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Solvent exposed occupations and risk of Parkinson disease in Finland

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ABSTRACT

Introduction: Epidemiologic and toxicology studies suggest that exposure to various solvents, especially chlorinated hydrocarbon solvents, might increase Parkinson disease (PD) risk.
Methods: In a population-based case-control study in Finland, we examined whether occupations with potential for solvent exposures were associated with PD. We identified newly diagnosed cases age 45–84 from a nationwide medication reimbursement register in 1995–2014. From the population register, we randomly selected non-PD controls matched on sex, along with birth and diagnosis years (age). We included 11,757 cases and 23,236 controls with an occupation in the 1990 census, corresponding to age 40–60. We focused on 28 occupations with ≥ 5% probability of solvent exposure according to the Finnish Job Exposure Matrix. We estimated odds ratios (ORs) and 95% confidence intervals (CIs) by logistic regression modeling, adjusting for age, sex, socioeconomic status, and smoking probability.
Results: Similar proportions of cases (5.5%) and controls (5.6%) had an occupation with potential exposure to any solvents. However, all occupations with a point estimate above one, and all significantly or marginally significantly associated with PD (electronic/telecommunications worker [OR = 1.63, 95% CI 1.05–2.50], laboratory assistant [OR = 1.40, 95% CI 0.98–1.99], and machine/engine mechanic [OR = 1.23, 95% CI 0.99–1.52]) entailed potential for exposure to chlorinated hydrocarbon solvents, specifically. Secondary analyses indicated exposure to polycyclic aromatic hydrocarbons and some metals might contribute to the association for mechanics.
Conclusion: PD risk might be slightly increased in occupations with potential exposure to chlorinated hydrocarbon solvents. Confirmation is required in additional studies that adjust for other occupational exposures and smoking.

1. Introduction

Many studies in humans and animals suggest that solvents might act as basal ganglia neurotoxicants. Parkinsonism has been observed in humans following exposure to lacquer thinner [1], n-hexane [2], carbon tetrachloride [3], mixed solvent exposures [4], and other solvents [5,6]. In addition, there have been several case reports of Parkinson disease (PD) following occupational exposure to trichloroethylene (TCE) [7–9]. Some analytic epidemiologic studies also suggest a potential association between occupational exposure to solvents and PD [10,11], especially TCE and other chlorinated hydrocarbon (CHC) solvents [10]. TCE crosses the blood brain barrier and animal studies demonstrate a reduction in dopaminergic neurons in the substantia nigra and locomotor activity following exposure to TCE [12]. Confirmation of associations between specific solvents and PD might inform public policy regarding occupational and environmental exposure to solvents. Therefore, we examined PD risk in relation to occupations with potential for solvent exposure in Finland.

2. Methods

2.1. Study overview

We conducted a population-based case-control study of PD with five nationwide datasets (Fig. 1). Administrative data from population,

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medication reimbursement, and occupation registers were linked via an 11-digit personal identifier for Finnish residents, except those who opted out of data sharing for research. We then linked these individual-level data to nationwide occupation-specific data on smoking/alcohol use [13] and probability of exposure to solvents and other agents according to the Finnish Job Exposure Matrix (FINJEM) [14,15]. We included 11,757 newly diagnosed PD cases and 23,236 controls, all diagnosed/selected while age 45–84 during 1995–2014. We restricted to those with an occupation in the 1990 national census (our source of occupational data) and age 40–60 (midlife) then, i.e., likely to have attained their primary occupation. We applied these dual age criteria by restricting to subjects born in 1930–1950. The only additional criterion was primarily speaking Finnish or Swedish (>99.5% of these birth cohorts). The Ethics Board at the Finnish Institute of Occupational Health and the Human Research Protection Office at Washington University in St. Louis approved this study.

2.2. Case ascertainment

We identified cases through a register of reimbursement for medication maintained by the Social Insurance Institution of Finland (FSII), similar to a prior PD study [16]. All residents of Finland are eligible for reimbursement for prescription medications, including for PD. These anti-parkinsonian drugs (reimbursement code 110) include levodopa, dopamine agonists, monoamine oxidase inhibitors, catechol-O-methyltransferase inhibitors, and anticholinergics. FSII medical experts review a medical certificate submitted by the treating neurologist, and we used the date that reimbursement was first permitted as the diagnosis date. For those diagnosed in 2000–2014 we required an International Classification of Diseases (ICD) diagnosis code for PD (ICD-10 G20, ICD-9 332, or ICD-9 332.0). We did not require this in 1995–1999, when coding was less complete but non-PD codes uncommon (2.6%).

We included all PD cases diagnosed in 1995–2014 while age 45–84. PD is uncommon before age 45 [17], and under-ascertainment becomes more prominent at age 85 [18,19]. We restricted to more recent diagnosis years to further minimize under-ascertainment; preliminary analyses indicated lower age-specific incidence in men and women in the 1980s than later decades.

