



Severity of Daytime Sleepiness and Parkinsonian-Like Symptoms in Korean Adults Aged 50–64 Years

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Background and Purpose While excessive daytime sleepiness can predate Parkinson's disease in late-life, its association with parkinsonian-like (P-L) symptoms in middle age are unknown. Since neurodegeneration can appear decades before a diagnosis of Parkinson's disease, identifying clinical features associated with this early progression is important. The purpose of this study was to determine the association of daytime sleepiness with P-L symptoms in a population-based sample of middle-aged Korean adults.

Methods During 2013 and 2014, daytime sleepiness and P-L symptoms were assessed in 2,063 males and females aged 50–64 years who were participating in the Korean Genome and Epidemiology Study. The severity of daytime sleepiness was quantified by the score on the Epworth Sleepiness Scale (ESS). Self-reported P-L symptoms included nine motor disorders commonly associated with Parkinson's disease. Participants with parkinsonism and related conditions are excluded.

Results The prevalence of excessive daytime sleepiness (ESS score >10) was 7.0%. The frequencies of P-L symptoms ranged from 0.5% (for “trouble buttoning buttons”) to 18.4% (for “handwriting smaller than it once was”). After adjustment for covariates and multiple testing, the relative odds of P-L symptoms comparing the 80th and 20th percentiles of ESS scores was 1.6 ($p=0.001$) for “voice is softer than it once was,” 2.1 ($p<0.001$) for “balance when walking is poor,” and 1.5 ($p=0.002$) for “loss of facial expression.” The prevalence of excessive daytime sleepiness increased from 6.3% to 19.8% when the number of symptoms increased from zero to three ($p=0.004$).

Conclusions In Korean adults aged 50–64 years, daytime sleepiness is significantly associated with P-L symptoms. Whether coexisting daytime sleepiness and P-L symptoms predate extrapyramidal and other impairments in later life warrants further investigation.

Keywords daytime sleepiness; sleep disorders; Parkinson disease; parkinsonism.

Received February 8, 2021

Revised June 25, 2021

Accepted June 25, 2021

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INTRODUCTION

Excessive daytime sleepiness is known to predate the clinical onset of Parkinson's disease.¹ Excessive daytime sleepiness is also associated with Parkinson's disease pathogenesis via the aggregation of α -synuclein and the formation of Lewy pathology.² The latter condition is a noteworthy subclinical benchmark of neuropathological processes and histological changes in Parkinson's disease, which can originate in middle age well before the onset of Parkinson's disease in later life.^{3,4} Given this early initiation of Parkinson's disease neurodegeneration, identifying clinical features associated with related parkinsonian-like (P-L) symptoms in adults in middle age could be important for understanding or monitoring the progression of Parkinson's disease and susceptibility to the development of extrapyramidal disorders. It is not known whether the associations of excessive daytime sleepiness with

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Parkinson's disease and its early neuropathological benchmark also include relationships with clinical findings of P-L symptoms in middle age.

Based on questionnaire data, the purpose of this study was to determine the cross-sectional relationship between the severity of daytime sleepiness and P-L symptoms in a population-based sample of Korean adults aged 50–64 years. Finding such a relationship could be important in promoting investigations of daytime sleepiness and P-L symptoms in an age range where the frequency of clinical Parkinson's disease is low but where underlying Parkinson's disease pathogenesis can first begin.^{3,4} It is also useful to determine if coexisting daytime sleepiness and P-L symptoms are associated with their increased severity in later life. The potential for the combined presence of severe daytime sleepiness and P-L symptoms in middle age to presage extrapyramidal disorders and other impairments is worthy of attention.

METHODS

Background and study sample

The Korean Genome and Epidemiology Study (KoGES) was launched in 2001 as an ongoing population-based follow-up of 5,012 Korean adults aged 40–69 years. The participants include residents of Ansan-si, an industrialized community 32 km southwest of Seoul in the Republic of Korea. At the time of enrollment, cohort members underwent comprehensive physical examinations along with the collection of data on demographic characteristics, medical history, health conditions, family disease history, and lifestyle. The subjects have subsequently been followed biennially in repeated examinations. The study procedures adhered to institutional guidelines with approval from the Korea University Ansan Hospital Institutional Review Board (2006AS0045). All participants provided informed consent. Further details are available elsewhere⁵ and on the Korea National Institute of Health KoGES website (<https://nih.go.kr/contents.es?mid=a40401020000>).

