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# Occupational Stress and Risk for Parkinson's Disease: A Nationwide Cohort Study

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**ABSTRACT: Background**: Stress has been suggested as a contributing factor in the etiology of Parkinson's Disease (PD), but epidemiological evidence is sparse.
**Objective**: The objective of this study was to explore the association between occupational stress according to the job demands-control model and the risk for PD.
**Methods**: We conducted a population-based cohort study with 2,544,748 Swedes born 1920 to 1950 who had an occupation reported in the population and housing censuses in 1980 or, if missing, in 1970. Job demands and control were measured using a job-exposure matrix. Incident PD cases were identified using Swedish national health registers from 1987 to 2010. Data were analyzed with Cox regression with age as the underlying time scale, adjusting for sex, education, and chronic obstructive pulmonary disease as a proxy for smoking.
**Results**: During a mean follow-up time of 21.3 years, 21,544 incident PD cases were identified. High demands were associated with increased PD risk among men, most evident in men with high education. High control was associated with increased PD risk among the low educated. This association was more pronounced in women. High-strain jobs (high demands and low control) was only associated with increased PD risk among men with high education, whereas active jobs (high demands and high control) were associated with increased PD risk among men with low education.
**Interpretation**: High job demands appear to increase PD risk in men, especially in men with high education, whereas high job control increases PD risk among low educated, more strongly in women. © 2018 The Authors. Movement Disorders published by Wiley Periodicals, Inc. on behalf of International Parkinson and Movement Disorder Society.

**Key Words**: Parkinson's disease; stress; occupational stress; cohort study; risk factor

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The etiology of PD is not well understood. Although there are rare forms of monogenic PD, most PD cases are idiopathic (>90%) and probably caused by an interplay between genetic and environmental factors.[1] Genetic studies have identified increasing numbers of risk polymorphisms, but surprisingly little is known about environmental risk factors and how these affect PD risk.

One environmental factor that has been proposed as a risk factor for PD is stress.[2,3] The role of chronic stress, dysregulation of the hypothalamic-pituitary-adrenal axis and cortisol levels in relation to PD risk and progression have been previously discussed.[4,5] Cortisol levels have been found to be increased in PD patients.[6,7] It is also well known that stress can worsen motor symptoms in PD patients,[8] but there are few

epidemiological studies on stress as a risk factor for PD, and the findings have been inconsistent.[9–12] However, the hypothesis is supported to some extent by animal studies of PD. For example, chronic restraint stress and corticosterone treatment have been shown to separately impair motor function and accelerate nigral neuronal loss in a 6-hydroxydopamine rat model of PD.[13] Furthermore, pretreatment with corticosterone at doses chosen to mimic physiological stress caused an enhanced neuroinflammatory response to methamphetamine and increased dopaminergic neurotoxicity in mice.[14] Another study using the lipopolysaccharide model of PD showed that exposure to chronic stress prior to lipopolysaccharide treatment resulted in a higher inflammatory response associated with more severe degeneration of dopaminergic neurons and more characteristic features of PD.[15]

Adverse psychosocial work conditions are a potential source of chronic stress relevant for public health as most people spend a substantial portion of life at work. The job demand-control model[16,17] is one of the most influential models of work-related stress that has been linked to salivary cortisol[18] and the cortisol/dehydroepiandrosterone sulfate ratio.[19] The model consists of the following 2 dimensions: job demands and job control. The demand component measures time pressure and psychological/cognitive demands, whereas job control refers to a combination of decision-making authority (eg, influence over time use and planning of work) and skill discretion (eg, varied task content and possibility to learn new things). These dimensions can be combined into the following 4 categories of occupations: low strain (high control/low demands), passive (low control/low demands), active (high control/high demands), and high strain (low control/high demands). According to the model, low control, high demands and especially the combination of these (high strain) are hypothesized to cause enduring strain and predict adverse health outcomes. The model has been particularly predictive for cardiovascular disease,[20,21] mental health disorders,[22] and musculoskeletal problems.[23] Occupational stress has not been studied in relation to PD.

The objective of this study was to examine whether occupational stress measured according to the demand-control model is a risk factor for PD by conducting a prospective population-based register study.