2.3. Control selection

The Population Register Centre in Finland, which maintains records of all permanent residents, randomly selected controls. For each case they selected two controls of the same sex who lived in Finland on the case's diagnosis date, while also matching on birth year, in effect by age. They followed the incidence density sampling method when selecting controls.

2.4. Identification of occupation

We obtained from Statistics Finland each person's occupation from the nationwide census in 1990, when they were age 40–60. This is the one census that uses the same occupational coding system as FINJEM [14,15] and was the most recent census before an economic downturn that affected employment patterns. Given study restrictions and matching, all subjects held this occupation before PD diagnosis or selection as a control, and the amount of time between the census and diagnosis/selection was similar between cases and controls.

2.5. Assessment of occupational exposure to solvents

We linked each subject's occupation to 1985–1994 FINJEM period estimates of the probability of exposure in 1990 to each of seven individual solvents and four classes of solvents (Supplemental Table). Of 310 possible occupations, 28 entailed ≥ 5% probability of exposure to ≥1 solvent/solvent class. We focused on these occupations because a 5% prevalence of exposure for a given agent is the minimum required for formal exposure estimation in FINJEM [14]. We considered occupations with probabilities as low as 5% because for

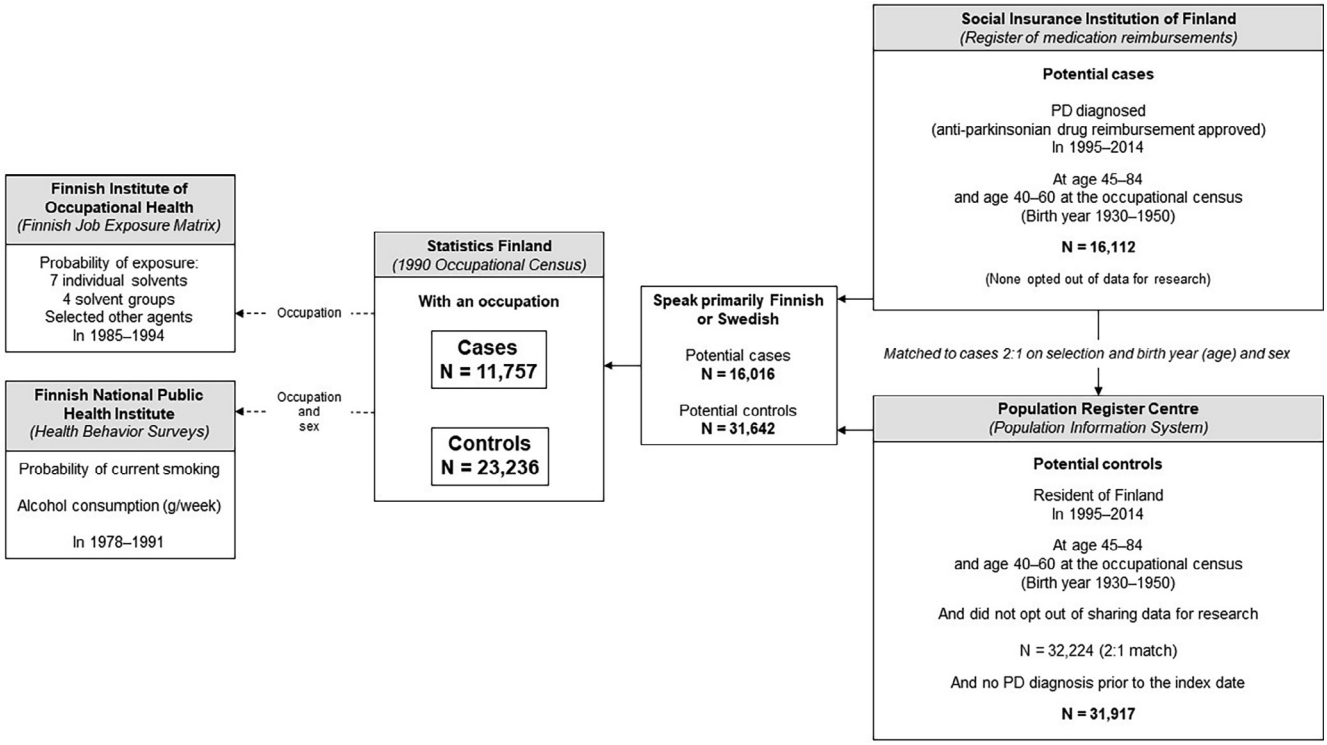

Fig. 1. Population-based case-control study of incident Parkinson disease (PD) using five national datasets, Finland 1995–2014.

the solvents of greatest *a priori* interest (CHC solvents, especially TCE) exposure probability usually was ~5% in periods relevant to our study (Supplemental Table). We also used FINJEM [14,15] to identify the probability of occupational exposure to 56 other agents.