Determination of daytime sleepiness severity and P-L symptoms

Data used in this study are from the seventh examination cycle applied to 3,000 KoGES participants (during 2013 and 2014). At that time, questionnaires were used to cross-sectionally collect data on the severity of daytime sleepiness and the prevalence of P-L symptoms. The daytime sleepiness severity was quantified as a score from a weighted sum of sleep tendencies associated with eight activities from the Epworth Sleepiness Scale (ESS).⁶ Scores can range from 0 to 24, with higher scores indicating more-severe levels of daytime sleepiness. P-L symptoms were assessed using a questionnaire for

Table 1. Prevalence of P-L symptoms in the 2,063 KoGES participants

P-L symptom	Prevalence
Difficulty arising from a chair	4.0 (82)
Handwriting smaller than it once was	18.4 (379)
Voice is softer than it once was	8.6 (177)
Balance when walking is poor	3.1 (63)
Feet suddenly seem to freeze in doorways	1.2 (25)
Loss of facial expression	12.1 (249)
Arms and legs shake	2.0 (42)
Trouble buttoning buttons	0.5 (10)
Shuffling feet and tiny steps when walking	1.8 (37)

Data are % (n) values.

KoGES, Korean Genome and Epidemiology Study; P-L, parkinsonian-like.

screening Parkinson's disease.^{7,8} The questionnaire is easy to self-administer, and it addresses the presence of nine motor symptoms commonly associated with Parkinson's disease (Table 1).

Other characteristics

Other characteristics included age, sex, current smoking status, body mass index, regular exercise, cognitive function, depressed mood, sleep-related features, and the use of sleep medications. Body mass index was measured as the ratio of a subject's weight divided by their height squared. Regular exercise was defined as ≥ 30 minutes of exercise that resulted in sweating on at least three occasions per week. Cognitive function was assessed using performance scores on the Montreal Cognitive Assessment (MoCA) instrument with modifications suitable for Korean samples,⁹ with lower scores reflecting worse cognition. Depressed mood was defined as a Beck Depression Inventory score of ≥ 16 .¹⁰⁻¹²

Sleep-related features include questionnaire responses to the nighttime sleep duration, nap times, insomnia, and habitual snoring. For nighttime sleep duration, subjects were asked to provide their actual nighttime sleep times in hours and minutes on weekends and weekdays. Nighttime sleep duration was then defined in whole hours and fractions thereof as $2/7 \times (\text{weekend duration}) + 5/7 \times (\text{weekday duration})$. Typical nap times were recorded in minutes. Insomnia was defined when this occurred on ≥ 3 nights/week for > 1 month, while habitual snoring was defined as this occurring ≥ 4 times/week. The use of sleep medications was defined as taking pharmacological aids for improving sleep behavior (prescribed or over the counter) at any time during the previous month.

Data exclusions

Subjects ≥ 65 years of age ($n=724$) and those with missing or incomplete data on P-L symptoms ($n=102$) were excluded. Subjects with a self-reported history of parkinsonism, stroke,

head trauma, restless leg syndrome, narcolepsy, or depression were also excluded ($n=111$). Seven subjects were reported to have parkinsonism, 37 had stroke, 17 had head trauma, 3 had restless leg syndrome, 1 had narcolepsy, and 46 had depression. The final sample available for analysis comprised 2,063 individuals (998 males and 1,065 females) aged 56.6 ± 3.5 years (mean \pm standard deviation, age range 50–64 years).

Statistical methods

The prevalence of each P-L symptom as obtained from the Parkinson's disease screening survey is reported as the overall percentage value. Study characteristics are presented as mean \pm standard deviation or percentage values for subjects across three strata of daytime sleepiness severity based on the ranges of ESS scores. The strata of daytime sleepiness severity were defined as low (ESS scores of 0–5), moderate (ESS scores of 6–10), and high (ESS scores >10). An ESS score of >10 is commonly considered to be evidence of excessive daytime sleepiness.

