worsening of sleep quality was related to a subsequent increase in Parkinson's disease risk (HR per SD increase 1.76, 95% CI 1.12-2.78), as was a shortening of sleep duration (HR per SD increase 1.72, 95% CI 1.08-2.72; Table 2). Results were independent of the absolute average level of sleep quality or duration (Table 2). Also, additional adjustment for depressive symptoms at baseline did not attenuate results. Associations of sleep quality (HR 1.23, 95% CI 0.83-1.83) and sleep duration (HR 1.45, 95% CI 0.99-2.13) with incident parkinsonism were less pronounced. When examining hazard ratios over increasing epochs of follow-up time measured from the follow-up visit, we found that worsening of sleep quality, and shortening of sleep duration, were associated with parkinsonism on the short term, but not the longer term (Supplementary Fig. 4). For both sleep parameters, risk of Parkinson's disease was also slightly higher on the short than on the long term.

Table 2. Association of changes in sleep quality and duration between the baseline and follow-up visit, and risk of parkinsonism and Parkinson's disease

Determinant (unit)	Parkinsonism		Parkinson's disease	
	Cases/N	HR (95% CI)	Cases/N	HR (95% CI)
Change sleep quality (worse sleep)	25/5,206	1.23 (0.83-1.83)	17/5,244	**1.76 (1.12-2.78)**
Change sleep duration (shorter sleep)	25/5,244	1.45 (0.99-2.13)	17/5,238	**1.72 (1.08-2.72)**

Changes in sleep quality were modeled per standard deviation increase ('worsening') of global Pittsburgh Sleep Quality Index score, and changes for sleep duration were modeled as standard deviation decrease ('shortening') of sleep duration from the baseline visit to the follow-up visit. Hazard ratio estimates are adjusted for age at baseline, sex, educational level, smoking status and time interval between measurements. Additional adjustment for depressive symptoms at baseline minimally changed point and interval estimates (data not shown). After additional adjustment for the average level of sleep quality or sleep duration of the two measurements, point and interval estimates for the relation with parkinsonism barely changed. Estimates for associations of change in sleep quality (HR 1.87, 95% CI 1.12-3.10) and change in sleep duration (HR 1.85, 95% CI 1.14-2.98) with risk of Parkinson's disease increased. **Bold** estimates indicate statistically significant results at p<0.05. Abbreviations: CI=Confidence interval; HR=Hazard ratio; N=Sample size.

DISCUSSION

In the general population, baseline sleep quality and duration within the next 2 years relate to incident parkinsonism, and specifically to Parkinson's disease. Similarly, deterioration over 6 years in these parameters is associated with incident parkinsonism and Parkinson's disease.

Several methodological considerations should be mentioned. First, our study focused on subjectively measured sleep, which does not necessarily reflect similar constructs as objective measurements. While the first incorporates the experience of sleep, objective measurements indicate physiological sleep. Therefore, subjective measures cannot provide similar insight in underlying biological processes as objective measures (e.g. polysomnography). Second, we did not include individuals with cognitive impairment to minimize information bias of sleep quality[40,41] and duration[40,42], but these individuals are at increased risk of having prodromal parkinsonism[43] which could bias our associations. In addition, persons with cognitive impairment are also predisposed to develop REM sleep behavior disorder,[44] which has been suggested to be associated to a longer sleep duration in the general population.[45] This could lead to an underestimation of associations of sleep duration with parkinsonism and Parkinson's disease. Third, although the PSQI is used in patients with Parkinson's disease,[46] it may miss Parkinson's disease-specific sleep disturbances.[47,48] Patients with prodromal disease may thus underreport sleep problems, or overstate their sleep quality. If so, we have even underestimated especially short-term effect estimates of worse sleep quality with increased risk of parkinsonism and Parkinson's disease risk. Fourth, the number of parkinsonism and Parkinson's disease cases in our study is small, which may have unpowered us to detect small effects. Fifth, subjective assessment of sleep may be more prone to measurement error than objective methods. This lack of precision may have precluded us from detecting small effect sizes. Sixth, we cannot exclude any residual confounding of medication use beyond those questioned in the PSQI in our estimates.

We found associations of poor sleep quality and short sleep duration with increased risk of parkinsonism, and especially Parkinson's disease, in the first 2 years of follow-up, attenuating with incremental follow-up. Our study adds to the previous findings by showing that associations evidently change with incremental follow-up time. This is in line with findings of large registry-based studies in general practice that show increases in insomnia diagnoses 2 years,[22,49] but not 5 and 10 years before diagnosis of Parkinson's disease [22]. Such results suggest that sleep disturbances occur as prodromal features rather than as causes of Parkinson's disease and related synucleinopathies, as sleep is measured closer to the diagnosis of an incident case when follow-up is short. Our measurements of sleep likely represent common, subclinical sleep problems as well as

those severe enough to diagnose a sleep disorder, and therefore fit well with the variety of sleep disturbances preceding Parkinson's disease.[12]