2.6. Identification of demographic variables

The Population Register Centre provided data on age and sex. Socioeconomic status (SES), based on each worker's education and work tasks, was available from the 1990 occupational census. We determined the probability of regularly smoking tobacco (hereafter "smoking") and grams of alcohol consumed per week in 1990 according to sex and occupation using data from random samples of working age Finnish residents in 1978–1991 [13].

2.7. Statistical analysis

We conducted all statistical analyses with SAS version 9.4. We fit multivariable logistic regression models to examine the association between occupation and PD. Given the application of matching for a limited number of demographic variables only, we treated the case-control data as frequency matched, rather than individually matched, i.e., we used unconditional logistic regression models, rather than conditional logistic regression models, in order to improve statistical precision [20]. We report the odds ratio (OR) and 95% confidence interval (CI) as an estimate of the incidence rate ratio given our sampling method [21,22]. In our primary analyses, we attempted one model for each occupation with ≥5% probability of exposure to solvent(s). The independent variable of interest was a dichotomous variable that indicated whether the person worked in the occupation in 1990 (midlife). In secondary analyses, the independent variable was a continuous variable, representing the FINJEM-derived probability of exposure to an individual solvent or solvent group. We coded this probability as 0–≤1, such that the OR represents the rate ratio of PD in workers with 100% vs. 0% probability of exposure to the respective solvent or solvent group, i.e., ever/never exposure in 1990. Previous studies on occupational solvent exposure and PD have used a similar approach [11] or confirmed the importance of taking into account probability of exposure [23].

Because we used unconditional logistic regression models, we adjusted for the matching variables age and sex in all models [20]. We also adjusted *a priori* for SES and smoking because failure to adjust for SES and/or smoking biases associations for PD such that occupations that require less education appear to be protective [24]. We adjusted for SES in four categories and for smoking probability as a continuous variable (0–≤1) [19]. In the secondary analyses based on the probability of solvent exposure, we examined the effect of adjusting for the probability of occupational exposure to 56 other FINJEM agents (each coded as 0–≤1) and alcohol consumption (continuous). Our review of the literature and FINJEM [15] indicated that along with SES and smoking, alcohol and potential solvent co-exposures assessed in FINJEM (e.g., selected metals) were the strongest potential confounders on the association between occupational solvent exposure and PD.

In sensitivity analyses, we examined the consistency of results between men and women, across age groups, and when using alternative ways to calculate probability of exposure to solvents. (The 1990 census occurred in or near two FINJEM periods, 1960–1984 and 1985–1994, and in addition to a time-weighted mean probability we considered the maximum across the two periods as well as the probability in the 1985–1994 period alone). In addition to these sensitivity analyses, we explored whether cases who had an occupation with the potential for exposure to solvents were diagnosed with PD earlier in life than cases in other occupations. While restricting to cases, we attempted to fit a linear regression model for each of the above 28 occupations, with age as the outcome variable and occupation as an independent variable. We adjusted for sex, SES, and smoking, and then compared results to a parallel model for controls to account for generic temporal trends.

2.8. Data sharing

The administrative data used in these analyses were and remain accessible only to approved individuals in Finland.

3. Results

3.1. PD and demographic characteristics

Age- and sex-matched cases and controls differed according to SES, with higher SES among cases than controls (p = 0.02; Table 1). After adjustment for SES, a very strong inverse association between smoking and PD remained (OR = 0.57, 95% CI 0.42–0.76). Even with adjustment for both SES and smoking, alcohol consumption also was inversely associated with PD (OR = 0.89, 95% CI 0.76–1.04, per ten 12-gram portions per week, p_{trend} = 0.16).

3.2. Occupations with potential for solvent exposure and PD risk

At the 1990 census, 647 (5.5%) cases and 1,305 (5.6%) controls worked in an occupation with ≥5% probability of exposure to solvents. We observed significant or borderline significant associations for three occupations (Table 2). There was a slightly increased PD risk for machine/engine mechanics, the most prevalent occupation with any potential for solvent exposure. We also observed increased risk for electronic/telecommunications workers and laboratory assistants. ORs for the remaining occupations had wide CIs, were close to unity, or fell below unity.

In our secondary analysis with ORs representing ever/never potential for occupational exposure in midlife to selected FINJEM agents, point estimates were very close to unity for most solvents and solvent groups (Table 3). Exceptions were CHC solvents as a group, the four individual CHC solvents in FINJEM, and the aromatic hydrocarbon styrene, but CIs were very wide. For the most part, there was little evi-

Table 1
Characteristics of Parkinson disease cases and controls, Finland 1995–2014.

