



Original Contribution

A Prospective Study of Night Shift Work, Sleep Duration, and Risk of Parkinson's Disease

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The authors prospectively investigated whether working rotating night shifts was associated with the risk of Parkinson's disease among 84,794 female nurses who reported years of night shift work in 1988 (the US Nurses' Health Study). After 975,912 person-years of follow-up (1988–2000), 181 incident Parkinson's disease cases were documented. Compared with nurses who never worked rotating night shifts, those with 15 years or more of night shift work had a 50% lower risk of Parkinson's disease after adjustment for age and smoking (95% confidence interval: 0.26, 0.97; $p_{\text{trend}} = 0.01$). Sleep duration was positively associated with Parkinson's disease risk: The relative risk was 1.84 (95% confidence interval: 0.99, 3.42) when comparing nurses who reported 9 or more hours of sleep per day with those who slept 6 hours or less ($p_{\text{trend}} = 0.005$). These data suggest that working night shifts may be protective against Parkinson's disease or that low tolerance for night shift work is an early marker of Parkinson's disease. Conversely, habitual longer sleep duration may be an earlier marker of Parkinson's disease. Because of the novelty and the exploratory nature of these findings, confirmation is needed.

cohort studies; Parkinson disease; sleep; sleep disorders, circadian rhythm

Abbreviation: NSAID, nonsteroidal antiinflammatory drug.

Working rotating night shift disrupts circadian rhythms and may have a wide range of physiologic, psychological, and social effects on shift workers (1). In previous studies, shift work has been linked to higher risks of some chronic diseases, including cardiovascular disease and certain types of cancers (1–5). Shift work may further induce physical or mental stresses (6) and hormonal changes (7) that potentially may have implications on the etiology of Parkinson's disease (8, 9). However, to our knowledge, there have been no epidemiologic data on whether working rotating night shift is associated with the risk of Parkinson's disease. The Nurses' Health Study, a large prospective cohort of nurses with decades of follow-up, has collected information on the

work history of rotating night shifts in 1988 and thus provided a unique opportunity to examine this association. Because shift workers may have abnormal sleep patterns (10), we also examined whether sleep duration was related to Parkinson's disease risk.

MATERIALS AND METHODS

Study population

The Nurses' Health Study cohort included 121,700 registered nurses who provided detailed information about

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their medical history and lifestyle practices in 1976 (11). Follow-up questionnaires have been mailed to participants every 2 years thereafter to update information on potential risk factors for chronic diseases and to ascertain whether major medical events have occurred. A question on lifetime occurrence of Parkinson's disease was first included in 1994, and new occurrence was subsequently assessed biennially. Information on work history of rotating night shifts was elicited in the 1988 questionnaire. The current analyses were limited to nurses who were free of Parkinson's disease and provided information on their night work history in 1988. We followed 84,794 eligible nurses from baseline in 1988 to the date of first Parkinson's disease symptoms, the date of death, or the end of the follow-up (May 31, 2000), whichever occurred first. The study was approved by the Human Subjects Committee at the Brigham and Women's Hospital.

Parkinson's disease case ascertainment

The identification of Parkinson's disease cases in this study has been detailed elsewhere (12). Briefly, after obtaining permission from participants who reported a new diagnosis of Parkinson's disease, we asked the treating neurologist (or internist if the neurologist did not respond) to complete a questionnaire to provide her/his judgment on the certainty of the diagnosis or to send a copy of the medical record. From the questionnaire, we also elicited information on the date that the first symptoms of Parkinson's disease were noticed and the date when the disease was first clinically diagnosed. A case was confirmed if the Parkinson's disease diagnosis was considered definite or probable by the treating neurologist or internist, or if the medical record included either a final diagnosis of Parkinson's disease made by a neurologist or clinical evidence of at least two of the three cardinal signs (rest tremor, rigidity, and bradykinesia) in the absence of an alternative diagnosis for the parkinsonian symptoms. Review of medical records was conducted by investigators who were blinded to the exposure status. Overall, more than 80 percent of the diagnoses were confirmed by the treating neurologists (13).