Mechanisms behind sleep disturbances marking prodromal Parkinson's disease remain speculative. Sleep may be disturbed by early-stage dysfunction of serotonergic neurons in the dorsal raphe nuclei and sleep-promoting areas in the basal forebrain.[50] Such dysfunction may also negatively impact switching between sleep and wake.[51] Additionally, early spread of pathology to the coeruleus/subcoerulus complex may disturb REM sleep independent of REM sleep behavior disorder.[15] Sleep may also be impaired via circadian dysfunction occurring around the time of diagnosis,[2] via hypothalamic neuron loss,[52,53] or via the loss of dopaminergic modulation.[54]

Of note, results do not exclude that sleep disturbances may cause Parkinson's disease. An effect of sleep disturbance on neurodegenerative disease is plausible, as sleep deprivation has been shown to increase levels of beta-amyloid, a pathological hallmark of Alzheimer's disease. Mechanisms include decreased clearance,[55] or activity-dependent increased production, of beta-amyloid. The sleep wake cycle has also been shown to regulate tau levels, and sleep deprivation can increase extracellular levels of tau and, interestingly, alpha-synuclein.[56] A recent study importantly showed that increased actigraphy-derived sleep fragmentation in old individuals without Parkinson's disease was associated with an increased burden of Parkinson's disease pathology at brain autopsy.[13] This indicates that objective disturbances, besides subjectively impaired sleep, relates to Parkinson's disease pathology. Unfortunately, the cross-sectional design does not allow inference on temporality of the association. Authors speculate that potential pathways between sleep fragmentation and disease risk may include increased oxidative stress, or reduced clearance of metabolic waste including extracellular α-synuclein.[13]

Analyses of changes in sleep quality and duration suggest that sleep in prodromal Parkinson's disease already deteriorates over 2 years prior to diagnosis in the general population, independent from baseline depressive symptoms, and the absolute levels over which the changes occurred. To our knowledge, the only study investigating changes in sleep has been performed in patients with REM sleep behavior disorder.[57] This study, however, reported opposite findings: improving insomnia symptoms and increasing self-reported sleep duration increased the risk for conversion to Parkinson's disease and dementia with Lewy bodies. Differences in findings could results from their selection of patients prone to develop a severe, cognitively more impaired subtype of prodromal Parkinson's disease,[58] but differences may additionally be explained by non-recognition of sleep problems due to including subjects with subclinical cognitive deficits.[59-61] Their study not only had a high incidence (50%) of Lewy body dementia patients, but also showed underreporting (reporting increased sleep duration and quality discrepant from objective decreases in total sleep time) in those developing neurodegenerative disease.[57]

If aforementioned changes in sleep were driven by a specific sleep disorder, REM sleep behavior disorder may not be a likely candidate: Persons with REM sleep behavior disorder in a population-based polysomnography study had a similar sleep quality, and even longer sleep duration, than others.[45] REM sleep behavior disorder patients also did not perceive their sleep as worse, or shorter, than healthy controls.[57]

After excluding persons with comorbid depressive symptoms or anxiety disorders, results remained mostly similar. Noteworthy was that hazard ratio estimates of the relation of sleep duration with Parkinson's disease risk were all slightly higher. This resulted in an association of longer sleep duration with increased Parkinson's disease risk in the overall follow-up. Given the number of associations investigated in our sensitivity analyses, and the small number of cases when restricting the sample, this result may be a spurious finding and should be interpreted with caution.

A methodological explanation is that in these sensitivity analyses persons in a late prodromal phase of Parkinson's disease may have been selectively excluded, as depression and anxiety are both part of the prodromal phase and considered predominantly late features.[22,62,63] This could have resulted in selective exclusion of susceptible individuals[39] resulting in a decreased long-term risk of Parkinson's disease in those remaining individuals with short sleep duration. It is also possible that short sleep duration is merely symptomatic of (prodromal emergence of) depression, which explains why exclusion of persons with depression resulted in an inverse association of sleep duration with Parkinson's disease. Nevertheless, we re-emphasize the small number of cases in our analyses, which may have compromised the robustness of these findings.

Analogous to aforementioned sensitivity analysis, stratified analyses on the presence of parkinsonian signs might also select participants based on either a more advanced stage of an underlying neurodegenerative process, or its absence. A statistical interaction with sleep quality could guide future investigations of identifying high risk groups for parkinsonism or Parkinson's disease risk.

Patterns of associations between separate PSQI components and Parkinson's disease risk over time indicate that, aside from sleep duration, efficiency may mark prodromal disease. This applies to sleep quality, latency and daytime dysfunction to a lesser extent. Although these aspects of sleep may correlate well to known markers of prodromal Parkinson's disease such as pain or autonomic failure,[22] or excessive daytime sleepiness,[12,64] results also warrant further investigation of these easily measured aspects of sleep in etiological or risk prediction efforts. Future studies on prodromal Parkinson's disease are needed to investigate associations with objective measures of sleep, and to assess the predictive value of (perceived) shortening or worsening of sleep over known (sleep) markers of prodromal parkinsonism.

In conclusion, poor sleep quality and short sleep duration increased the risk of parkinsonism and Parkinson's disease in the next 2 years. Moreover, sleep quality and dura-

tion change for the worse over 2 years prior to a diagnosis of parkinsonism, especially Parkinson's disease. Both are congruent with presence of prodromal Parkinson's disease progressively deteriorating sleep.