	Cases N = 11,757 n (%)	Controls N = 23,236 n (%)
Female	4,706 (40.0)	9,505 (40.9)
Year of diagnosis or selection		
1995–1999	1,224 (10.4)	2,487 (10.7)
2000–2004	2,321 (19.7)	4,557 (19.6)
2005–2009	3,541 (30.1)	6,971 (30.0)
2010–2014	4,671 (39.7)	9,221 (39.7)
Socioeconomic status[a]		
Upper level employees	2,198 (18.7)	3,900 (16.8)
Employer/entrepreneur	2,424 (20.6)	4,642 (20.0)
Lower level employees	3,433 (29.2)	6,754 (29.1)
Manual workers	3,702 (31.5)	7,940 (34.2)
	Mean (SD)	**Mean (SD)**
Age at diagnosis or selection,[b] years	67.8 (7.0)	67.7 (7.0)
Time between occupational assessment and diagnosis or selection,[b] years	16.6 (5.2)	16.3 (5.2)

[a] Based on occupation and level of education, determined from the Finnish occupational census in 1990.
[b] All cases and controls were age 40–60 at the time of the Finnish occupational census in 1990 and age 45–84 at diagnosis/selection, with four or more years between the census and diagnosis/selection for all cases and controls.

Table 2
Occupations with ≥ 5% probability of exposure[a] to solvents and risk of Parkinson disease, Finland 1995–2014.

Occupation[b]	Cases N = 11,757 n (%)	Controls N = 23,236 n (%)	OR (95% CI)[c]
Chemical, physical, and biological work			
Chemist	7 (0.1)	19 (0.1)	0.66 (0.28–1.58)
Laboratory assistant	52 (0.4)	76 (0.3)	1.40 (0.98–1.99)
Sales work			
Service station attendant	14 (0.1)	46 (0.2)	0.67 (0.37–1.23)
Manufacturing and related work			
Upholsterer	12 (0.1)	18 (0.1)	1.46 (0.70–3.04)
Leather cutter for footwear	0 (0)	8 (0.03)	—[d]
Shoe sewer	4 (0.03)	9 (0.04)	—[d]
Laster/sole fitter	3 (0.03)	4 (0.02)	—[d]
Other footwear worker	3 (0.03)	15 (0.1)	—[d]
Smelting/metallurgic/foundry worker	11 (0.1)	16 (0.1)	1.50 (0.70–3.24)
Turner/toolmaker/machine-tool setter	96 (0.8)	186 (0.8)	1.08 (0.84–1.39)
Machine/engine mechanic	134 (1.1)	231 (1.0)	1.23 (0.99–1.52)
Metal plating/coating worker	2 (0.02)	10 (0.04)	—[d]
Assembler/other machine/ metalware	59 (0.5)	125 (0.5)	1.03 (0.76–1.41)
Electronic/telecommunications worker	37 (0.3)	47 (0.2)	1.63 (1.05–2.50)
Electronic equipment assembler	24 (0.2)	71 (0.3)	0.76 (0.48–1.21)
Wooden surface finisher	1 (0.01)	10 (0.04)	—[d]
Painter/lacquerer/floor layer	68 (0.6)	144 (0.6)	1.02 (0.76–1.37)
Printer	10 (0.1)	26 (0.1)	0.80 (0.38–1.65)
Lithographer	6 (0.1)	19 (0.1)	0.65 (0.26–1.62)
Graphics worker	9 (0.1)	22 (0.1)	0.87 (0.40–1.89)
Distiller	0 (0)	0 (0)	N/A
Cooker/furnace worker	5 (0.04)	6 (0.03)	1.73 (0.53–5.66)
Crusher/grinder/calender operator	0 (0)	0 (0)	N/A
Refinery/chemical industry worker	30 (0.3)	68 (0.3)	0.91 (0.59–1.41)
Rubber products worker	13 (0.1)	28 (0.1)	1.00 (0.52–1.93)
Plastic products worker	22 (0.2)	46 (0.2)	1.07 (0.64–1.78)
Maintenance crew/supervisor	9 (0.1)	24 (0.1)	0.83 (0.38–1.78)
Service work			
Laundry worker	16 (0.1)	31 (0.1)	1.12 (0.61–2.05)

[a] ≥5% probability of exposure in 1990 in Finland, according to FINJEM [14,15].
[b] Occupation at the 1990 occupational census, which occurred during midlife (age 40–60) and four or more years prior to PD diagnosis or control selection, by occupational group.
[c] Adjusted for age, sex, socioeconomic status, and probability of smoking.
[d] Not calculated due to small numbers.
Abbreviations: CI = confidence interval; FINJEM = Finnish Job Exposure Matrix; N/A = not applicable; OR = odds ratio

dence that other FINJEM agents were associated with increased PD risk. Accordingly, the OR for potential CHC solvent exposure only was altered by >10% by adjustment for potential for exposure to one agent, polycyclic aromatic hydrocarbons (PAH). This adjustment fully attenuated the PD-CHC solvent association (and partially attenuated ORs for individual CHC solvents). Adjustment for potential for exposure to benzo(a)pyrene (a specific PAH assessed in FINJEM at a lower threshold), or to chromium or nickel, resulted in partial attenuation of the PD-CHC solvent association. The only potential occupational exposures that strengthened the PD-CHC solvent association were agents not known as inversely associated with PD, and the effect on the OR was <10%. Environmental tobacco smoke at work did not alter the PD-CHC solvent OR, even though we confirmed an inverse association between this exposure and PD. Alcohol consumption also did not materially alter the PD-CHC solvent OR.