# Methods

## Study Design

This nationwide, population-based register study included all individuals born in Sweden between 1920 and 1950 who had an occupation linkable to a job exposure matrix reported in the population and housing censuses in 1980 or 1970 and were living in Sweden at start of follow-up on January 1, 1987 (n = 2,578,971). The population and housing censuses were performed by Statistics Sweden, and all Swedish residents older than the age of 16 were required by law to respond to the questionnaires, and thus the response rate was very high (>99%).[24,25]

Individuals with a PD diagnosis (n = 1,089) and individuals who were not continuously living in Sweden prior to start of follow-up (n = 33,134) were excluded. This resulted in a final study cohort of 2,544,748 individuals.

The study cohort was linked to other Swedish population registers using the unique Swedish personal identification number, which permits unambiguous individual-level linkage.

The study was approved by the Regional Ethics Review Board, Stockholm, Sweden.

## Ascertainment of Parkinson's Disease

Incident cases of PD were identified through the National Patient Register (NPR) and the Cause of Death Register (CDR). The NPR was initiated in 1964 but has complete nationwide coverage since 1987 and contains information about discharge records from all hospitals in Sweden. Each record contains date of admission, 1 primary diagnosis, and up to 7 secondary diagnoses coded according to the International Classification of Diseases (ICD). The primary diagnosis is the main condition that was treated or investigated at the hospital episode. The secondary diagnoses are comorbidities and/or complications that may or may not contribute to the primary diagnosis. Since 2001, the NPR also includes records from outpatient specialist clinics. The CDR has nationwide coverage since 1961 and contains information from death records, including the underlying cause of death and contributory causes coded according to the ICD.

Incident cases of PD were defined as having a primary diagnosis of PD in the NPR or the CDR. ICD codes for PD were the following: 342.00 (ICD-8), 332.A (ICD-9), G20 (ICD-10). Date of ascertainment was defined as the first date of any PD diagnosis in the NPR or date of death in the CDR for those cases only identified at death. A previous validation study concluded that the NPR and CDR are valid data sources in epidemiological studies of PD with generally good accuracy and sensitivity.[26]

## Occupational Stress

Indicators of occupational stress were derived from a job exposure matrix (JEM), the construction[27] and a validation[28] of which can be found elsewhere. Briefly, the JEM was developed based on a random sample of 12,084 employed Swedish citizens aged 25 to 74 years

who answered the Swedish Survey of Living Conditions collected by Statistics Sweden in 1977 and 1979. Response rate was 81% in 1977 and 89% in 1979. The JEM was developed by aggregating survey responses of individuals to arrive at occupationally representative scores of job control and job demands for 261 occupational categories. As work conditions differed markedly between men and women within the same occupation, 2 different JEMs were developed—1 for each sex. The job-control scale was based on 12 items and measured job authority and skill discretion. The job-demand scale was based on 2 items on hectic time schedule and psychological demands. Both scales were multiplicatively transformed into continuous scales that could possibly range from 0 to 10. In our study population, job demands scores ranged from 0.6 to 9.3 (mean = 4.6, standard deviation [SD] = 1.4) and job control from 1.4 to 8.8 (mean = 5.0, SD = 1.3). Examples of jobs with high or low levels of demands and control that were common in men and women by educational level are presented in Supporting Information Table 1.

The appropriate JEM was then used to assign scores to each individual in the study population based on their sex and the occupation reported in the 1980 or 1970 census. Occupations were coded according to the Nordic version (Nordisk yrkesklassificering (NYK)) of the 3-digit International Standard Classification of Occupation manual. Information was primarily taken from the 1980 census, but for those not having an occupation registered in the 1980 census, information about occupation was retrieved from 1970 census (8% of the cohort). Among those who had an occupation linkable to the job exposure matrix reported in both the 1970 and 1980 censuses, 49% had a work title with the same NYK code and 60% were categorized in the same control/demand quintile. Only 18% changed more than 1 demand quintile, and 15% changed more than 1 control quintile.

## Education

Information on highest level of education was collected from the Education Register. Education was categorized as elementary schooling, upper secondary schooling, or university/college.