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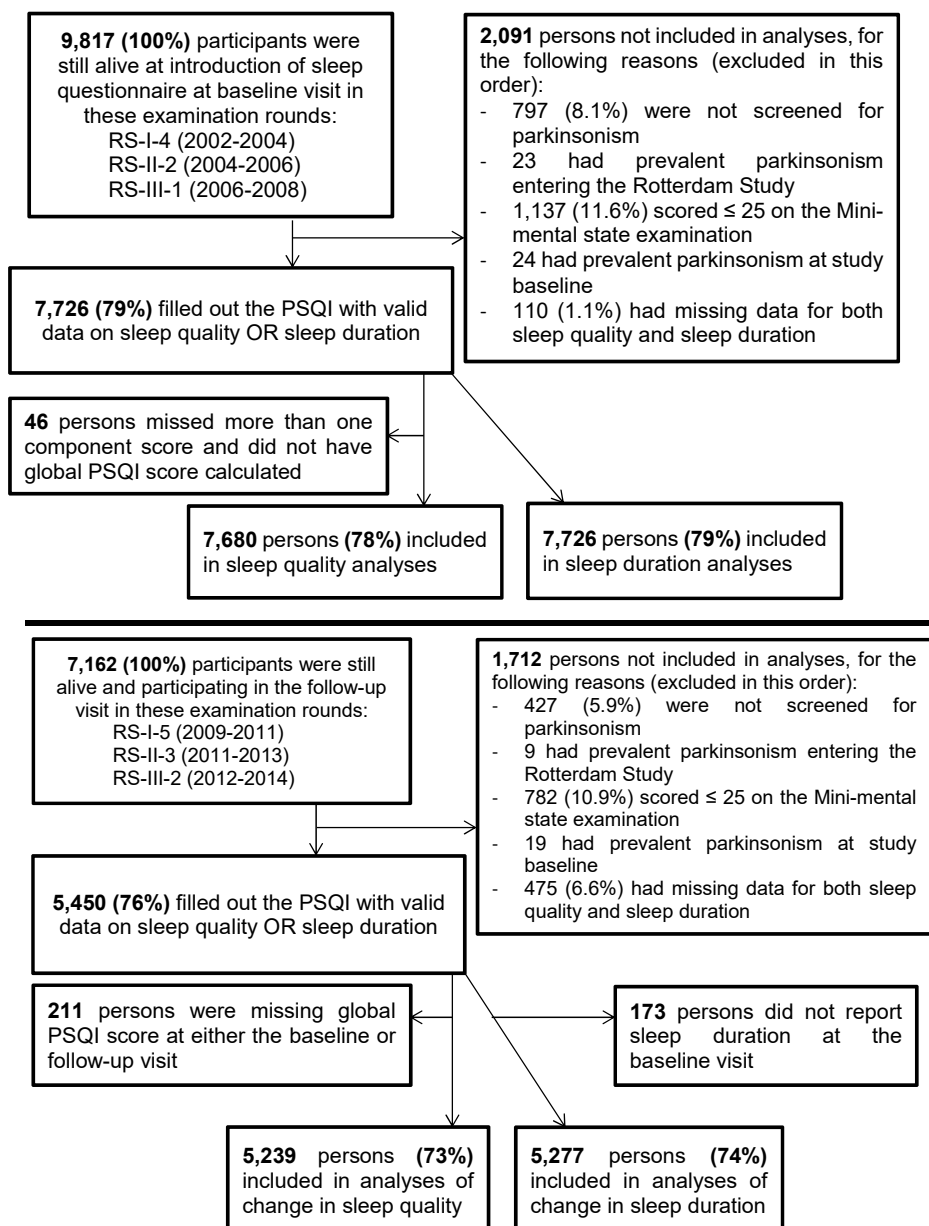
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SUPPLEMENTARY TABLES AND FIGURES

9,817 (100%) participants were still alive at introduction of sleep questionnaire at baseline visit in these examination rounds:
RS-I-4 (2002-2004)
RS-II-2 (2004-2006)
RS-III-1 (2006-2008)

2,091 persons not included in analyses, for the following reasons (excluded in this order):
- 797 (8.1%) were not screened for parkinsonism
- 23 had prevalent parkinsonism entering the Rotterdam Study
- 1,137 (11.6%) scored ≤ 25 on the Mini-mental state examination
- 24 had prevalent parkinsonism at study baseline
- 110 (1.1%) had missing data for both sleep quality and sleep duration

7,726 (79%) filled out the PSQI with valid data on sleep quality OR sleep duration

46 persons missed more than one component score and did not have global PSQI score calculated

7,680 persons **(78%)** included in sleep quality analyses

7,726 persons **(79%)** included in sleep duration analyses

7,162 (100%) participants were still alive and participating in the follow-up visit in these examination rounds:
RS-I-5 (2009-2011)
RS-II-3 (2011-2013)
RS-III-2 (2012-2014)

1,712 persons not included in analyses, for the following reasons (excluded in this order):
- 427 (5.9%) were not screened for parkinsonism
- 9 had prevalent parkinsonism entering the Rotterdam Study
- 782 (10.9%) scored ≤ 25 on the Mini-mental state examination
- 19 had prevalent parkinsonism at study baseline
- 475 (6.6%) had missing data for both sleep quality and sleep duration

5,450 (76%) filled out the PSQI with valid data on sleep quality OR sleep duration

211 persons were missing global PSQI score at either the baseline or follow-up visit

173 persons did not report sleep duration at the baseline visit

5,239 persons **(73%)** included in analyses of change in sleep quality

5,277 persons **(74%)** included in analyses of change in sleep duration

Supplementary Figure 1. Flowchart inclusion of study participants at the baseline and follow-up visits

Supplementary Text

Statistical analysis

For our main analyses, we used Cox proportional hazard models to determine the association of sleep quality, measured with the global PSQI score, and sleep duration at baseline with incident parkinsonism and Parkinson's disease, using follow-up time as timescale. We repeated the main analysis after categorizing sleep quality and duration (sleep duration according to international recommendations for elderly individuals[65]).