Exposure and covariate assessments

In 1988, Nurses' Health Study participants were asked for the total years of rotating night shifts, which were defined as "having worked rotating night shifts with at least three nights per month in addition to working days or evenings in that month." Eight categories were provided (in years): never, 1–2, 3–5, 6–9, 10–14, 15–19, 20–29, 30 or more. Information on smoking, body weight, physical activity, menopausal status, postmenopausal hormone use, and physical examination during the previous 2 years was also collected in 1988 and on all consecutive follow-up questionnaires. Adult height was asked on the 1976 questionnaire, and body mass index was calculated as weight (kg)/height (m)². The use of aspirin and other nonsteroidal antiinflammatory drugs (NSAIDs) was assessed in 1980. Participants who took nonaspirin NSAIDs as two or more tablets per day were defined as regular users.

On the 1986 questionnaire, we collected information on total hours of sleep in a 24-hour period with 1-hour increments from "5 hours or less" to "11 hours or more." Dietary information, including consumption of caffeinated drinks and alcohol, was also collected in 1986 with a widely validated food frequency questionnaire and was updated every 4 years thereafter (14).

Statistical analyses

Nurses who reported having worked more than 15 years of rotating night shifts were grouped together for sample size considerations. Similarly, we categorized hours of sleeping into four levels from sleeping 6 hours or less to 9 hours or more. Relative risks were derived from Cox proportional hazards models, controlling for age (in years) and smoking status (never smoker, past smoker, or current smoker: 1–14 or ≥ 15 cigarettes/day). Further adjustment for alcohol consumption (0, 1–4.9, 5–9.9, 10–14.9, ≥ 15 g/day), physical activity (in quintiles), body mass index (< 23 , 23–24.9, 25–26.9, 27–29.9, and ≥ 30 kg/m²), caffeine intake (in quintiles), postmenopausal estrogen use (premenopause, nonusers, and current users), and regular use of nonaspirin NSAIDs (yes/no) did not materially change the results. Therefore, we present age- and smoking-adjusted relative risks in our main analyses. The *p* value for linear trend was calculated by using the median of each category as a continuous variable in the Cox models. To minimize residual confounding due to cigarette smoking and to examine whether the night shift–Parkinson's disease relation was modified by smoking status, we repeated the analyses separately among never smokers and ever smokers. Stratified analyses were also conducted according to age groups (< 60 and ≥ 60 years). For all relative risks, we calculated 95 percent confidence intervals and two-tailed *p* values.

The analyses on sleep duration and Parkinson's disease risk included Nurses' Health Study participants who were free of Parkinson's disease and provided sleep information in 1986 ($n = 82,574$). Because sleep disorders are very common among Parkinson's disease patients (15) and their temporal relation to Parkinson's disease occurrence is not clear, we performed further lag time analyses by excluding the first 4 or 8 years of follow-up to minimize the possibility of reverse causality and to explore the temporal relation. Finally, to examine whether years of shift work and hours of sleep were independent of each another in their relations to Parkinson's disease, we included them simultaneously in the same analytical model.

RESULTS

Compared with women who never worked on rotating night shifts, nurses who reported 15 or more years of night shift work were older and more likely to be current smokers and regular users of nonaspirin NSAIDs, to drink more coffee but less alcohol, and to have a higher body mass index (table 1). Night shift workers also tended to sleep slightly less and were slightly more likely to seek medical

TABLE 1. Age-adjusted population characteristics according to years of working rotating night shifts reported in 1988 among participants of the Nurses' Health Study*

	Years of night shift				
	0	1–2	3–5	6–14	≥15
Participants (no.)	34,176	20,265	14,172	9,806	6,375
Age, years (mean)	54.0	53.7	55.1	55.1	56.8
Current smokers (%)	17.5	16.9	18.7	22.8	24.7
Past smokers (%)	37.1	38.9	38.7	36.2	33.3
Caffeine intake in 1986 (mg/day)	276.3	273.5	281.9	297.3	316.9
Alcohol intake in 1986 (g/day)	6.2	6.5	6.3	5.8	5.2
Hours of sleep in 1986 (hours/day)	7.1	7.0	7.0	6.9	6.7
Physical activity (MET†-hours/day)	13.5	14.5	15.0	14.5	14.9
Body mass index (kg/m ²)	25.3	25.3	25.7	26.2	26.9
Physical examination in previous 2 years (%)	82.6	83.0	83.1	83.8	84.4
For symptoms (%)	18.1	19.1	20.5	21.2	21.5
Regular use of nonaspirin NSAIDs† in 1980 (%)	3.2	3.6	3.7	3.9	4.4
Ever use of postmenopausal hormone (%)	40.3	41.0	41.0	41.0	39.1

* Except for number of participants and age, the means and proportions were directly standardized to the age distribution of the cohort.