## Chronic Obstructive Pulmonary Disease

Smoking has been consistently associated with a reduced risk for PD and is therefore important to consider as a potential confounder. As we did not have data on smoking status, lifetime chronic obstructive pulmonary disease (COPD) was used as a proxy for smoking. Lifetime COPD was defined as having a diagnosis of COPD in the NPR or CDR occurring for the first time after age 40.

## Statistical Analysis

All study participants were followed from baseline (January 1, 1987) until a diagnosis of PD or censoring (date of death, emigration, or end of follow-up on December 31, 2010), whichever came first. Initially, we calculated age-adjusted PD incidence rates per 100,000 person-years, by confounder and exposure levels, using 5-year age strata standardized to the age distribution in the entire population. To further explore the association between occupational stress and PD risk, we then estimated hazard ratios with 95% confidence intervals for PD using Cox proportional hazards regression[29] with attained age as the underlying timescale. Sex, education, and lifetime COPD were considered as confounders and were also tested for interactions with demands and control.

Control and demands were analyzed as categorical variables divided into tertiles with the lowest tertile used as reference group. The combination of demands and control was further analyzed as a categorical variable by combining high and low (median split) levels of demands and control into 4 job-strain groups: low-strain jobs (low demands, high control), passive jobs (low demands, low control), active jobs (high demands, high control), and high-strain jobs (high demands, low control).

## Sensitivity Analysis

We also conducted further sensitivity analyses. To control for a potential calendar effect, we performed all analyses including birth year as a covariate. We also conducted an analysis including only those who had a job and were categorized in the same stress level in both 1970 and 1980. As farming and rural living has been associated with an increased risk for PD,[30] we also performed all analyses excluding farmers and related occupations (NYK codes 401-419). To test the stability of our results, control and demands were also analyzed divided by the median, in quartiles and quintiles. Using logistic regression we also tested whether people who were later diagnosed with PD changed jobs more often than others between 1970 and 1980, adjusting for sex, age, and educational level.

All analyses were performed with Stata statistical software, version 13 (StataCorp LP, College Station, TX).

## Results

The study population consisted of 2,544,748 persons with a slightly higher proportion of men than women. During a mean follow-up time of 21.3 years (SD = 5.5), we identified 21,544 incident PD cases. Mean age at PD ascertainment was 71.1 years (SD = 7.8). As expected, the age-adjusted PD incidence was higher in men, in individuals without COPD, and among those

**TABLE 1.** Characteristics of study population

| | N (%) | PD cases | IR[a] (95% CI) | HR[b](95% CI) |
|---|---|---|---|---|
| Total study population | 2,544,748 (100) | 21,544 | | |
| **Sex** | | | | |
| Male | 1,358,266 (53.4) | 13,335 | 48.4 (47.6-49.2) | 1 (ref.) |
| Female | 1,186,482 (46.6) | 8,209 | 30.9 (30.2-31.6) | 0.61 (0.60-0.63) |
| **Education** | | | | |
| Elementary schooling | 1,075,530 (42.3) | 9,786 | 51.5 (50.6-52.4) | 1 (ref.) |
| Upper secondary schooling | 954,279 (37.5) | 7,468 | 54.7 (53.6-55.8) | 1.16 (1.13-1.20) |
| University/college | 506,968 (19.9) | 4,216 | 63.7 (61.9-65.6) | 1.42 (1.37-1.47) |
| Missing data | 7,971 (0.3) | 74 | | |
| **COPD** | | | | |
| Yes | 141,897 (5.6) | 889 | 39.6 (37.4-41.8) | 1 (ref.) |
| No | 2,402,851 (94.4) | 20,655 | 55.6 (55.0-56.3) | 0.56 (0.53-0-60) |
| **Demands tertiles** | | | | |
| Low | 925,546 (36.4) | 7,606 | 53.9 (52.9-54.9) | 1 (ref.) |
| Middle | 781,922 (30.7) | 13,944 | 50.2 (49.1-51.2) | 0.97 (0.94-1.01) |
| High | 837,280 (32.9) | 21,544 | 59.1 (58.0-60.3) | 1.19 (1.16-1.23) |
| **Control tertiles** | | | | |
| Low | 850,968 (33.4) | 7,134 | 52.4 (51.3-53.4) | 1 (ref.) |
| Middle | 841,978 (33.1) | 6,507 | 48.6 (47.6-49.6) | 0.99 (0.96-1.02) |
| High | 851,802 (33.5) | 7,903 | 62.9 (61.7-64.1) | 1.30 (1.26-1.34) |
| **Job strain groups** | | | | |
| Low strain | 492,134 (19.3) | 3,529 | 49.4 (48.0-50.8) | 1 (ref.) |
| Passive | 783,466 (30.8) | 6,670 | 52.7 (51.6-53.8) | 1.03 (0.99-1.07) |
| High strain | 496,829 (19.5) | 4,018 | 50.0 (48.7-51.3) | 1.02 (0.97-1.06) |
| Active | 772,319 (30.4) | 7,327 | 62.8 (61.5-64.0) | 1.34 (1.29-1.40) |