When investigating the assumption of proportional hazards of the Cox model through visually examining and statistically testing the scaled *Schoenfeld* residuals, we found slight (0.01<p<0.05) violations of proportionality for both sleep determinants in the main analyses on Parkinson's disease. This indicates that the hazard ratio, which provides an average of the relative risk over the included follow-up time, is a poor representation of the changes occurring over time within the study timeframe.[39] To examine these changes over time, we repeated the main analyses for both outcomes after restricting follow-up to shorter study duration by censoring participants at 2, 4, 6, 8, and 10 years after baseline, using Firth's penalized Cox regression analysis to account for low cumulative incidences of outcomes after short follow-up.[66,67] Such an approach shows how the choice of follow-up time from baseline affects the hazard ratio.[39] Of note, proportionality was not violated for analyses of 6 years after baseline or shorter (for the association of sleep duration and Parkinson's disease), or at 2 years after baseline (for the association of sleep quality and Parkinson's disease). To further examine hazard ratio changes over time, we used a stratified Cox model by stratifying by follow-up time intervals of 0-2, 2-4, 4-6, 6-8, 8-10, and 10-13 years. Hazard ratios were obtained by modeling the interaction of the determinant with a term of categorized follow-up time, and combining the coefficients of point and interval estimation for the determinant and that stratum.

Next, to investigate if any associations found for global PSQI score were driven by specific components, we also investigated the relation between PSQI component scores (quality, latency, efficiency, disturbances, medication and daytime dysfunction) and incident parkinsonism or Parkinson's disease, in overall and shorter follow-up durations similarly as described above. As sleep duration was already investigated separately, we did not additionally investigate the duration component of the PSQI (which categorizes reported sleep duration[32]). Also, we performed the main analyses in persons without any comorbid clinically relevant depressive symptoms (CES-D score ≥16) and without any anxiety disorders. Furthermore, we studied possible effect modification in the main analyses by median age, sex, and presence versus absence of any of four parkinsonian signs (scoring details published previously[62]), by performing stratified analyses and formally testing for multiplicative interaction. Proportionality was not violated in the tests of multiplicative interaction.

We also examined how changes in sleep quality and duration between the baseline and follow-up visit were related to subsequent risk of parkinsonism and Parkinson's disease. Follow-up time was calculated from the follow-up visit, and analyses were additionally adjusted for the time interval between the baseline and follow-up visit. A change in sleep quality was modeled by subtracting the baseline global PQSI score from the score at the follow-up visit, so that positive values indicated worsening of sleep quality over time. Change in sleep duration was modeled as shorter sleep duration, by subtracting self-reported sleep duration at the follow-up visit from that at baseline. We repeated analyses after i) additionally adjusting for averaged global PSQI score, or sleep duration, over baseline and follow-up visits to examine if effects were dependent on absolute levels (i.e. if decreases in e.g. sleep duration from 9 to 7 hours would be different from decreases from 7 to 5 hours); ii) adjusting for depressive symptoms at baseline to see if sleep changes were driven by depression. As we also observed non-proportionality of hazard ratios ($0.01 < p < 0.05$) in the analyses of changes in sleep quality and duration between the baseline and follow-up visit on the risk of parkinsonism, we also obtained period-specific hazard ratios for these relations.

To obtain normally distributed values and minimize the effect of outliers, we log-transformed (ln(variable + 1)) right-skewed variables (global PSQI score) and subsequently winsorized (i.e. transformed towards the mean) outliers to three standard deviations from the mean (1.3% of observations for global PSQI score, 0.8% for sleep duration). Both variables were then standardized (subtracting the mean and dividing by the standard deviation) to facilitate comparison of effect sizes.

Missing data on covariates (missing values in covariates at baseline: median=1.6%, maximum=29.7% (smoking status)) were imputed using five multiple imputation based on all variables used in our analyses. Statistical testing was performed two-sided at p<0.05. Data were analysed using *SPSS Statistics*, version 21 (IBM Corp., Armonk, NY), and with the open *R* software (packages: 'survival', 'coxphf').

Supplementary references

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Supplementary Table 1. Overview of incident parkinsonism diagnoses

Clinical diagnosis	After the baseline visit (N=7,726)	After the follow-up visit (N=5,450)
Probable Parkinson's disease	47 (63%)	17 (68%)
Vascular parkinsonism	3 (4%)	1 (4%)
Medication-induced parkinsonism	5 (7%)	1 (4%)
Progressive supra-nuclear palsy	1 (1%)	0
Multiple system atrophy	0	0
Corticobasal degeneration	1 (1%)	1 (4%)
Lewy body dementia	2 (3%)	0
Parkinsonism with dementia – not Lewy body type	2 (3%)	0
Unspecified parkinsonism*	14 (19%)	5 (20%)
All parkinsonism diagnoses	75 (100%)	25 (100%)

Number of diagnoses expressed as frequency (%), for the samples used in analyses at the baseline and follow-up visits.

