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Authors

Leng, Yue
Goldman, Samuel M
Cawthon, Peggy M
et al.

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Excessive daytime sleepiness, objective napping and 11-year risk of Parkinson's disease in older men

Yue Leng,[1]* Samuel M Goldman,[2] Peggy M Cawthon,[3] Katie L Stone,[3] Sonia Ancoli-Israel[4] and Kristine Yaffe[5]

[1]Department of Psychiatry, [2]Department of Neurology, University of California, San Francisco, CA, USA, [3]Department of Research Institute, California Pacific Medical Center, San Francisco, CA, USA, [4]Department of Psychiatry, University of California, San Diego, CA, USA and [5]Departments of Psychiatry, Neurology, and Epidemiology, University of California, and San Francisco VA Medical Center, San Francisco, CA, USA

*Corresponding author. San Francisco VA Medical Center, 4150 Clement Street, San Francisco, CA, USA.
E-mail: yue.leng@ucsf.edu

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Abstract

Background: It is unknown whether subjective daytime sleepiness or objective napping could precede the risk of Parkinson's disease (PD) in the long term.

Methods: We studied 2920 men (mean age 76 years) without a history of PD and followed them for 11 years. Excessive daytime sleepiness (EDS) was defined as having an Epworth Sleepiness Scale score >10. Objective naps were defined as ≥ 5 consecutive minutes of inactivity as measured by actigraphy, and napping duration was the accumulated time of naps outside the main sleep period. We used logistic regression to compare PD risk across four groups: no EDS& napping <1 h/day ($N=1739$, 59.5%; referent group), EDS& napping <1 h/day ($N=215$, 7.4%), no EDS& napping ≥ 1 h/day ($N=819$, 28.1%) and EDS& napping ≥ 1 h/day ($N=147$, 5.0%).

Results: We identified 106 incident PD cases over 11 years. After multivariable adjustment, men with napping $\geq$ 1h/day alone were twice as likely [odds ratio (OR) $=1.96$, 95% confidence interval (CI) 1.25–3.08], and men with both EDS and napping ≥ 1 h/day were almost three times as likely to develop PD (2.52, 1.21–5.27), compared with the referent group. Compared with those with naps for <30 min, men who napped for ≥ 1 h/day had more than double the risk of PD. No association was found for EDS alone and PD risk. Further adjustment for chronotype and circadian stability, or excluding PD cases identified within 2 years after napping measurements, showed similar results.

Conclusions: Objective long napping rather than subjective EDS was prospectively associated with a higher risk of PD in older men. Objective measures of napping might be valuable as a preclinical marker for PD.

Key words: Daytime napping, sleep, daytime sleepiness, Parkinson's disease, longitudinal study

Key Messages

- Daytime sleepiness and napping are very common in older adults, especially those with Parkinson's disease (PD). However, it is unknown whether objectively measured napping could be associated with the risk of developing PD in the future.
- Older men who experienced long (≥1 h/day) objective napping and reported excessive daytime sleepiness (EDS) had almost a 3-fold increase in the risk of PD over 11 years. Longer napping durations were associated with a higher PD risk.
- No association was observed for those who only reported EDS but had objective napping <1 h/day.
- The association was independent of comorbidities, cognitive function, night-time sleep disturbances and chronotype, and remained when excluding PD cases developed within the first 2 years after the measure of napping.
- Napping as a noticeable behaviour might be valuable as a prodromal sign of PD. This is potentially important for the early detection of individuals at high risk for PD and thus could help slow down or prevent PD progression in the long run.

Introduction

Many patients with Parkinson's disease (PD) experience some form of sleep disturbances,[1,2] with excessive daytime sleepiness (EDS) and napping occurring in up to 50% of PD patients.[3–6] Although common with the disease, it is unclear whether daytime somnolence could be a prodromal factor or even a risk factor for PD. Longitudinal studies with long follow-up periods are essential to answer this question.

Of the few studies found, only two prospective studies[7,8] have investigated napping and risk of PD. Both reported a strong association, but napping was self-reported which is less reliable and valid, especially for older adults.[9–11] Moreover, self-reported napping only reflects subjective sleepiness and tendency to fall asleep, whereas objectively-measured napping assesses the actual inactive time. Therefore, it is critical to study these two different measures in order to understand which is driving the association between napping and risk of PD.