COPD, chronic obstructive pulmonary disease.
[a]Age-adjusted incidence rates (IR) by 100,000 person years.
[b]Hazard ratios (HR) estimated by Cox proportional hazard regression with attained age as underlying time scale.

with higher education (Table 1). Both high demand and high control were associated with a significantly increased risk of PD when compared with low levels in models only adjusted for attained age. The distribution of men and women between job-strain groups by education is presented in Supporting Information Table 2.

The exposures had significant interactions with sex and education on PD risk. There were also significant 3-way interaction effects between these variables. The effects of demands and control on PD risk are therefore presented for the overall study population, by sex, by educational level, and by the combination of sex and education (Table 2). High levels of job demands were associated with a significantly increased risk of PD in the overall sample. Similar results were observed in all educational groups and in both sexes, but the effect was more pronounced in men (Table 2, models 2 and 3). When analyzing the 3-way interaction effect, high demand was only significantly associated with PD risk among men with high and low education. In this model, there were no significant associations between job demands and PD among women (Table 2, model 4).

High levels of job control were associated with an increased PD risk in the overall sample and in both men and women (Table 2, models 1 and 2). High control was associated with increased PD risk in low and middle educated with the strongest effect among low

educated, whereas there was no significant effect among high educated (Table 2, model 3). In the final model with the 3-way interaction effect, high control was only associated with increased PD risk among low educated, and more pronounced in women than men (Table 2, model 4).

High-strain jobs (high demands and low control) were associated with PD risk in highly educated men, whereas active jobs (high demands, high control) were associated with increased PD risk in men with low education (Table 3). There were no associations between job strain groups and PD among women.

To adjust for a potential cohort effect, for example, the result of an increasing educational level over time, we additionally included birth year in all models with minimal changes in the estimates. As the effect of work-related stress was nested within occupations, we wanted to examine whether farmers accounted for or suppressed the effect of demands and control on PD risk in a sensitivity analysis. Excluding farmers and related occupations only changed the estimates marginally. In general, significant associations were strengthened after the exclusion of farmers. Furthermore, restricting the analyses to those who did not change stress levels between 1970 and 1980 yielded similar results. We also analyzed demands and control divided by the median in quartiles and in quintiles. The hazard