Other than age, the average and percentage values were adjusted for age across the daytime sleepiness strata based on standard covariance analysis methods.^{13,14} General linear regression was used to model continuous dependent variables, with age and daytime sleepiness strata appearing as independent variables. Logistic regression was applied to dependent variables that were dichotomous. While strata of daytime sleepiness were selected to illustrate patterns of association, tests for trends were based on modeling daytime sleepiness (without the use of cutoff points) across the full range of actual ESS scores (i.e., 0–24). Although an ESS score of >10 is commonly used to define excessive daytime sleepiness, it is not a universally accepted demarcation since the alternative criteria range from >7 to >15 .^{15–19} These discrepancies form the basis for our decision to model excessive daytime sleepiness across the full range of ESS scores, which also meant that the results were invariant to the arbitrary selection of strata for defining excessive daytime sleepiness.

Estimated age-adjusted percentages for each P-L symptom are also provided across strata of daytime sleepiness severity using the same analysis-of-covariance procedures and logistic regression models described in the previous paragraph. In the presence of a small number of P-L symptoms, logistic regression models were analyzed using exact testing methods.²⁰ Models were also analyzed after adjusting for additional covariates. When modeling the severity of daytime sleepiness using actual ESS scores (ranging from 0 to 24), regression coefficients provided estimates of the relative odds of each P-L symptom for the 80th versus the 20th percentile of ESS scores (along with 95% confidence intervals). Among the P-L

symptoms that were significantly associated with daytime sleepiness severity, age- and covariate-adjusted percentages of subjects with moderate and high daytime sleepiness severities were derived according to the P-L symptom count.

All reported p values are based on two-sided tests of significance and adjusted for multiple testing using Bonferroni correction.

RESULTS

Among the 2,063 KoGES participants, the frequencies of low, moderate, and high daytime sleepiness severities were 58.8% ($n=1,213$), 34.2% ($n=705$), and 7.0% ($n=145$), respectively. For P-L symptoms (Table 1), the prevalence was highest for “handwriting smaller than it once was” (18.4%) and “loss of facial expression” (12.1%), and lowest for “feet suddenly seem to freeze in doorways” (1.2%) and “trouble buttoning buttons” (0.5%).

The prevalence of each P-L symptom across strata of daytime sleepiness severity is presented in Table 2. After age adjustment and correcting for multiple testing, the frequency of “voice is softer than it once was” increased monotonically from 6.6% to 16.5% as the daytime sleepiness severity increased ($p<0.001$). There were also monotonic increases in the frequencies of “balance when walking is poor” (from 1.7% to 7.5%, $p<0.001$) and “loss of facial expression” (from 9.2% to 20.0%, $p<0.001$). While the frequencies of “difficulty arising from a chair” and “shuffling feet and tiny steps when walking” were high in the most-severe daytime sleepiness stratum, consistent increases with daytime sleepiness severity were modest or less clear. For the remaining P-L symptoms there were only weak associations with daytime sleepiness.

Table 3 provides further information on the KoGES sample in terms of potential confounders of the relationship between daytime sleepiness severity and P-L symptoms. Among the variables, daytime sleepiness was unrelated to age, cigarette smoking, body mass index, or the frequency of regular exercise. The percentage of KoGES subjects who were female decreased with increasing daytime sleepiness severity ($p<0.001$). Females comprised 37.3% of those with high daytime sleepiness severity, compared with around 50% of those whose daytime sleepiness severity was low or moderate. Cognitive function decreased (mean MoCA score from 24.3 to 23.7, $p=0.017$) and the frequency of depressed mood increased (from 6.0% to 17.9%, $p<0.001$) as the severity of daytime sleepiness increased.

Among the concomitant sleep features in Table 3, the mean duration of nighttime sleeping decreased as the daytime sleepiness severity increased ($p<0.001$). The mean sleep duration was 18 minutes (0.3 hours) shorter in the highest than

Table 2. Age-adjusted percentages of subjects with a P-L symptom according to daytime sleepiness severity

PL-symptom	Daytime sleepiness severity*			p [†]	Adjusted p [‡]
	Low (n=1,213, 58.8%)	Moderate (n=705, 34.2%)	High (n=145, 7.0%)		
Difficulty arising from a chair	2.9 (36)	5.5 (38)	5.5 (8)	0.003	0.029
Handwriting smaller than it once was	16.6 (201)	21.4 (151)	18.6 (27)	0.006	0.053
Voice is softer than it once was	6.6 (81)	10.3 (72)	16.5 (24)	<0.001	<0.001
Balance when walking is poor	1.7 (21)	4.5 (31)	7.5 (11)	<0.001	<0.001
Feet suddenly seem to freeze in doorways	0.1 (12)	0.7 (5)	5.5 (8)	0.031	0.275
Loss of facial expression	9.2 (112)	15.3 (108)	20.0 (29)	<0.001	<0.001
Arms and legs shake	2.0 (24)	1.7 (12)	4.1 (6)	0.496	1.0
Trouble buttoning buttons	0.3 (4)	0.7 (5)	0.7 (1)	0.285	1.0
Shuffling feet and tiny steps when walking	1.4 (17)	1.9 (13)	4.8 (7)	0.005	0.044

Data are % (n) values.