† MET, metabolic equivalent; NSAID, nonsteroidal antiinflammatory drug.

examination for symptoms. The duration of night shift work was, however, not related to physical activity and the use of postmenopausal hormones.

During 975,912 person-years of follow up, a total of 181 Parkinson's disease cases were identified. There was a significant inverse association between years of working night shifts and the risk of Parkinson's disease (table 2). The association persisted after further adjustment for other potential confounders or after excluding the first 4 years of follow-up (table 2). Similar results were obtained in analyses stratified by age groups or smoking status, although the number of cases included in each subgroup analysis was small. The relative risk of Parkinson's disease, comparing the extreme two categories, was 0.68 among nurses aged 60 years or younger ($p_{\text{trend}} = 0.3$) and 0.40 among older

nurses ($p_{\text{trend}} = 0.02$), and it was 0.35 among never smokers ($p_{\text{trend}} = 0.04$) and 0.69 among ever smokers ($p_{\text{trend}} = 0.1$).

Longer sleep duration was associated with a higher risk of Parkinson's disease after adjustment for age and smoking (table 3). Similar risk estimates with significant trends were found in the multivariate analysis and analysis excluding the first 4 or 8 years of follow-up (table 3). When adjusted simultaneously, sleep hours and years of shift work were each independently associated with Parkinson's disease risk. Compared with the risk for nurses who slept 6 hours or less, the relative risks for those who slept 7, 8, and 9 hours were 1.10, 1.59, and 1.80, respectively ($p_{\text{trend}} = 0.008$); using nurses without night shift experience as the referent, we found the relative risks for nurses who had worked on night shift for 1–2 years, 3–5 years, 6–14 years, and 15 years

TABLE 2. Relative risk of Parkinson's disease according to years of working rotating night shifts among participants of the Nurses' Health Study, 1988–2000

	Years of night shift					P_{trend}
	0	1–2	3–5	6–14	≥15	
Person-years	394,171	234,441	163,171	112,105	72,025	
No. of cases	87	36	34	14	10	
Relative risk (95% confidence interval)						
Age and smoking adjusted	1.0	0.71 (0.48, 1.05)	0.85 (0.57, 1.26)	0.52 (0.30, 0.92)	0.50 (0.26, 0.97)	0.01
Multivariate*	1.0	0.71 (0.48, 1.04)	0.86 (0.58, 1.28)	0.54 (0.31, 0.95)	0.54 (0.28, 1.04)	0.03
Excluding the first 4 years of follow-up†	1.0	0.79 (0.51, 1.24)	0.89 (0.56, 1.42)	0.59 (0.31, 1.12)	0.51 (0.23, 1.11)	0.05

* Further adjustment for caffeine intake, use of estrogen, use of nonaspirin nonsteroidal antiinflammatory drugs, alcohol consumption, body mass index, and physical activity.

† Adjusted for age and smoking.

TABLE 3. Relative risk of Parkinson's disease according to hours of sleep among participants of the Nurses' Health Study, 1986–2000

	Hours of sleep				<i>P</i> _{trend}
	≤6	7	8	≥9	
Person-years	334,104	456,622	261,913	51,356	
No. of cases	44	72	59	13	
Relative risk (95% confidence interval)					
Age and smoking adjusted	1.0	1.23 (0.84, 1.78)	1.65 (1.11, 2.43)	1.84 (0.99, 3.42)	0.005
Multivariate*	1.0	1.20 (0.82, 1.74)	1.61 (1.09, 2.38)	1.81 (0.97, 3.37)	0.007
Excluding the first 4 years of follow-up†	1.0	1.19 (0.77, 1.82)	1.77 (1.14, 2.74)	2.02 (1.02, 3.98)	0.003
Excluding the first 8 years of follow-up†	1.0	1.15 (0.67, 1.97)	1.68 (0.97, 2.91)	1.73 (0.70, 4.26)	0.05

* Further adjusted for caffeine intake, use of estrogen, use of nonaspirin nonsteroidal antiinflammatory drugs, alcohol consumption, body mass index, and physical activity.

† Adjusted for age and smoking.

or more to be 0.71, 0.85, 0.53, and 0.52, respectively ($P_{\text{trend}} = 0.02$).