**TABLE 2.** Hazard Ratios for PD by job demands and control tertiles.

| | Demands | HR[a] | 95% CI | Control | HR[a] | 95% CI |
|---|---|---|---|---|---|---|
| **Model 1** | Low | 1.00 | Ref. | Low | 1.00 | Ref. |
| | Middle | 0.97 | 0.94-1.01 | Middle | 0.98 | 0.95-1.02 |
| | High | 1.19 | 1.15-1.23 | High | 1.29 | 1.25-1.33 |
| **Model 2** | | | | | | |
| Men | Low | 1.00 | Ref. | Low | 1.00 | Ref. |
| | Middle | 1.04 | 1.00-1.09 | Middle | 1.09 | 1.04-1.15 |
| | High | 1.19 | 1.14-1.23 | High | 1.16 | 1.11-1.20 |
| Women | Low | 1.00 | Ref. | Low | 1.00 | Ref. |
| | Middle | 1.01 | 0.95-1.06 | Middle | 1.07 | 1.02-1.12 |
| | High | 1.13 | 1.07-1.20 | High | 1.17 | 1.10-1.24 |
| **Model 3** | | | | | | |
| Low education | Low | 1.00 | Ref. | Low | 1.00 | Ref. |
| | Middle | 0.92 | 0.88-0.96 | Middle | 0.94 | 0.89-0.98 |
| | High | 1.09 | 1.03-1.16 | High | 1.23 | 1.16-1.29 |
| Middle education | Low | 1.00 | Ref. | Low | 1.00 | Ref. |
| | Middle | 1.03 | 0.97-1.09 | Middle | 0.90 | 0.85-0.96 |
| | High | 1.09 | 1.03-1.15 | High | 1.18 | 1.12-1.25 |
| High education | Low | 1.00 | Ref. | Low | 1.00 | Ref. |
| | Middle | 1.07 | 0.95-1.20 | Middle | 0.93 | 0.78-1.11 |
| | High | 1.10 | 1.01-1.21 | High | 1.02 | 0.86-1.21 |
| **Model 4** | | | | | | |
| Men | | | | | | |
| Low education | Low | 1.00 | Ref. | Low | 1.00 | Ref. |
| | Middle | 1.00 | 0.94-1.06 | Middle | 1.00 | 0.94-1.07 |
| | High | 1.09 | 1.02-1.16 | High | 1.07 | 1.01-1.14 |
| Middle education | Low | 1.00 | Ref. | Low | 1.00 | Ref. |
| | Middle | 1.02 | 0.94-1.10 | Middle | 0.98 | 0.90-1.08 |
| | High | 1.03 | 0.97-1.11 | High | 1.00 | 0.93-1.07 |
| High education | Low | 1.00 | Ref. | Low | 1.00 | Ref. |
| | Middle | 1.17 | 1.01-1.35 | Middle | 1.00 | 0.79-1.25 |
| | High | 1.14 | 1.01-1.27 | High | 0.86 | 0.69-1.06 |
| Women | | | | | | |
| Low education | Low | 1.00 | Ref. | Low | 1.00 | Ref. |
| | Middle | 1.01 | 0.94-1.08 | Middle | 1.06 | 0.99-1.13 |
| | High | 1.00 | 0.90-1.12 | High | 1.18 | 1.05-1.33 |
| Middle education | Low | 1.00 | Ref. | Low | 1.00 | Ref. |
| | Middle | 1.04 | 0.95-1.13 | Middle | 0.97 | 0.89-1.05 |
| | High | 1.03 | 0.94-1.13 | High | 0.97 | 0.87-1.09 |
| High education | Low | 1.00 | Ref. | Low | 1.00 | Ref. |
| | Middle | 0.98 | 0.80-1.19 | Middle | 1.04 | 0.79-1.37 |
| | High | 1.08 | 0.92-1.26 | High | 1.02 | 0.78-1.34 |

[a]Hazard ratios (HR) estimated by Cox proportional hazard regression with attained age as underlying time scale adjusting for lifetime chronic obstructive pulmonary disease, without any further adjustments (model 1), including an interaction term with sex (model 2), including an interaction term with education (model 3), and including an interaction with both sex and education (model 4).

ratios for the groups with the highest exposure levels were in general stable around 1.3 for control and 1.2 for demands. However, for our main models including 3-way interactions, the Akaike information criterion (AIC) values were lowest when using tertiles. Last, PD cases were less likely to change jobs between 1970 and 1980, although the difference was marginal (odds ratio = 0.96; 95% confidence interval = 0.93-0.99).

## Discussion

In this large prospective cohort study, we found evidence for associations between indicators of occupational stress and PD risk. As expected, high demands were associated with an increased risk of PD in men. However, job demands did not affect PD risk in women after taking education into consideration. Somewhat unexpected, high control was also associated with an increased PD risk. This effect was only evident in low educated, especially in women. According to the job demand-control model, high levels of control are supposed to buffer the negative effects of high levels of demands (active jobs), whereas the combination of low control and high demands (high-strain jobs) is believed to be particularly harmful. High-strain jobs were a risk factor for PD among highly educated men only. In contrast, active jobs were associated with increased PD risk among men with low education.