*Daytime sleepiness severity: Low, ESS score 0-5; Moderate, ESS score 6-10; High, ESS score >10; †Test for trend across increasing ESS scores (from 0 to 24); ‡Adjusted for multiple testing.

ESS, Epworth Sleepiness Scale; P-L, parkinsonian-like.

Table 3. Age and age-adjusted averages and percentages of selected study characteristics and related sleep features according to daytime sleepiness severity

Sample characteristic	Daytime sleepiness severity*			p [†]
	Low (n=1,213)	Moderate (n=705)	High (n=145)	
Age (yr)	56.7±3.4	56.4±3.5	56.7±3.4	0.251
Sex, female	54.1 (656)	50.3 (355)	37.3 (54)	<0.001
Cigarette smoker	14.6 (176)	15.0 (107)	11.1 (16)	0.396
Body mass index (kg/m ²)	24.6±2.9	24.7±3.0	24.4±3.2	0.764
Regular exercise	50.2 (608)	50.5 (357)	42.8 (62)	0.138
MoCA score	24.3±2.9	24.0±2.9	23.7±2.9	0.017
Depressed mood	6.0 (73)	10.8 (76)	17.9 (26)	<0.001
Related sleep feature				
Nighttime sleeping (hr)	6.3±1.2	6.2±1.2	6.0±1.3	<0.001
Napping (min)	19±35	24±38	29±45	<0.001
Insomnia	18.8 (228)	24.4 (171)	37.2 (54)	<0.001
Habitual snoring	21.7 (264)	24.2 (170)	28.2 (41)	0.066
Sleep medications	2.1 (25)	2.1 (15)	3.4 (5)	0.486

Data are mean±standard deviation or % (n) values. Some data were missing for napping duration (n=1) and MoCA scores (n=2). All had low severity of daytime sleepiness.

*Daytime sleepiness severity: Low, ESS score 0-5; Moderate, ESS score 6-10; High, ESS score >10; †Test for trend across increasing ESS scores (from 0 to 24).

ESS, Epworth Sleepiness Scale; MoCA, Montreal Cognitive Assessment.

the lowest daytime sleepiness severity stratum. As a possible consequence, the duration of daily napping increased with the daytime sleepiness severity (p<0.001). The mean nap duration was 10 minutes longer in the highest than the lowest daytime sleepiness severity stratum. Additionally, the frequency of insomnia increased with the daytime sleepiness severity (from 18.8% to 37.2%, p<0.001). Although the find-

Table 4. Covariate-adjusted* relative odds of a P-L symptom comparing the 80th and 20th percentiles of ESS scores[†]

P-L symptom	Relative odds (95% CI)	p [†]	Adjusted p [‡]
Difficulty arising from a chair	1.5 (1.0-2.1)	0.039	0.196
Handwriting smaller than it once was	1.2 (1.0-1.5)	0.066	0.330
Voice is softer than it once was	1.6 (1.2-2.1)	<0.001	0.001
Balance when walking is poor	2.1 (1.4-3.0)	<0.001	<0.001
Loss of facial expression	1.5 (1.2-1.9)	<0.001	0.002

*Adjusted for age, sex, cigarette smoking, body mass index, regular exercise, MoCA score, and depressed mood; †80th and 20th percentiles correspond to ESS scores of 8 and 2, respectively; ‡Test for trend across increasing ESS scores (from 0 to 24); §Adjusted for multiple testing. CI, confidence interval; ESS, Epworth Sleepiness Scale; MoCA, Montreal Cognitive Assessment; P-L, parkinsonian-like.

ing was not significant (p=0.066), habitual snoring also became more frequent as the daytime sleepiness severity increased. The use of sleep medications was too uncommon to allow for an assessment of its relationship with daytime sleepiness.