*Denotes parkinsonism patients that did not have any of the above clinical diagnoses

Supplementary Table 2. Association between categories of sleep quality or duration and risk of incident parkinsonism or Parkinson's disease

Determinant	Categories	Parkinsonism		Parkinson's disease	
		Cases/N	HR (95% CI)	Cases/N	HR (95% CI)
Global PSQI score	≤5 ('good' quality)	55/5,565	1.00 (reference)	36/5,562	1.00 (reference)
	>5 ('poor' quality)	20/2,115	0.97 (0.57-1.66)	11/2,112	0.79 (0.39-1.59)
Sleep duration	<7 hours	21/3,155	1.00 (reference)	13/3,150	1.00 (reference)
	≥7 - ≤8 hours	45/4,033	1.61 (0.95-2.71)	28/4,031	1.65 (0.86-3.21)
	>8 hours	9/538	2.19 (1.00-4.81)	6/537	2.54 (0.96-6.72)

Hazard ratios were obtained from Cox regression models, adjusted for age at baseline, sex, educational level, and smoking status, expressed in reference to the lowest global PSQI score, or sleep duration, category. Categorization of sleep duration in three categories is based on the US National Sleep Foundation recommended sleep duration for elderly persons.[65]

Abbreviations: HR=Hazard ratio; N=sample size; PSQI=Pittsburgh Sleep Quality Index.
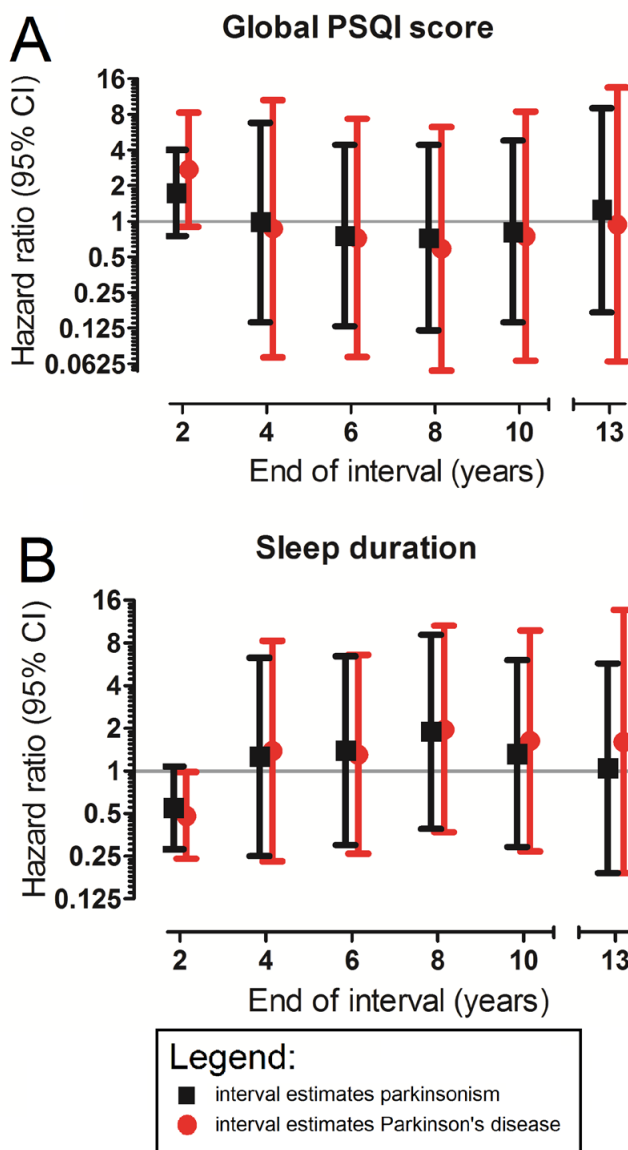
Supplementary Figure 2. Associations of sleep quality and duration with risk of parkinsonism and Parkinson's disease, over separate intervals of follow-up time