Most workers with potential for exposure to CHC solvents were men. However, even in men, CIs were quite wide, including for CHC solvents as a group (OR = 2.35, 95% CI 0.72–7.67). In men ORs for CHC solvents, individually and as a group, were all well above unity, whereas ORs for all other solvent groups remained close to unity, regardless of the exact approach used for calculating probability of exposure within or across FINJEM periods. In age-specific analyses, positive associations for CHC solvents were stronger among younger subjects than older subjects. Among subjects age 45–64 at diagnosis/selection, the PD-CHC solvent OR was 2.47 (95% CI 0.56–10.8) overall and 5.03 (95% CI 0.69–36.8) among men.

3.3. Occupations with potential for solvent exposure and age at PD diagnosis

For three occupations with potential for solvent exposure, cases were diagnosed with PD at a significantly younger age than other cases. Two of these associations did not appear to be due to temporal trends in occupations: laboratory assistants (2.2, 95% CI 0.31–4.13 years earlier) and refinery/chemical industry workers (3.5, 95% CI 1.0–6.0 years earlier).

4. Discussion

In this large, population-based case-control study we observed a slightly greater risk of PD in workers in some occupations that entail potential exposure to CHC solvents. This is notable because prior studies in humans and animals on the potential role of solvents in PD are particularly compelling for TCE [7–10,12,25], which is a CHC solvent. Our primary and secondary analyses together indicated possible associations between PD and not only TCE, but also the other individual CHC solvents assessed in FINJEM (1,1,1-trichloroethane, methylene chloride, and perchloroethylene) and carbon tetrachloride. In our primary analysis, the strongest association was for electronic/telecommunications workers, with a significant 63% increased risk of PD. CHC solvents are the only type of solvents to which these workers are potentially exposed in Finland, including 1,1,1-trichloroethane, TCE, perchloroethylene, and methylene chloride [14,15]. The latter three solvents have been previously associated with PD [10]. We also observed that laboratory assistants had a 40% increased risk of PD, and we note that others have found an increased risk of PD among medical lab technicians [26]. Carbon tetrachloride is the CHC solvent used in Finnish laboratories. Currently it is restricted to analysis and research use, and even in the relevant years for our study, laboratory assistants only had a 7.9% probability of exposure to CHC solvents [14,15]. Nonetheless, prior studies suggest an association between carbon tetrachloride and PD [3,10]. We observed a more modest 23% increased risk of PD for machine/engine mechanics, who are potentially exposed to a wide variety of solvents including the aromatic hydrocarbon styrene and the CHC solvents 1,1,1-trichloroethane, TCE, and methylene chloride [14,15]. Previous literature on the association between occupation as a mechanic and risk of PD is mixed [26–28]. While CHC solvents, individually or as a group, were not significantly associated with PD, the point estimates were among the largest ORs observed across all FINJEM agents considered. Furthermore, there was almost no evidence of increased PD risk in relation to any

Table 3
Risk of PD in relation to occupational exposure[a] to chlorinated hydrocarbon (CHC) solvents and other agents, and their potential to confound the PD-CHC solvent association, Finland 1995–2014.