No study to date has prospectively examined the association between objectively-measured napping and long-term risk of PD, or compared EDS and objective napping in relation to PD risk. Additionally, although napping is closely tied to night-time sleep,[12,13] little has been done to take into account of the effects of night-time sleep disturbance which may confound the association between daytime napping and PD. Given the high prevalence of night-time sleep disorders among PD patients,[2] it is important to understand whether the link between napping and PD is independent of night-time sleep duration and quality.

We prospectively investigated the association between both reported EDS and actigraphy-measured napping and risk of developing PD over the subsequent 11 years, and explored whether this is independent of night-time sleep disturbances, in a large cohort of community-dwelling older men.

Methods

The Osteoporotic Fractures in Men Study (MrOS)[14,15] is a longitudinal study of community-dwelling men aged 65 years or older, enrolled from 2000 to 2002 at six clinical centres in the USA: Birmingham, Alabama; Minneapolis, Minnesota; Palo Alto, California; the Monongahela Valley near Pittsburgh, Pennsylvania; Portland, Oregon; and San Diego, California. In order to participate, men needed to be able to walk without assistance and must not have had a bilateral hip replacement.

After excluding men with a baseline history of PD ($n = 58$), our final analytical sample included 2920 men who had napping and EDS measured from 2003 to 2005 and who completed at least one clinic visit and questionnaire over the subsequent 11 years. All men provided written informed consent and the study was approved by the institutional review board at each site.

Napping was measured objectively using an actigraph (SleepWatch-O, Ambulatory Monitoring, Inc., Ardsley, NY), worn continuously on the non-dominant wrist for a minimum of five consecutive 24-h periods (mean 5.2 ± 0.9 days). Actigraphy is a reliable non-invasive tool for estimating sleep-wake activities.[16,17] It measures movement using a piezoelectric biomorph-ceramic cantilevered beam, and generates a voltage each time the actigraph is moved; these voltages are gathered continuously and stored in 1-min epochs. The University of California, San Diego (UCSD) scoring algorithm in the ActionW-2 software (Ambulatory Monitoring, Inc., Ardsley, NY) is used to analyse the actigraphy data and differentiate sleep from

wake times.[18,19] Participants also completed sleep logs for the period they wore the actigraph, and reported information regarding times they got into and out of bed, when the actigraph was removed and times they napped; these data were used to edit the actigraph records. This standardised scoring protocol has been found to have high inter-scorer reliability.[20]

We considered periods of extreme inactivity as at least 5 consecutive minutes scored as sleep (inactivity) outside the main sleep interval.[21,22] For convenience, these periods of daytime inactivity will be referred to as 'napping' throughout the rest of the manuscript. Daily napping duration was calculated by summing up the duration of napping periods throughout the day and averaging across all days of recording. As in a previous study,[11] we dichotomized the daily napping duration into <1 h and ≥ 1 h for the main analysis and considered those with napping duration of ≥ 1 h/day as having long objective napping. We evaluated subjective daytime sleepiness using the Epworth Sleepiness Scale (ESS).[23,24] The ESS is an eight-question survey in which subjects are asked to rate, on a scale of 0 to 3 (never, slight, moderate or high), how likely they were to doze in each of eight different situations: sitting and reading, watching television, as a passenger in a car for an hour without a break, sitting inactive in a public place, lying down to rest in the afternoon, sitting and talking to someone, sitting quietly after lunch without alcohol, and in a car while stopping for few minutes in traffic. The test yields a score of 0 to 24, with 0 indicating no daytime sleepiness and 24 indicating the most severe sleepiness. An ESS score of 10 has been reported to be two standard deviations above the mean in healthy individuals; a score of 11 or greater is commonly used to define significant sleepiness. This scale has not been validated in older people or demented populations.

During the follow-up, participants were asked to report at every visit or questionnaire contact if they ever had PD diagnosed by a physician. Participants were also asked to bring in all prescription and non-prescription medications taken in the past 30 days, and these were entered into an electronic database with each matched to its ingredient(s) based on the Iowa Drug Information Service (IDIS) Drug Vocabulary (College of Pharmacy, University of Iowa, Iowa City, IA).[25] We subsequently derived the information on PD and sleep medication use from this database. PD medication use was defined as the use of Sinemet (carbidopa/ levodopa), Mirapex or Elderpryl. Incident PD cases were defined as either physician-diagnosed PD or PD medication use.

Participants completed examinations and questionnaires, which included information on demographics, smoking, physical activity, depressive symptoms and medical history. Level of physical activity was examined using the Physical Activity Scale for the Elderly (PASE),[26] and depressive symptoms were assessed using the Geriatric Depression Scale (GDS).[27] Global Cognitive function was evaluated using the Modified Mini-Mental State (3MS) examination.[28] Body mass index (BMI; weight in kilograms divided by height in metres squared) was also measured.