The associations of (A) sleep quality and (B) sleep duration with incident parkinsonism and Parkinson's disease are shown for separate intervals of follow-up duration within the study timeframe, using a stratified Cox model. Hazard ratio were estimated for the intervals 0-2 years, 2-4 years, 4-6 years, 6-8 years, 8-10 years, and 10-13 years (end of follow-up) and obtained from modeling the interaction of the determinants with follow-up time strata. Hazard ratio estimates were adjusted for age at baseline, sex, educational level and smoking status, are expressed per standard deviation increase of (A) worse sleep quality, or (B) longer sleep duration, and are plotted at a logarithmic (base 2) scale. Abbreviations: CI=Confidence Interval; PD=Parkinson's disease; PSQI=Pittsburgh Sleep Quality Index
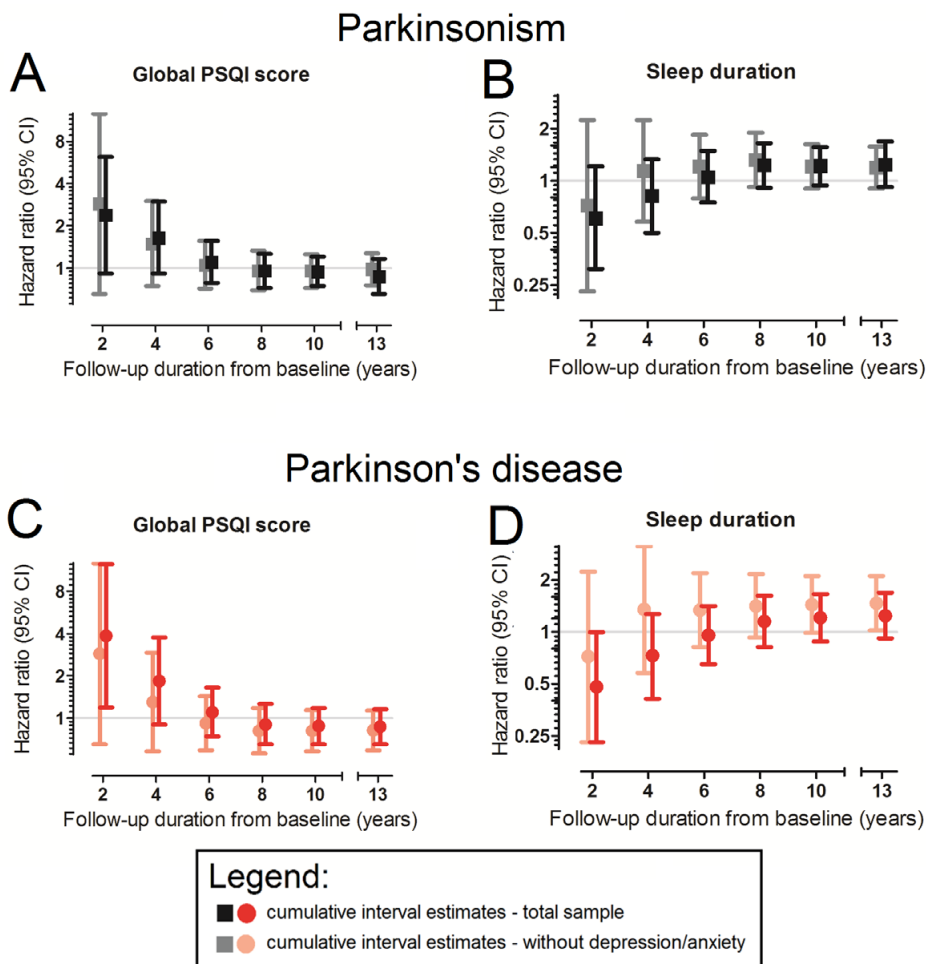
Supplementary Table 3. Associations of Pittsburgh Sleep Quality Index component scores with risk of parkinsonism and Parkinson's disease, per cumulatively increasing duration of follow-up

PSQI component	Outcome	N	Duration of follow-up time in years					
			≤2	≤4	≤6	≤8	≤10	Overall
			Hazard ratio per point increase (worse sleep) on the component score (95% CI)					
Quality	PS	7716	3.16 (0.95; 10.46)	2.33 (1.05; 5.17)	1.16 (0.68; 1.98)	1.08 (0.69; 1.69)	1.07 (0.73; 1.56)	1.09 (0.76; 1.57)
	PD	7709	3.90 (1.04; 14.58)	2.57 (1.01; 6.57)	1.17 (0.63; 2.18)	1.01 (0.60; 1.70)	0.93 (0.57; 1.50)	0.95 (0.60; 1.50)
Latency	PS	7718	2.48 (0.90; 6.83)	2.27 (1.14; 4.51)	1.54 (0.99; 2.40)	1.27 (0.87; 1.86)	1.11 (0.80; 1.55)	1.15 (0.84; 1.57)
	PD	7712	2.94 (0.97; 8.87)	2.16 (0.97; 4.79)	1.53 (0.91; 2.56)	1.19 (0.76; 1.85)	1.05 (0.70; 1.59)	1.06 (0.71; 1.57)
Efficiency	PS	7473	2.78 (0.97; 7.98)	1.98 (1.04; 3.77)	1.42 (0.90; 2.24)	1.05 (0.68; 1.60)	1.05 (0.73; 1.51)	0.99 (0.70; 1.41)
	PD	7466	4.54 (1.27; 16.18)	2.35 (1.09; 5.07)	1.65 (1.00; 2.73)	1.17 (0.73; 1.88)	1.09 (0.69; 1.71)	1.00 (0.64; 1.56)
Disturbances	PS	6840	0.70 (0.15; 3.25)	0.85 (0.29; 2.44)	1.08 (0.53; 2.21)	0.94 (0.52; 1.69)	0.75 (0.45; 1.23)	0.78 (0.48; 1.26)
	PD	6835	1.08 (0.20; 6.01)	0.96 (0.27; 3.34)	0.96 (0.42; 2.21)	0.76 (0.38; 1.52)	0.64 (0.34; 1.19)	0.64 (0.35; 1.18)
Sleep medication	PS	7725	1.08 (0.14; 8.32)	0.54 (0.09; 3.23)	1.28 (0.49; 3.33)	1.00 (0.42; 2.37)	1.29 (0.65; 2.56)	1.08 (0.55; 2.14)
	PD	7718	1.54 (0.19; 12.76)	0.73 (0.11; 4.68)	1.04 (0.32; 3.41)	0.95 (0.34; 2.66)	1.19 (0.50; 2.85)	1.06 (0.45; 2.52)
Daytime dysfunction	PS	7689	2.49 (0.48; 12.81)	3.00 (1.01; 8.89)	1.64 (0.72; 3.74)	1.40 (0.68; 2.87)	1.10 (0.56; 2.14)	0.94 (0.48; 1.82)
	PD	7684	3.34 (0.60; 18.55)	2.31 (0.62; 8.71)	1.24 (0.44; 3.51)	1.04 (0.41; 2.63)	0.85 (0.34; 2.10)	0.76 (0.31; 1.89)