Agent, by type		Cases N = 11,757 n (%)	Controls N = 23,236 n (%)	PD-agent OR (95% CI)[b]	Agent-adjusted PD-CHC solvent OR (95% CI)[b,c]	Confounding by agent[d]
Solvents: Chlorinated hydrocarbon	Any CHC solvents	919 (8)	1,761 (8)	1.18 (0.51-2.73)		
	1,1,1-Trichloroethane	513 (4)	1,002 (4)	3.06 (0.46-20.1)		
	Trichloroethylene	404 (3)	771 (3)	5.92 (0.56-62.2)	N/A	N/A
	Methylene chloride	356 (3)	691 (3)	16.5 (1.44-189)		
	Perchloroethylene	85 (1)	178 (1)	1.67 (0.09-30.8)		
Solvents: Aromatic hydrocarbon	Any aromatic hydrocarbon solvents	1,917 (16)	3,941 (17)	0.97 (0.72-1.30)	1.26 (0.51-3.07)	7%
	Styrene	798 (7)	1,612 (7)	1.72 (0.52-5.66)	1.11 (0.47-2.61)	-7%
	Benzene	389 (3)	775 (3)	0.70 (0.25-1.96)	1.24 (0.53-2.89)	5%
	Toluene	317 (3)	663 (3)	0.96 (0.67-1.37)	1.25 (0.52-3.00)	6%
Solvents: Other types	Aliphatic/alicyclic hydrocarbon solvents	542 (5)	1,094 (5)	1.01 (0.75-1.36)	1.20 (0.49-2.95)	2%
	Other organic solvents	603 (5)	1,253 (5)	0.99 (0.74-1.31)	1.22 (0.51-2.94)	3%
Combustion/ petroleum products	Carbon monoxide	1,655 (14)	3,271 (14)	1.04 (0.95-1.13)	1.20 (0.52-2.76)	2%
	Gasoline engine exhaust	1,041 (9)	2,213 (10)	1.05 (0.87-1.27)	1.19 (0.51-2.75)	1%
	Diesel engine exhaust	1,031 (9)	2,170 (9)	1.07 (0.84-1.34)	1.19 (0.52-2.76)	1%
	Polycyclic aromatic hydrocarbons	464 (4)	878 (4)	1.18 (1.01-1.37)	0.99 (0.42-2.36)	**-16%**
	Benzo(a)pyrene	398 (3)	763 (3)	1.29 (0.96-1.72)	1.07 (0.46-2.51)	-9%
	Gasoline (automotive or aviation)[e]	197 (2)	393 (2)	0.64 (0.18-2.22)	1.21 (0.52-2.79)	3%
	Bitumen (asphalt) fumes	129 (1)	256 (1)	1.12 (0.17-7.45)	1.18 (0.51-2.73)	0%
Sulfurous gases	Volatile sulfur compounds	1,635 (14)	3,013 (13)	1.08 (0.90-1.30)	1.19 (0.52-2.76)	1%
	Sulphur dioxide	90 (1)	202 (1)	0.99 (0.47-2.09)	1.18 (0.51-2.73)	0%
Dusts: General	Any respirable dust	3,812 (32)	7,583 (33)	1.06 (0.98-1.15)	1.19 (0.51-2.75)	1%
Dusts: Inorganic	Asbestos	1,305 (11)	2,696 (12)	1.04 (0.80-1.35)	1.18 (0.51-2.73)	0%
	Other mineral dusts	695 (6)	1,401 (6)	1.16 (0.98-1.37)	1.25 (0.54-2.88)	6%
	Quartz dust	452 (4)	867 (4)	1.23 (1.01-1.49)	1.26 (0.55-2.91)	7%
	Synthetic polymer dust	197 (2)	432 (2)	0.87 (0.33-2.27)	1.21 (0.52-2.82)	3%
Dusts: Organic	Plant dust	2,193 (19)	4,151 (18)	1.09 (0.96-1.23)	1.20 (0.52-2.78)	2%
	Animal dust	1,548 (13)	2,804 (12)	1.12 (0.96-1.31)	1.20 (0.52-2.78)	2%
	Wood dust	1,187 (10)	2,202 (9)	1.07 (0.92-1.23)	1.20 (0.52-2.78)	2%
	Hardwood dust	1,187 (10)	2,202 (9)	1.08 (0.90-1.29)	1.20 (0.52-2.77)	2%
	Softwood dust	1,187 (10)	2,202 (9)	1.08 (0.91-1.27)	1.20 (0.52-2.78)	2%
	Flour dust	591 (5)	1,270 (5)	0.68 (0.42-1.11)	1.16 (0.50-2.68)	-2%
	Pulp or paper dust	526 (4)	1,138 (5)	0.64 (0.40-1.03)	1.16 (0.50-2.67)	-2%
	Textile dust	193 (2)	448 (2)	0.90 (0.68-1.20)	1.18 (0.51-2.73)	0%
	Leather dust	13 (0.1)	56 (0.2)	0.11 (0.01-0.85)	1.19 (0.52-2.76)	1%
Metals and related	Lead	909 (8)	1,917 (8)	0.89 (0.66-1.21)	1.28 (0.55-3.02)	8%
	Chromium	789 (7)	1,675 (7)	1.16 (0.84-1.61)	1.08 (0.45-2.57)	-8%
	Nickel	715 (6)	1,472 (6)	1.20 (0.86-1.66)	1.08 (0.46-2.55)	-8%
	Manganese-containing welding fume[e]	648 (6)	1,339 (6)	0.99 (0.82-1.20)	1.18 (0.51-2.73)	0%
	Iron	648 (6)	1,339 (6)	1.06 (0.91-1.23)	1.14 (0.49-2.65)	-3%
	Cadmium	557 (5)	1,113 (5)	1.28 (0.69-2.38)	1.16 (0.50-2.68)	-2%
	Arsenic	326 (3)	679 (3)	0.65 (0.10-4.24)	1.18 (0.51-2.72)	0%
	Metalworking fluid mist	404 (3)	777 (3)	1.11 (0.87-1.41)	1.13 (0.48-2.64)	-4%
Pesticides	Fungicides	1,581 (13)	2,894 (12)	1.45 (1.02-2.04)	1.22 (0.53-2.81)	3%
	Herbicides	1,497 (13)	2,744 (12)	1.14 (0.92-1.40)	1.20 (0.52-2.76)	2%
	Insecticides	1,456 (12)	2,616 (11)	1.88 (1.02-3.47)	1.20 (0.52-2.78)	2%
Other chemical agents	Environmental tobacco smoke at work[e]	7,743 (66)	15,756 (68)	0.84 (0.52-1.35)	1.18 (0.51-2.73)	0%
	Detergents, excluding solvents	3,779 (32)	7,219 (31)	1.13 (1.04-1.22)	1.18 (0.51-2.74)	0%
	Formaldehyde	561 (5)	1,248 (5)	0.95 (0.61-1.48)	1.21 (0.52-2.83)	3%
Radiation/ ultrasound	Low frequency magnetic fields	2,808 (24)	5,771 (25)	0.99 (0.92-1.06)	1.19 (0.52-2.76)	1%
	Ultraviolet radiation	2,672 (23)	5,017 (22)	1.18 (0.97-1.43)	1.24 (0.54-2.87)	5%
	Ionizing radiation	915 (8)	1,713 (7)	3.39 (0.35-32.6)	1.18 (0.51-2.74)	0%
	Low-frequency ultrasound	486 (4)	945 (4)	1.56 (0.74-3.25)	1.17 (0.50-2.70)	-1%
	Radio frequency radiation	73 (1)	177 (1)	0.64 (0.17-2.49)	1.19 (0.51-2.74)	1%
Extreme temperature	Cold	5,419 (46)	10,859 (47)	1.02 (0.93-1.12)	1.22 (0.52-2.84)	3%
	Heat	2,554 (22)	5,030 (22)	0.99 (0.93-1.06)	1.19 (0.51-2.75)	1%
Noise/vibration	Mean noise >80 decibels	3,000 (26)	6,369 (27)	1.06 (0.90-1.25)	1.18 (0.51-2.72)	0%
	Noise impulsiveness	222 (2)	455 (2)	1.13 (0.77-1.63)	1.17 (0.51-2.70)	-1%
	Hand vibration	101 (1)	234 (1)	0.71 (0.40-1.29)	1.23 (0.53-2.87)	4%