We used night-time sleep duration and efficiency (SE; the average percentage of time asleep while in bed) recorded by actigraphy to represent night-time sleep quality. The apnoea-hypopnoea index (AHI, total number of obstructive and central apnoeas and hypopnoeas associated with $\geq 3\%$ oxygen desaturation), measured by unattended in-home polysomnography (PSG, Safiro Ambulatory EEG system; Compumedics, Abbotsford, Australia) following a standardized protocol as described previously,[29] was used to account for the effects of sleep-disordered breathing. In addition, we used sleep midpoint time, a calculated halfway point between bedtime and wakeup times, to indicate morningness-eveningness, and its standard deviation (SD) to show circadian stability.

Statistical analysis

We first divided the participants into four categories according to their subjective EDS and objective napping status: no EDS and napping <1 h, EDS and napping <1 h, no EDS and napping ≥ 1 h and EDS and napping ≥ 1 h, and compared baseline characteristics of these participants with analysis of variance (ANOVA) for normally distributed continuous variables, the Kruskal-Wallis test for skewed variables and the chi-square test for categorical variables. We used multivariable logistic regression to examine the relationship between EDS/napping status and the risk of PD. The Hosmer-Lemeshow (HL) test was firstly performed to test the goodness-of-fit for logistic models. The likelihood ratio test was used to examine the linear relationship between napping durations and risk of PD. Models were adjusted for age, BMI, smoking, physical activity, depressive symptoms, medical comorbidities, cognitive function, sleep medication use and night-time sleep [duration, efficiency and sleep-disordered breathing (AHI ≥ 15)]. We performed a number of sensitivity analyses including: (i) adjusting further for sleep midpoint time and its SD to explore if the relationship was moderated by chronotype and circadian stability; (ii) a lag time of 2 years, only including PD cases identified after 2 years following the measurement of napping in order to ensure that the EDS or napping preceded PD diagnosis; and (iii) including only PD cases that have been identified by both physician diagnosis and PD medication use. In order to help address the limitation of defining naps using

Table 1. Participants characteristics by excessive daytime sleepiness/objective napping status in 2920 older men

Characteristics Mean ± SD or *N* (%)	EDS/napping status				*P*-value
	No EDS and napping <1 h/day (*N* = 1739)	EDS and napping <1 h/day (*N* = 215)	No EDS and napping ≥1 h/day (*N* = 819)	EDS and napping ≥1 h/day (*N* = 147)	
Age	75.9±5.2	75.2±4.9	77.3±5.9	77.4±5.8	<0.01
Body mass index	26.9±3.6	27.2±4.0	27.6±4.0	28.3±4.3	<0.01
Physical Activity Scale for the Elderly score	152.9±70.3	146.2±69.8	136.9±71.7	128.2±73.9	0.80
Geriatric Depression Scale score	1.5±1.9	2.3±2.3	1.9±2.2	2.9±2.9	<0.01
Modified Mini-Mental State score	93.2±5.5	93.3±5.3	92.4±6.4	90.9±7.7	<0.01
Current smoking	28 (1.6)	5 (2.3)	20 (2.4)	5 (3.4)	0.29
Stroke history	47 (2.7)	12 (5.6)	35 (4.3)	13 (8.8)	<0.01
Coronary heart disease	269 (15.5)	37 (17.2)	165 (20.1)	28 (19.1)	0.03
Hypertension	833 (47.9)	89 (41.4)	450 (54.8)	86 (58.5)	<0.01
Diabetes	201 (11.6)	29 (13.5)	128 (15.6)	28 (19.1)	<0.01
Sleep medication	209 (12.0)	27 (12.6)	83 (10.1)	20 (13.7)	0.40
Nocturnal sleep duration (h)	388.7±68.4	362.8±77.9	387.0±78.2	353.5±89.6	<0.01
Nocturnal sleep efficiency (%)	78.2±11.3	75.2±13.7	79.6±11.6	75.4±16.1	<0.01
Apnoea-hypopnoea index	16.0±14.0	18.7±16.2	17.7±14.9	19.2±16.1	0.01
Sleep mid-point time (SD)	2:50am (29 min)	2:50am (30 min)	2:56am (32 min)	3:03am (35 min)	<0.01
Number of PD cases	47 (2.7)	7 (3.3)	41 (5.0)	11 (7.5)	<0.01

actigraphy, we additionally performed the analysis using ≥10 rather than ≥5 consecutive minutes scored as sleep (inactivity) to define naps. Results are presented as odds ratios (OR) with 95% confidence intervals. Analyses were performed using Stata, version 14.1 (Stata Corp LP, College Station, TX).