The associations of the PSQI components with incident parkinsonism and Parkinson's disease are provided for cumulatively increasing follow-up duration within the study timeframe. Hazard ratio estimates were obtained from multivariate Firth's penalized Cox regression models by censoring all participants still at risk at year 2, 4, 6, 8 and 10 after baseline, and after the total follow-up of 13 years. Estimates are adjusted for age at baseline, sex, educational level, and smoking status, and are expressed per category increase in component score. To ensure sufficient (>10%) observations in each category, we combined scores 2 and 3 for components quality, latency and efficiency, and scores 1, 2 and 3 for components disturbances, medication and daytime dysfunction.

Abbreviations: CI=Confidence interval; N=Sample size; PD=Parkinson's disease; PS=parkinsonism; PSQI=Pittsburgh Sleep Quality Index.
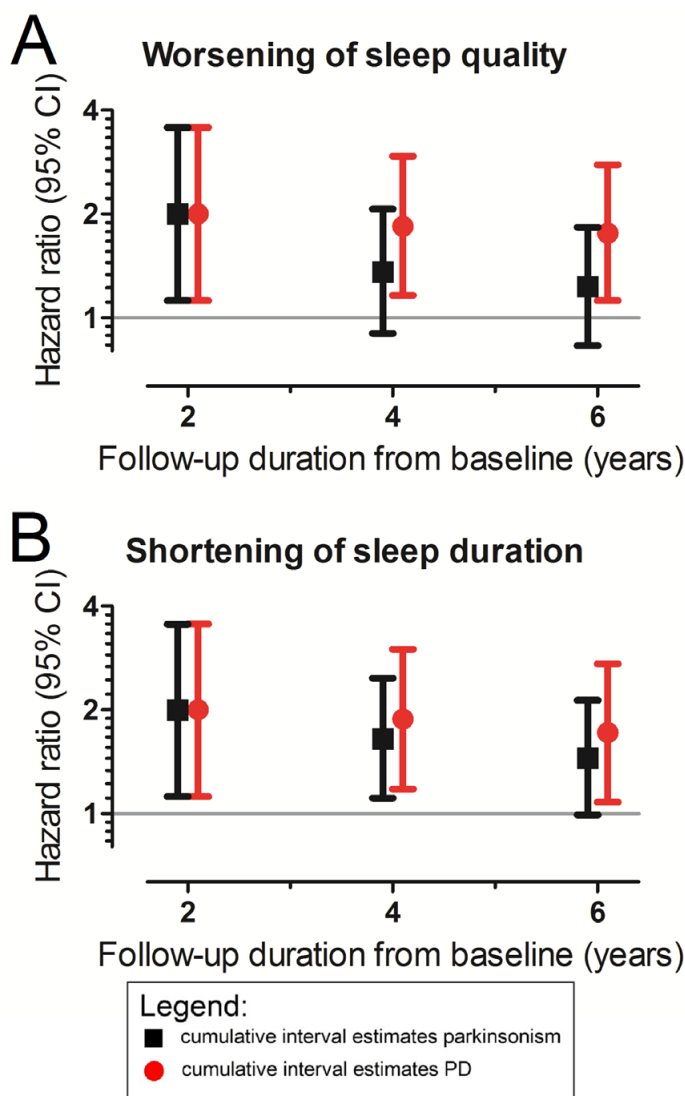
Parkinsonism

Parkinson's disease

Supplementary Figure 3. Associations of sleep quality and duration with parkinsonism and Parkinson's disease in persons without comorbid depression and anxiety, per cumulatively increasing duration of follow-up

Associations of (A) sleep quality and (B) sleep duration with incident parkinsonism, and (C) sleep quality and (D) sleep duration with incident Parkinson's disease, analyzed both in the total sample and in persons without clinically relevant depressive symptoms and anxiety disorders. Associations are depicted for cumulatively increasing follow-up duration within the study timeframe. Hazard ratio estimates were obtained from multivariate Firth's penalized Cox regression models by censoring all participants still at risk at year 2, 4, 6, 8 and 10 after baseline, and after the total follow-up of 13 years. Estimates were adjusted for age at baseline, sex, educational level and smoking status, are expressed per standard deviation increase of PSQI score or sleep duration, and are plotted at a logarithmic (base 2) scale. Abbreviations: CI=Confidence Interval; PSQI=Pittsburgh Sleep Quality Index