Table 4 adds to Table 2 by providing estimates of the relative odds of each P-L symptom comparing the 80th and 20th percentiles of ESS scores after further adjustment for sex, cigarette smoking, body mass index, regular exercise, MoCA score, and depressed mood. Here, the 80th and 20th percentiles correspond to ESS scores of 8 and 2, respectively. Findings for four of the nine P-L symptoms in Table 2 are not provided since their prevalence was low (additional adjustment for covariates also prevents a meaningful assessment of their relationship with daytime sleepiness).

Three of the five remaining P-L symptoms continued to have significant associations with daytime sleepiness severity after correcting for multiple testing. For these three symptoms, the relative odds of P-L symptoms comparing the 80th

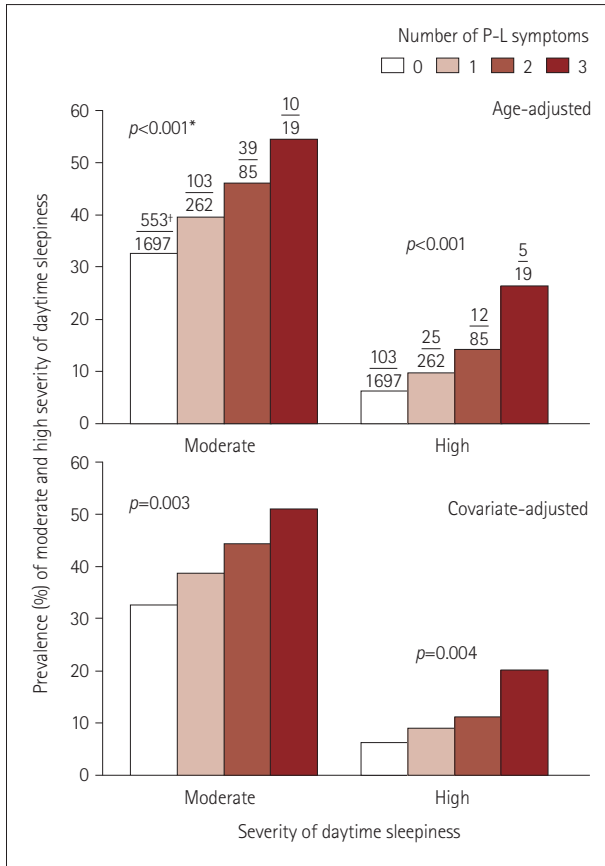


Fig. 1. Age- and covariate-adjusted percentages of subjects with moderate and high severities of daytime sleepiness according to the number of P-L symptoms. P-L symptoms include those that are significant in Table 4 (“voice is softer than it once was,” “balance when walking is poor,” and “loss of facial expression”). Covariate-adjusted percentages include adjustment for age, sex, cigarette smoking, body mass index, regular exercise, Montreal Cognitive Assessment score, and depressed mood. *Test for trend; †Number with this level of daytime sleepiness/sample size. P-L, parkinsonian-like.

and 20th percentiles of ESS scores was 1.6 ($p=0.001$) for “voice is softer than it once was,” 2.1 ($p<0.001$) for “balance when walking is poor,” and 1.5 ($p=0.002$) for “loss of facial expression.” The findings remained significant after adjustment for concomitant sleep features (nighttime sleep and nap durations, insomnia, and habitual snoring). Additionally, there was no evidence that the association between daytime sleepiness severity and each P-L symptom varied with the levels of the other sleep behaviors.

Fig. 1 further describes the frequencies of moderate and high daytime sleepiness severities as the prevalence of the three P-L symptoms increased among the cohort members. As the symptom count increased from zero to three, the covariate-adjusted prevalence of moderate daytime sleepiness severity increased from 32.8% to 50.8% (bottom-left panel of Fig. 1, $p=0.003$). The corresponding prevalence of high daytime sleepi-

ness severity increased from 6.3% to 19.8% (bottom-right panel of Fig. 1, $p=0.004$).