Results

Of the 2920 men studied, most were White (90%) and had a mean age of 76.3 years. A total of 215 men (7.4%) reported EDS but had objective napping <1 h per day, 819 (28.1%) had napping ≥1 h/day but did not report EDS and 147 (5.0%) both had EDS and objective napping ≥1 h/day. Men had a mean napping duration of 54 min (range 0–434 min) per day, with 1107 (37.9%) men napping for less than 30 min, 847 (29.0%) napping for 30–59 min and 966 (33.1%) napping for at least 1 h per day. Table 1 shows participants' characteristics by EDS/objective napping status. Men with both EDS and objective napping ≥1 h/day were older, had higher BMI and depressive symptoms, lower cognitive function and were more likely to have a history of stroke, coronary heart disease, hypertension or diabetes.

After 11 years of follow-up, a total of 106 men were diagnosed with PD. The HL test shows good fit of the logistic models ($P = 0.6$). Relative to those with no EDS and napping <1 h/day, the unadjusted OR (95% CI) associated with EDS and napping <1 h/day, no EDS and napping ≥1 h/day, and EDS and napping ≥1 h/day were 1.21 (0.54–2.72), 1.89 (1.23–2.90) and 2.91 (1.48–5.74), respectively. Figure 1 shows the multivariable-adjusted ORs of PD risk for different EDS/napping status groups, using no EDS and napping <1 h/day as the reference group. After adjustment for all covariates, men who napped ≥1 h/day but did not report EDS were almost twice as likely to develop PD (OR= 1.96, 95% CI = 1.25–3.08), and men with both EDS and napping ≥1 h/day were almost three times as likely to develop PD (OR 2.52, 95% CI 1.21–5.27), compared with those with neither EDS nor long objective napping. We did not find an increased risk of PD among men who only reported EDS but had objective napping <1 h/day.

Figure 2 shows the multivariable-adjusted ORs and 95% CIs associated with different categories of napping durations. Longer napping durations were associated with a higher PD risk (overall $P = 0.001$, after multivariable adjustment). Men with a napping duration of at least 1 h per day were more than twice as likely to develop PD compared with those who napped for less than 30 min per day.

Results for sensitivity analyses are summarized in Table 2. Results were similar with further adjustment for sleep midpoint time and its SD. The association remained if we only included PD cases identified at least 2 years after the napping measurement (93 cases) or included cases with both physician diagnosis and PD medication use (47 cases). Effect sizes were largely similar

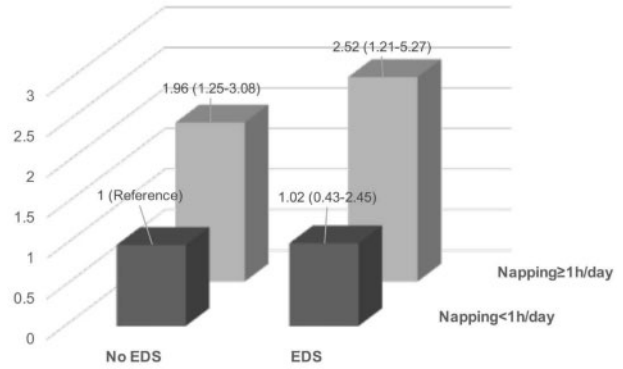

Figure 1. Multivariable-adjusted odds ratios[a] of 11-year Parkinson's disease risk by excessive daytime sleepiness/ objective napping. [a]Adjusted for age, BMI, smoking, physical activity, depression, medical comorbidities, cognitive function, sleep medication use, sleep efficiency, sleep duration and apnoea-hypopnoea index; using no EDS and napping <1 h/day as the reference group. EDS, excessive daytime sleepiness.