(*continued on next page*)

Table 3 (*continued*)

Agent, by type		Cases N = 11,757 n (%)	Controls N = 23,236 n (%)	PD-agent OR (95% CI)[b]	Agent-adjusted PD-CHC solvent OR (95% CI)[b,c]	Confounding by agent[d]
Night work	Night work	5,404 (46)	11,220 (48)	0.89 (0.75-1.04)	1.17 (0.50-2.70)	-1%
	Ergonomic/physiologic stress		Work with video display units[e]	7,205 (61)	14,219 (61)	0.83 (0.71-0.97)
1.20 (0.52-2.77)	2%			Perceived physical work load	6,457 (55)	12,647 (54)
1.16 (1.05-1.27)	1.17 (0.51-2.70)	-1%				
	Manual handling of burdens	3,652 (31)	7,454 (32)	1.05 (0.93-1.18)	1.20 (0.52-2.77)	2%
	Inconvenient/difficult work postures	3,496 (30)	6,646 (29)	1.17 (0.98-1.41)	1.22 (0.53-2.81)	3%
	Repetitive work movements	2,908 (25)	6,249 (27)	0.96 (0.83-1.12)	1.17 (0.51-2.71)	-1%
	Sedentary work	2,220 (19)	4,419 (19)	1.00 (0.89-1.11)	1.18 (0.51-2.73)	0%
	High accident risk	2,120 (18)	4,597 (20)	0.89 (0.73-1.09)	1.13 (0.49-2.63)	-4%
	Standing work	1,396 (12)	2,517 (11)	1.30 (1.00-1.70)	1.08 (0.46-2.53)	-8%

[a] Potential for exposure as determined from each subject's occupation in the 1990 census and from the probability of exposure to the respective agent in the 1960–1984 and 1985–1994 periods in FINJEM [14,15]. Specifically, we used a time-weighted value based on the probabilities in the 1960–1984 and 1985–1994 FINJEM periods and which calendar years each worker ranged from age 30–60 (or the age five years prior to PD diagnosis, whichever was younger). We applied the probability of exposure to the respective solvent for the 1960–1984 FINJEM period to the portion of the age range that fell into this calendar year range, given their birth year and year of diagnosis, while we applied the probability for the 1985–1994 FINJEM period to the remaining portion. We then calculated the mean probability across the total period. For all cases and controls the 1990 census was four or more years prior to diagnosis/selection.