**TABLE 3.** Hazard ratios for PD by job strain

| Sex | Education | Job strain[a] | HR[b] | 95% CI |
|---|---|---|---|---|
| Men | Low | Low strain | 1.00 | Ref. |
| | | Passive | 1.09 | 1.00-1.19 |
| | | High strain | 1.08 | 0.98-1.20 |
| | | Active | 1.20 | 1.09-1.32 |
| | Middle | Low strain | 1.00 | Ref. |
| | | Passive | 1.05 | 0.95-1.16 |
| | | High strain | 1.08 | 0.96-1.21 |
| | | Active | 1.05 | 0.96-1.15 |
| | High | Low strain | 1.00 | Ref. |
| | | Passive | 1.02 | 0.79-1.31 |
| | | High strain | 1.25 | 1.04-1.51 |
| | | Active | 1.11 | 0.99-1.24 |
| Women | Low | Low strain | 1.00 | Ref. |
| | | Passive | 0.94 | 0.86-1.02 |
| | | High strain | 0.96 | 0.88-1.06 |
| | | Active | 1.00 | 0.87-1.15 |
| | Middle | Low strain | 1.00 | Ref. |
| | | Passive | 1.06 | 0.96-1.18 |
| | | High strain | 1.01 | 0.93-1.11 |
| | | Active | 1.00 | 0.88-1.12 |
| | High | Low strain | 1.00 | Ref. |
| | | Passive | 1.16 | 0.85-1.57 |
| | | High strain | 1.16 | 0.97-1.38 |
| | | Active | 1.07 | 0.92-1.24 |

[a]Job-strain groups: low strain = high control and low demands; passive = low control and low demands; high strain = low control and high demands; active = high control and high demands. low/high levels of control and demands are based on median split.
[b]Hazard ratios (HR) estimated by Cox proportional hazard regression with attained age as underlying time scale adjusting for lifetime chronic obstructive pulmonary disease and an interaction term with sex and education.

Our study is the first to explore the association between occupational stress and PD risk, but epidemiological studies have addressed other aspects of stress in relation to PD.[9–12] Three studies explored the effect of major life events on PD risk with inconsistent findings.[9–11] Two other prospective cohort studies have associated vital exhaustion[11] (a state of excessive fatigue and irritability often attributed to stress) and adjustment disorder[12] (a diagnosis made in the presence of a stressful event) with an increased PD risk, supporting the hypothesis of a relation between an excessive stress response and PD. In summary, studies on perceived stress[10]or measures of a stress response[11,12] have found associations between stress and PD, whereas studies on exposure to an objective number of stressors generally did not find associations with PD.[9,11] Thus, future studies need to distinguish between stressors and stress response and to consider the duration of stress exposure.

Contrary to the hypothesis, high control was associated with increased PD risk. Job control has generally been considered beneficial, but the relationship between job control and health may be more complex.[31] An alternative interpretation is that high control may work as a stressor depending on various organizational, individual, and social factors. High control may, for example, lead to excessive work hours, more interpersonal conflicts, and more work-to-home interference.[31] Furthermore, active jobs have been associated with higher cortisol/dehydroepiandrosterone sulfate ratio compared to high-strain jobs, indicating that high control may be worse than low in combination with high demands.[19] Other studies have also shown that high control or active jobs were associated with negative outcomes in women, for example, depressive symptoms,[32] coronary heart disease,[33] and mortality.[34] It is possible that women may not derive the same benefits of positions of authority as men. In a study on subjectively reported and externally assessed work stress, women in active jobs had more externally assessed hindrances and less externally assessed influence than men in active jobs.[35] This may explain why the effect of high control on PD risk was stronger in women than men. Furthermore, the job demand-control model has been criticized for being more valid for men, with generally larger effect sizes or effects only present in men.[20,22] Thus, this could explain why we only found associations between job strain and PD in high-educated men.

PD is a slowly progressing disorder, and the neurodegeneration may start up to decades before the first movement symptoms appear. According to Braak's staging, the preclinical period may start with Lewy body pathology in the enteric nervous system that slowly spreads through the vagal nerve and lower brain stem and much later affecting the substantia nigra.[36] Epidemiological studies support a long preclinical period characterized by various nonmotor symptoms, and some may be present decades before PD diagnosis.[37] Our observed associations might therefore be explained by reverse causation as people in prodromal phases of PD might change from stressful or physically demanding jobs due to impaired stress coping or job performance. In contrast, in our sample, people who were later assigned as PD cases changed jobs less frequently between 1970 and 1980 than others, and we therefore find it unlikely that people have to change jobs as a consequence of prodromal symptoms.