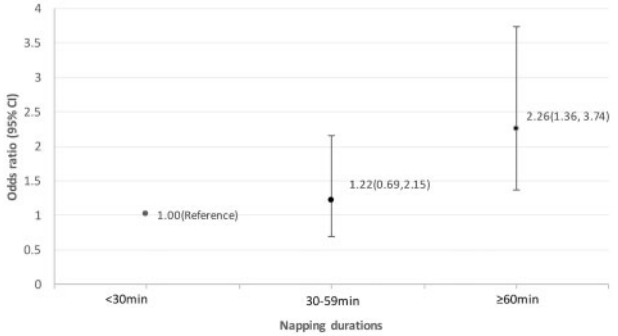

Figure 2. Multivariable[a]-adjusted association of objective napping durations and 11-year Parkinson's disease risk, odds ratio and 95% confidence interval. [a]Adjusted for age, BMI, smoking, physical activity, depression, medical comorbidities, cognitive function, sleep medication use, sleep efficiency, sleep duration and apnoea-hypopnoea index.

when using ≥10 consecutive minutes of inactivity to define naps, despite lower statistical power in certain groups due to the more strict criteria in the definition of naps (data not shown).

Discussion

Among older men, objectively measured long napping was associated with an increased risk of PD 11 years later. Men with both EDS and objective napping ≥ 1 h/day were almost three times as likely to develop PD compared with those with neither EDS nor long napping. Longer napping duration was associated with a higher risk of PD. The association was not explained by comorbidities, cognitive function or night-time sleep disturbances (including sleep apnoea), suggesting that objective measures of napping might be a potentially useful early marker of future risk for PD.

This is the first study, to our knowledge, to report on a longitudinal relationship between objectively measured napping and risk of PD, and to consider the different combinations of the presence of objective napping and subjective reports of EDS in the same population. Previous findings from the Honolulu-Asia Aging Study suggested a more than 3-fold increase in PD risk among older men who reported EDS, but it is unknown whether these men would have had napping if measured objectively.[8] EDS is a well-established symptom among PD patients.[6,30–32] It is not surprising that self-reported EDS or reported napping has been shown to be more strongly related to higher odds of established and recent PD cases.[7] However, our finding did not support a link between subjective EDS without long objective napping and long-term risk of PD. On one hand, questionnaire report of sleepiness is prone to measurement errors that could lead to underestimation of napping behaviours[10,33] and dilution of the overall association between napping and PD risk. On the other hand, reported EDS might only reflect perceived sleepiness but is less likely to capture unplanned naps such as dozing off in front of the television. Older adults might indeed start experiencing excessive unintentional naps without realizing or reporting it, years before the development of clinical PD. Future work should carefully monitor napping behaviours in older adults rather than relying on their reported sleepiness.

One key question in the study of sleep and PD is the direction of the relationship. Our previous study found that the odds of napping among women with PD was seven times as high as the odds among those without PD.[11] In this study, we showed that napping was associated with the development of PD over the subsequent 11 years, and we found similar results when excluding PD cases developed within 2 years after baseline. Therefore, it is likely that napping precedes the diagnosis of PD.

It is well documented that PD patients experience a wide range of sleep disorders.[6,34,35] It has also been hypothesized that sleepiness or napping might arise as a result of night-time sleep disorders,[36,37] which could emerge as a prodromal state to PD.[38] In our study, the association between napping and PD risk remained after adjustment for night-time sleep duration, efficiency or measures of sleep-disordered breathing, making it unlikely that the association was entirely due to these night-time sleep disturbances. Moreover, even if daytime sleepiness results from night-time sleep disorders, napping is a more noticeable behaviour than many other sleep disorders that require costly methods of assessment including polysomnography. Thus, napping might be particularly valuable as a simple preclinical marker for PD.

Table 2. Sensitivity analysis on excessive daytime sleepiness/objective napping status and 11-year Parkinson's disease risk

	OR (95% CI)		
	Multivariable[a] + sleep mid-point time and its SD	[a]Only cases developed > 2 years following napping measurement	[a]Only cases confirmed by both physician diagnosis and medication use
No EDS and napping <1 h/day	1.00 (reference)	1.00 (reference)	1.00 (reference)
EDS and napping <1 h/day	1.02 (0.42, 2.43)	0.99 (0.38, 2.55)	0.87 (0.20, 3.84)
No EDS and napping ≥1 h/day	2.00 (1.27, 3.14)	1.80 (1.11, 2.90)	2.73 (1.37, 5.45)
EDS and napping ≥1 h/day	2.55 (1.22, 5.34)	2.75 (1.27, 5.94)	3.50 (1.22, 10.08)

[a]Adjusted for age, BMI, smoking, physical activity, depression, medical comorbidities, cognitive function, sleep medication use, sleep efficiency, sleep duration and apnoea-hypopnoea index.