DISCUSSION

This study found that the severity of daytime sleepiness was significantly associated with P-L symptoms among Korean adults aged 50–64 years. These findings are important since they relate to an age range where the frequency of clinical Parkinson’s disease is low. Additionally, since the pathogenesis of Parkinson’s disease can predate the diagnosis of this disease by as long as 30 years,^{3,4} identifying clinical features associated with P-L symptoms in middle age could be useful in monitoring the progression of Parkinson’s disease and susceptibility to the development of extrapyramidal impairments. Whether the combination of severe daytime sleepiness and P-L symptoms are a sign of an initiating phase in the pathogenesis of Parkinson’s disease deserves further investigation. Notwithstanding any relationship with this process, there exists the possibility of daytime sleepiness severity and P-L symptoms progressing to more-severe states of sleep disorders and physical dysfunction.

Associations between daytime sleepiness severity and P-L symptoms in the KoGES are also independent of other characteristics, making it difficult to identify mechanisms that explain the observed findings based on the suspected confounders analyzed in this study. Additionally, the cross-sectional design of this study means that the causal directions of associations between daytime sleepiness severity and P-L symptoms cannot be addressed. Whether excessive daytime sleepiness and P-L symptoms in middle age are associated with increased aggravation of sleep and movement disorders in later life would be best determined by longitudinal assessments. However, such assessments could be costly since they are likely to require enrollment of large cohorts of middle-aged individuals and involve long durations of follow-up into late-life.

While there is evidence that excessive daytime sleepiness can predate Parkinson’s disease,¹ relationships between daytime sleepiness severity and P-L symptoms in middle age might not be related to the risk of Parkinson’s disease. It might be reasonable that these conditions evolve together through shared pathophysiological processes within regions of the brain that jointly affect sleep, wakefulness, and motor dysfunction, such as the loss of neurons in the locus coeruleus, hypothalamus, and ascending reticular activating system. Impairments in noradrenergic, serotonergic, and dopaminergic activities might be involved. The neurocircuitry of motor control, such as in the basal ganglia, might also play a role in sleep–wakefulness regulation and in maintenance of daytime alertness.^{21,22}

The severity of daytime sleepiness could be related to P-L symptoms via the same mechanisms that link excessive daytime sleepiness with the aggregation of α -synuclein and the formation of Lewy pathology,² including glymphatic processes associated with the clearance of β -amyloid.²³⁻²⁵ In particular, neuroimaging studies have shown that excessive daytime sleepiness can longitudinally increase the deposition of β -amyloid.²⁶ Other studies suggest that the same glymphatic pathways could affect the accumulation of α -synuclein.^{23-25,27} Interstitial regions are important in glymphatic function, and reportedly include α -synuclein that can synergistically interact with β -amyloid,^{23,26,28} which possibly at least partially explains the appearance of Lewy pathology in most subjects with sporadic Alzheimer's disease.²⁵ Sleep disturbances have also been shown to be related to α -synuclein in the cerebrospinal fluid.²⁷

While the relationship between daytime sleepiness severity and each P-L symptom is independent of nighttime sleep and nap durations, insomnia, and habitual snoring, there is little evidence that these associations vary with the levels of these other sleep behaviors. The findings are consistent with those from the Honolulu-Asia Aging Study, which found that excessive daytime sleepiness had similar associations with the incidence of Parkinson's disease and the prevalence of Lewy pathology across strata of concomitant sleep features.^{1,2} Among sleep disorders, excessive daytime sleepiness is also the most common reason for referral to neurology sleep clinics.¹⁶

In spite of this study being based on simple (self-administered) questionnaires, it is noteworthy that the associations of excessive daytime sleepiness with Parkinson's disease and Lewy pathology in late-life also include associations between daytime sleepiness severity and P-L symptoms in middle age. Unfortunately, severe daytime sleepiness is clinically complex to measure and understand since it can involve numerous underlying causes. The quality of measurements often depends on questionnaire formats and the age distributions of study subjects. While this study focused on the severity of daytime sleepiness using actual ESS scores ranging from 0 to 24, estimates of the prevalence of excessive daytime sleepiness (often defined by different diagnostic criteria or ESS cutoffs¹⁵⁻¹⁹) can vary widely. In healthy controls or in the absence of Parkinson's disease, the prevalence of excessive daytime sleepiness is reported to range from 1% to 47%.^{1,2,15,17,29-31} Failing to recognize excessive daytime sleepiness in the elderly can lead to further underestimates of its frequency.¹⁵