Supplementary Table 4. Association of sleep quality or duration and risk of incident Parkinson's disease or parkinsonism, stratified by potential effect-modifiers

Effect-modifier	Strata	Cases/N	Parkinsonism HR per SD increase (95% CI)	P_{int}	Cases/N	Parkinson's dis. HR per SD increase (95% CI)	P_{int}
Sleep quality							
Age	≤67.5 y.	12/384	0.56 (0.31 – 1.00)	0.816	10/3837	0.62 (0.32 - 1.19)	0.683
	>67.5 y.	63/3,840	1.07 (0.82 - 1.38)		37/3837	0.95 (0.69 - 1.32)	
Sex	Male	42/3,305	1.01 (0.74 - 1.38)	0.289	24/3300	0.81 (0.53 - 1.22)	0.479
	Female	33/4,375	0.89 (0.63 - 1.25)		23/4374	0.93 (0.62 - 1.41)	
Park. signs	Present	16/804	**1.96 (1.07 - 3.59)**	**0.004**	12/802	1.53 (0.80 - 2.91)	**0.048**
	Absent	59/6,876	0.80 (0.62 - 1.03)		35/6872	**0.72 (0.52 – 1.00)**	
Sleep duration							
Age[a]	≤67.5 y.	12/3,863	1.84 (0.97 - 3.50)	0.778	10/3859	1.68 (0.82 - 3.47)	0.406
	>67.5 y.	63/3,863	1.11 (0.86 - 1.44)		37/3859	1.14 (0.82 - 1.60)	
Sex	Male	42/3,330	1.02 (0.73 - 1.43)	0.218	24/3323	1.26 (0.79 - 2.01)	0.870
	Female	33/4,396	1.39 (0.98 - 1.97)		23/4395	1.21 (0.80 - 1.82)	
Park. signs	Present	16/807	1.00 (0.62 - 1.60)	0.270	12/805	1.09 (0.64 - 1.86)	0.460
	Absent	59/6,919	1.29 (0.98 - 1.71)		35/6913	1.31 (0.91 - 1.89)	

The associations of sleep quality and sleep duration with incident parkinsonism and Parkinson's disease are shown stratified for several potential effect-modifiers. Hazard ratios were obtained from Cox regression models, adjusted for (if applicable) age at baseline, sex, educational level, and smoking status, and are expressed per standard deviation increase of global Pittsburgh Sleep Quality Index score or sleep duration. Multiplicative interaction was tested in a model including the main effects of the stratified variable, and a untransformed and non-standardized variable of sleep quality or sleep duration. Split at median age in sample. **Bold** indicates statistical significance at P<0.05. Abbreviations: CI=Confidence interval; dis=disease; HR=Hazard ratio; N=sample size; Park=parkinsonian; P_{int}=P-value interaction term; SD=standard deviation; y=years.

Supplementary Figure 4. Associations of changes in sleep quality and duration between the baseline and follow-up visit with risk of parkinsonism and Parkinson's disease, per cumulatively increasing duration of follow-up

The associations of changes in (A) sleep quality ('worsening') and (B) sleep duration ('shortening') between the baseline and follow-up visit with incident parkinsonism and Parkinson's disease are shown for cumulatively increasing follow-up duration within the six-year study timeframe. Hazard ratio estimates were obtained from multivariate Firth's penalized Cox regression models by censoring all participants still at risk at year 2, 4, and after the total follow-up of 6 years. Hazard ratio estimates were adjusted for age at baseline, sex, educational level, smoking status, and time interval between measurements, are expressed per standard deviation increase of (A) worsening sleep quality, or (B) shorter sleep duration, and are plotted at a logarithmic (base 2) scale. Abbreviations: CI=Confidence Interval; PD=Parkinson's disease; PSQI=Pittsburgh Sleep Quality Index.

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Supplementary Table 5. Characteristics of study population at follow-up visit

Characteristic (unit)	N = 5,450
Age at baseline (years)	68.4 ± 8.9
Female	3,127 (57%)
Educational level	
Primary education	398 (7%)
Lower/intermediate or lower vocational	2,161 (39%)
Higher or intermediate vocational	1,636 (30%)
Higher vocational or university	1,259 (23%)
Smoking status	
Never smoker	1,748 (32%)
Former smoker	3,068 (56%)
Current smoker	637 (12%)
Cognitive functioning (MMSE score)	29 (27-29)
Presence of any parkinsonian signs	806 (15%)
Time interval between baseline and follow-up visits (years)	6.0 ± 0.6
Missing	49 (1%)
Sleep quality (global PSQI score)	3 (1-6)
Missing	9 (0%)
Change in sleep quality compared to baseline (global PSQI score increase)	0.0 ± 3.1
Missing	211 (4%)
Sleep duration (hours)	6.9 ± 1.3
Change in sleep duration compared to baseline (hours decrease)	-0.1 ± 1.16
Missing	173 (3%)

Characteristics for eligible study population for analyses of sleep change at the follow-up visit. Values are expressed as frequency (%) for categorical variables and mean ± standard deviation or median (interquartile range) for continuous variables, unless specified otherwise. Includes imputed values for covariates. Abbreviations: MMSE=Mini-mental state examination; PSQI=Pittsburgh Sleep Quality Index.