There is no known physiological mechanism through which napping itself might cause PD, but it is possible that napping is an integral reflection of the pathological process of PD. In an animal study, it was shown that early abnormalities of the suprachiasmatic nuclei (SCN), which play a central role in regulating sleep-wakefulness cycles, preceded the onset of motor symptoms in a transgenic PD mouse model.[39] Human studies have also found circadian clock gene dysregulation and evidence of circadian rhythm disruption in early-stage PD patients.[40,41] A recent study suggested a link between sleep fragmentation and the presence of Lewy body pathology and substantia nigra neuron loss in older adults without PD.[42] The Braak model of brain pathology staging of PD predicts that the disease begins in the medulla and olfactory bulb and ascends to brainstem structures which regulate the body's circadian clock, before involving the basal ganglia.[43] It is thus plausible that older adults who later develop PD have had ongoing changes in SCN and the circadian rhythms for years, which are manifested by excessive napping, with or without intention. Our findings indicate that unintended naps might be particularly noteworthy, given that even men who showed excessive napping as recorded by actigraphy but without report of EDS had twice the risk of developing PD over 11 years of follow-up. Interestingly, the association remained largely unchanged after further adjustment for a measure of chronotype and circadian stability, suggesting that the association might be through mechanisms other than circadian dysregulation. Excessive unintentional naps as a prodromal feature of PD could help identify individuals at high risk for PD. Future longitudinal studies are needed to confirm our findings and further explore underlying mechanisms.

A few limitations need to be considered. PD diagnosis was based on self-reported physician-diagnosed PD or PD medication use. It is possible that some cases were missed using this approach and some non-cases were misclassified as PD. However, one previous study that used a similar approach has shown good agreement with cases confirmed by neurologists or by expert medical record review.[7] We also observed similar associations when including only cases that were identified by both physician diagnosis and medication use. We do not have information on the exact time when an individual developed PD, and thus are unable to examine by how long napping precedes the diagnosis of PD. However, results were similar when we excluded PD cases identified within the first 2 years of the napping measure, suggesting that napping precedes PD diagnosis by at least 2 years. We also do not have information about family history of PD, and thus were unable to determine if the association was driven by genetic factors. Napping was measured using actigraphy and defined as periods of extreme inactivity. Therefore, some of the episodes we refer to as naps may include periods of quiet wakefulness. We used the same approach as in a previous study in older women[11] to address this problem, by including only inactivity in blocks of at least 5 consecutive minutes as a nap and by defining long objective napping as when the total duration of ≥5-minute naps added up to at least 60 min per day. Since there is no gold standard for defining objective naps in the field, we further increased the threshold of the definition of naps from ≥5-min blocks to ≥10-min blocks of inactivity in sensitivity analysis, and found similar results. Therefore, it is unlikely that the association was mainly driven by the definition of napping. Finally, the Osteoporotic Fractures in Men Study (MrOS) mostly involves older men who are mostly White, and our findings may not be generalizable to women or younger populations. However, men tend to experience more sleepiness in PD[30] and have greater risk for PD.[44] Therefore, the study of napping and PD in men might be of particular interest to improving our understanding of the disease. Notably, whereas the prevalence of PD in the MrOS population is higher than that previously reported in an age-matched

population,[45] PD in general is not very common, and the association could have been underestimated due to the relatively small sample size. Future studies with larger sample sizes are needed to help understand this association.

Conclusions

In summary, our results are the first to show that objectively measured long napping was independently associated with an increased risk of developing PD over 11 years of follow-up among older men. Those with both objective napping $\geq$1 h/day and EDS had almost a 3-fold increase in the risk of PD. Excessive napping as a noticeable behaviour might represent prodromal PD and could be valuable as a preclinical marker for PD. Future research is needed to examine the underlying mechanisms and to explore the predictive value of long napping in addition to established risk predictors for PD. This might open up new avenues for the early detection of PD in the elderly. Identification of high-risk individuals will also allow for opportunities to test putative neuroprotective interventions that could slow down or even prevent PD progression. This will be critical for better management of PD in the long run.

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Author Contributions

Y.L. and K.Y. contributed to the concept and design of the study. Y.L., P.M.C, K.S., S.A.I. and K.Y. participated in the acquisition and analysis of data. Y.L., S.M.G., P.M.C, K.S., S.A.I. and K.Y. contributed to the draft of the manuscript and figures. The references have been checked for accuracy and completeness. Y.L. will act as guarantor for the paper.

Conflict of interest: S.A.I. is a consultant to Merck, Pfizer, Purdue, Acadia, Eisai. K.L.S. has project funding through Merck.

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