Another potential explanation is confounding by traits that predispose both to seeking specific types of jobs and to increased PD risk. PD has been associated with specific personality traits, such as low novelty seeking, high harm avoidance, introversion, and neuroticism.[38–40] As a result of the implication of dopamine in the dimension novelty seeking of Cloninger's neurobiological model of personality,[41] this trait has been particularly studied in relation to PD. Although not fully supported, there is some evidence for a role of alterations in dopaminergic function and altered striatal circuits in novelty seeking as well as harm avoidance in relation to PD.[42,43] Thus, underlying genetic or

neurobiological factors affecting the dopamine system may contribute to the observed associations. The same factors may also explain the observed positive association between education and PD risk given the role of dopamine biology in, for example, feedback learning[44] and possibly in educational continuation.[45] However, there is no clear evidence for presence of novelty seeking and harm avoidance prior to PD onset.[38–40] Furthermore, a study using choice of occupation as a proxy for personality found no evidence for an association between occupation-derived personality traits and PD.[46] On the other hand, neuroticism, a trait linked to increased stress vulnerability, has been associated with higher perceived job strain[47] and shown to precede PD diagnosis up to decades.[48,49]

Observed associations could also be caused by mediation by some environmental factor, for example, physical activity that has been associated with reduced PD risk. However, occupational physical activity alone does not seem to provide a protective effect for PD.[50,51] Furthermore, there may be an inverse relationship between occupational and leisure-time physical activity as low job control and high-strain jobs are related to leisure-time physical inactivity.[52] Therefore, we do not believe physical activity could have had an important impact on our observed associations. There is also a well-known relationship between smoking and reduced PD risk.[53] Furthermore, high job strain[54] and low control[55] have been associated with increased smoking. Thus, increased smoking in low control and high-strain occupations may be a possible explanation for the somewhat unexpected finding that high control increased PD risk and might also result in an underestimation of the effect of job strain on PD risk. However, we find it unlikely that smoking confounded the association between occupational stress and PD, as adjusting for COPD as a proxy for smoking did not change our results.

Major strengths of this study include the use of a large population-based cohort, the prospective design, and long follow-up time. This is also the first study on the relationship between occupational stress and PD. A limitation is the use of hospital admissions and outpatient visits as a proxy for incident PD, which leads to an underestimation of PD. A nondifferential underestimation of PD would lead to a bias toward the null. On the other hand, if occupational stress or other aspects related to occupation are associated with propensity to seek medical care, this could have differentially biased our results. To increase the accuracy of PD diagnoses, we only included hospital admissions and outpatient visits with PD as the main diagnosis, as suggested by a previous validation study.[26]

Another limitation is that we lacked individual-level information on stress. The use of a JEM may introduce misclassification as work conditions vary within job titles and there is an individual variation in how people perceive and react to the same type of stressor. There is also a risk that misclassification occurs on an aggregated level, for example, that the exposure associated with specific job titles may change over time. On the other hand, the use of a JEM might have an advantage over self-reported data, as it is not biased as a result of temporal changes in an individual's perception. Hence, JEMs might provide more stable estimates of the average exposure status over time. Furthermore, although misclassification may occur because of the change in magnitude of exposure within an occupational group over time or that individuals may change jobs at some time, it is less likely that the relative position changes. Hence, a JEM may still provide valid ordinal-level estimates of past exposure.[28] Furthermore, exit rate and job mobility were low in Sweden in the 1970s and 1980s.[56] Because of the prospective design, recall bias is not an issue, and misclassification of exposure is likely nondifferential and would only introduce bias toward the null.

In conclusion, our findings suggest that occupational stress is associated with PD risk such that having a high-demand occupation is a risk factor, and low control is protective. Thus, the meaning of job control and strain may need to be reconsidered in the context of PD. To better understand the relationship between occupational stress and PD risk, future studies may consider other models of occupational stress to elucidate whether occupational stress only is a risk factor for PD or if there are also aspects of stress that may be protective. ●

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