For identifying P-L symptoms, the questionnaire used in this study is considered valid and reliable for Parkinson's disease screening in community-based surveys involving elderly Korean adults (≥ 65 years of age).⁸ Unfortunately, the validity of each P-L screening item is not clear. For example, it is like-

ly that positive responses to "balance when walking is poor" include a broad array of balance impairments that may have nothing to do with parkinsonism or the underlying progression to Parkinson's disease. Indeed, the presence of a P-L symptom does not imply the presence of parkinsonism. The broad definition of parkinsonism can also include individuals with atypical or secondary parkinsonism. Although excessive daytime sleepiness is known to be associated with the future risk of Parkinson's disease, the positive predictive power is low (< 6 per 1,000 person-years of follow-up),¹ as is likely also the case for any individual P-L symptom. Whether the coexistence of the symptoms of "voice is softer than it once was," "balance when walking is poor," and "loss of facial expression" with excessive daytime sleepiness improves such predictions is unknown (Fig. 1).

For the younger KoGES sample (< 65 years of age), where the validation and reliability of the Parkinson's disease screening instrument have not been addressed, it was never our intent to identify cases of Parkinson's disease. We also expected the frequency of Parkinson's disease to be exceedingly low. The prevalence of Parkinson's disease in Korea is estimated to be 0.14% among those aged 55-59 years,³² while the age range of the KoGES subjects is 50-64 years. Based on self-reporting, there are no cases of parkinsonism in the KoGES data, and presumably the same is true for Parkinson's disease. Data on the use of medications that could potentially induce P-L symptoms in the KoGES sample are not available.

In contrast to screening for Parkinson's disease, our purpose was to identify movement disorders commonly associated with Parkinson's disease as they might exist in adults in middle age (< 65 years of age). P-L symptoms can also occur with a higher frequency than Parkinson's disease, making them easier to investigate in younger samples. In the KoGES, P-L symptoms reached frequencies as high as 18.4% for "handwriting smaller than it once was" and 12.1% for "loss of facial expression" (Table 1). While the frequency of P-L symptoms has been reported elsewhere for older individuals (≥ 65 years of age),³³ we are not aware of published findings for younger subjects.

Overall, analyses of KoGES data need to consider limitations that are common in large-scale population-based studies, many of which are difficult to avoid. While the initial design of the KoGES included the enrollment of a representative sample of subjects from the general Korean population (without selection of special groups of individuals), the generalizability remains uncertain, especially for other ethnicities within Korea and for Asian communities outside of Korea.

An additional constraint includes the inability to adjust for confounders that are unknown or were never measured. While adjustments were made for cognition (based on MoCA

screening), depressed mood (from the Beck Depression Inventory), use of sleep medications, and other sleep disorders, confounding remains an issue. Confounding is likely to continue after additionally excluding subjects with a self-reported history of parkinsonism, stroke, head trauma, restless leg syndrome, narcolepsy, and depression. However, in the absence of a direct pathway, observing a relationship between excessive daytime sleepiness and the accumulation of several P-L symptoms could still be useful in longitudinal monitoring.

While excessive daytime sleepiness has associations with the incidence of Parkinson's disease and its underlying pathogenesis,^{1,2} the late-life consequences of associations between daytime sleepiness severity and P-L symptoms in middle-aged adults are unknown. Whether daytime sleepiness and P-L symptoms in middle age are associated with increased impairment in these or related conditions in later life warrants further investigation. The use of simple questionnaires to assess daytime sleepiness severity and P-L symptoms in population-based studies could play an important role in addressing this issue.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

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Conflicts of Interest

Robert J. Thomas is co-inventor and patent holder of the ECG-derived sleep spectrogram, which may be used to phenotype sleep quality and central/complex sleep apnea. The technology is licensed by Beth Israel Deaconess Medical Center to MyCardio, LLC. Dr. Thomas is also co-inventor and patent holder of the Positive Airway Pressure Gas Modulator, being developed for treatment of central/complex sleep apnea. He is a consultant to Jazz Pharmaceuticals and GLG Councils and was a consultant in software development for DeVilbiss-Drive. There are no other disclosures or conflicts of interest to report.

Funding Statement

Supported by the Korea Centers for Disease Control and Prevention (grant numbers 2011-E71004-00, 2012-E71005-00, 2013-E71005-00, 2014-E71003-00, 2015-P71001-00, and 2016-E71003-00), the Ministry of Science and ICT (grant number 2012-0009830), and the Brain Pool Program from the National Research Foundation of Korea (grant numbers 2018H1D3A2065629 and 2019H1D3A2A01101353).

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