DISCUSSION

In this large prospective cohort of nurses, we found that working for more years on night shift was associated with a significantly lower risk of Parkinson's disease. Years of night shift work were positively associated with smoking status; however, the fact that shift workers also had lower Parkinson's disease risk among never smokers argued against the possibility of substantial residual confounding by smoking. Sleep duration was positively associated with the risk of Parkinson's disease, but this finding requires cautious interpretation because abnormalities of sleep patterns in Parkinson's disease patients may precede their diagnosis for an unknown number of years.

Shift work disrupts the body's circadian rhythm, which is controlled by a pacemaker in the brain; this disruption has a wide range of health impacts on shift workers (1). Some of these effects are transient, such as sleep disorders or an increased risk of accidents (1). Others may be chronic and long lasting: Night shift work has been linked to higher risks of gastrointestinal disorders, cardiovascular disease, and diabetes and, more recently, to certain types of cancer (1, 3–5).

The current study is the first epidemiologic study that examined potential associations between night shift work and Parkinson's disease risk and thus must be considered exploratory. Furthermore, biologically plausible explanations for these findings are lacking. Shift work has been linked to a lower circulating concentration of melatonin (7). However, the evidence on melatonin and Parkinson's disease risk has been limited to experimental studies and is contradictory. Although some experimental studies suggest that melatonin is protective for dopaminergic neurons (16), others demonstrated detrimental effects (17). Thus, no sound inferences for any melatonin-related biologic effects of night work on Parkinson's disease can yet be made. Further, shift work has been related to modest increases in plasma concentrations of estradiol and uric acid (7, 18), both of which may be protective against Parkinson's disease

(19–21). We were not able to measure these compounds in our study, and thus their relevance to our findings remains uncertain.

Our data support an association between longer hours of sleep and a higher risk of Parkinson's disease. However, the temporal relation between sleep and Parkinson's disease risk is difficult to establish, as many Parkinson's disease patients also suffer from a variety of sleep disorders including difficulties in falling asleep and keeping asleep, sleep fragmentations, and excessive daytime sleep (15). Although this association persisted in our lag analyses where up to 8 years of initial follow-up were excluded, we cannot rule out the possibility that Parkinson's disease patients might have developed sleep problems even earlier before any notable motor symptoms.

There are several potential limitations in the current study. The study was not designed to evaluate associations between night shift or sleep patterns and risk of Parkinson's disease. Working night shift was defined as having three or more rotating night shifts every month; while this definition included most nurses that had worked on night shifts, more detailed exposure assessments are desirable in future studies. In a prospective study of this size, we had to rely on the clinical diagnosis of neurologists for case identification. In a recent clinicopathologic study (22), 90 percent of the clinical diagnoses of Parkinson's disease made primarily by neurologists were confirmed at autopsy. Although it is likely that a few of the Parkinson's disease cases were misdiagnosed, this diagnostic error most likely caused a modest attenuation of the association, as the diagnoses were made independently of the exposure assessments. Likewise, some misclassification of the work shift was likely, but since this information was collected before the onset of Parkinson's disease, any misclassification was most likely unrelated to disease status and would also have attenuated the association. Although established risk factors such as age and smoking were controlled throughout the analyses and further adjustment for other potential confounders made little difference, we still could not exclude the possibility of confounding from unmeasured factors, such as depression (23, 24) and anxiety (25, 26). It is possible that the shift workers

who remained on shift schedules were healthier than those who worked on daytime schedules or those who switched back to day routines for health reasons (27). However, this would be in contrast to our findings that shift nurses were more likely to seek medical attention for health problems and that they had higher risks of cancers in this cohort (4, 5). It is still possible, however, that the observed inverse association reflects a lack of interest in or a low tolerance for night shifts among individuals who are predisposed to developing Parkinson's disease (28, 29). Pathologic changes in the brain are likely to start several years before the onset of Parkinson's disease and may affect sleep and the ability to work at night.

In summary, in this large prospective cohort of nurses we observed that working rotating night shifts was associated with a lower risk of Parkinson's disease, whereas a long average duration of sleep was associated with an increased risk. The data suggest that either working rotating night shifts delays or prevents the onset of Parkinson's disease or, conversely, low tolerance for night shift work is an early marker of Parkinson's disease. Given the novelty of these findings, further studies are needed to evaluate this association.

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Conflict of interest: none declared.

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