[b] Probability of exposure is coded as 0 to ≤1 (continuous), such that the OR represents the risk ratio of PD in workers with 100% vs. 0% probability of exposure to the respective agent. All ORs are adjusted for age, sex, SES, and probability of smoking.

[c] Also adjusted for the FINJEM agent specified in the respective row.

[d] Change in estimate, a measure of potential confounding, calculated as the agent-adjusted PD-CHC solvent OR minus the PD-CHC solvent OR without adjustment for the respective agent, all divided by the latter, in order to assess whether the agent might confound the association between CHC solvents and PD. Percentages in excess of ±10% are bolded to indicate potential confounding of the PD-CHC solvent OR by this agent.

[e] Could be classified in multiple categories (gasoline contains benzene; welding fume and tobacco smoke also contain combustion byproducts; work with video display units also entails exposure to electromagnetic radiation).

Abbreviations: CHC = chlorinated hydrocarbon; CI = confidence interval; FINJEM = Finnish Job Exposure Matrix; N/A = not applicable; OR = odds ratio; PD = Parkinson disease; SES = socioeconomic status.

solvents other than CHC solvents. Moreover, this contrast remained clear when we restricted to men, who represented the majority of workers in our study with potential for exposure to solvents. The relative specificity of results across four classes of solvents, as well as across a wide variety of FINJEM agents, further supports the possibility that occupational exposure to CHC solvents might increase PD risk.

Important strengths of our study were the comprehensive method for identifying both PD cases and comparable controls throughout the population of Finland and an established case ascertainment method [16]. The Finnish medication register covers the entire population and provides independent verification of the need for antiparkinsonian medication. The demonstration of the previously observed inverse associations between PD and smoking [19,29], environmental tobacco smoke [30], alcohol consumption [31], and SES [24,32] further demonstrates the robustness of our approach. Another strength is that we considered individual solvents and solvent classes separately. Other important strengths include that the potential for exposure to solvents and other FINJEM agents was determined by expert assessment based on industrial measurements [14] and that the resulting job exposure matrix allowed for objective assessment of the potential for exposure to each agent. Combined with our census-based method for identifying occupation, any positive associations we observed for solvent exposed occupations or solvents cannot be attributed to differential recall, reporting, or exposure ascertainment between subjects with and without PD. In addition, because we focused on an occupation that each subject held four or more years before diagnosis of PD or selection as a control, it is unlikely that symptoms of prodromal PD affected results substantially.

Given the above strengths, the most obvious alternative explanations for the potential positive associations between CHC solvents and PD are either chance or confounding by occupational co-exposures that might increase the risk of PD. Notably, adjustment for PAH and some metals, particularly chromium and nickel, attenuated the relation between PD and CHC solvents. In addition, this association also could be confounded by co-exposures that are not in FINJEM, possibly polychlorinated biphenyls, for example.

While the potential for confounding by occupational co-exposures calls into question whether exposure to CHC solvents increases PD risk, this concern is at least partly balanced by study limitations. The associations between PD and most occupations that entail solvent exposure, as well as between PD and most agents in FINJEM, including solvents, were likely biased downward, potentially past unity. That is because most of these occupations and exposures are more common among individuals with lower levels of education, and our ability to adjust for education and its correlates, SES and smoking, was limited. This is a concern because a prior large, population-based study consistently observed greater PD mortality in higher SES occupations than lower SES occupations in general [24]. Most notably, both past and current smoking are strongly associated with a reduced risk of PD [29], and an interview-based study has shown that the association between PD and CHC solvents is biased downward without adjustment for SES and smoking [32]. However, in our records-based study we used a probabilistic measure of smoking based on occupation at one time point and sex. While it was a considerable strength that we were able to address both smoking and SES, residual confounding by both remains likely. In addition, we used one occupational census and

group-level ascertainment of exposures via a job exposure matrix, rather than individual-level ascertainment. Probability of exposure was based on occupation, without information on an individual's specific work tasks, use of personal protective equipment, and work environment (e.g., ventilation and temperature), which affect exposure [33]. We also did not assess cumulative exposure, which would encompass not only the probability of exposure, our focus, but also level and duration of exposure, which we did not consider. These various sources of exposure measurement error might have reduced our ability to detect associations. Compounding the above potential biases was a lack of statistical power for CHC solvents due to the low probability of exposure. Nevertheless, future studies that examine the association between CHC solvents and PD might be particularly useful in populations where there is a greater range of exposures and in studies with information on cumulative exposure, occupational co-exposures, and smoking.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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