

# A Cohort Study of Parkinson's Disease and Other Neurodegenerative Disorders in Danish Welders

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Mild and stainless-steel welding may be associated with the inhalation of fume particulates containing iron, manganese, zinc, copper, chromium (chromium alloyed steel), and trace amounts of several other metals, including vanadium and nickel, as well as gases such as ozone, carbon monoxide, and carbon dioxide.<sup>1-3</sup> Although heavy occupational exposure to manganese among foundry workers and miners has been associated with a neurological disorder that resembles Parkinson's disease (PD),<sup>4</sup> the possibility has been raised that low-level exposure to manganese fumes or other compounds released into ambient air by metal welding also may increase the risk of PD<sup>5-8</sup> or accelerate age at onset of the disease.<sup>9</sup> Several case reports have described parkinsonism or manganese in welders,<sup>10-15</sup> but the evidence of causality based on such reports is equivocal, given the large numbers of welders worldwide and the extensive use of welding technology since the 1940s. Further, case-control studies of PD<sup>16-20</sup> have not established an association with occupational exposure to manganese or welding.

**Objective:** We sought to evaluate rates of hospitalizations for neurodegenerative disorders in a cohort of Danish metal manufacturing employees. **Methods:** A retrospective cohort study was conducted from 1977 to 2002 among 27,839 male Danish metal-manufacturing employees, with 9,817 of those employed in departments engaged in mild or stainless-steel welding and 6,163 welders. **Results:** The standardized hospitalization ratio and 95% confidence intervals (CI) for Parkinson's disease were 0.9 (CI = 0.7-1.2) for men in steel-manufacturing companies, 1.0 (CI = 0.7-1.5) for men in welding departments, and 0.9 (CI = 0.4-1.5) for welders. Observed numbers for other neurological conditions were small and not above population expectations. Analyses for time period worked, age, and duration of welding were unremarkable. **Conclusions:** This relatively large cohort study with long-term follow-up provides no support for the hypothesis that rates of hospitalization for Parkinson's disease or other neurological conditions are elevated under the exposure circumstances of these Danish workers. (J Occup Environ Med. 2005;47:466-472)

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An established cohort of Danish male mild and stainless-steel welders<sup>21</sup> gave us the opportunity to examine more fully the association between PD and other neurological conditions and welding. Using this cohort, we conducted a follow-up study among men working in companies in Denmark where mild or stainless-steel welding is performed.

To our knowledge, this is the first cohort study of PD and other neurologic diseases among welders.

## Materials and Methods

### Study Population

The study base consisted of 27,839 male employees, including both persons exposed and nonexposed to welding fumes, who were born before 1965, alive on January 1, 1977, and who had been employed for a minimum of 12 months during 1964 to 1984 in 1 of 79 selected iron and metal goods-manufacturing companies in Denmark with various degrees of metal-welding activities. This cohort originally was designed with the aim of studying lung cancer risk among welders; the subcohorts of welding exposed workers were established through several steps.<sup>21</sup>

Initially, companies were identified from a previous survey of Danish stainless-steel companies in 1982 and, after the exclusion of all shipyards (because of the potential for asbestos exposures confounding the relationship between welding and lung cancer risk in the original study) and companies with fewer than five stainless-steel workers, 74 companies remained, representing some 60% of all stainless-steel welders in Denmark. Additionally, five large companies with a substantial number of mild steel workers each were identified and included in the study. Because it was recognized that the employment records on previous workers kept at the 79 companies were incomplete, study cohort members were identified through the files of the National Supplementary Pension Fund on the basis of the unique tax-number of each of the 79 companies. Membership of this pension scheme has been compulsory for all employees in Denmark since April 1, 1964. Information on all employees with respect to name, unique personal identification number (PIN), company tax-number, and dates of start and end of each employment is computerized and retained even

after a person retires or dies, and data in this Registry are regarded as complete.<sup>22</sup> Since 1968, the PIN, a unique number that encodes both sex and date of birth, is assigned to all Danish citizens at birth by the Central Population Register. Use of the PIN secures valid linkage between registries such as the National Supplementary Pension Fund and the hospital registries.

All the selected 79 companies were visited when the original study was initiated in 1986 to identify the subgroup of welding-exposed workers. Through the collection of information from company records and interviews with supervisors and long-term workers, a subgroup of 9,817 of the 27,839 workers was verified as having worked in welding departments and potentially being exposed to welding fumes. Within this group, detailed information on occupational histories and tobacco smoking habits was obtained in 1986 by use of a self-administered questionnaire mailed to living workers (90%), or by interviews with next of kin or long-term colleagues of deceased workers, and those working specifically as welders were identified. The detailed information collected included first date ever employed in welding, type of welding (mild steel vs. stainless steel), use of ventilation, frequency of welding in small rooms, and smoking habits. Among the 9817 potential responders, information from the self-administered questionnaire or from the surrogate interviews of deceased workers was obtained for 8190 (83%).

### PD and Other Neurological Conditions

The disease experience of the cohort was identified by linkage with the Danish National Register of Patients, which since 1977 has maintained a computerized listing of all hospital admissions. A registration of all outpatient activities was added in 1995. Each admission or outpatient

visit initiates a record, which includes the PIN number of the patient, the date of discharge from hospital, or the date of the outpatient visit, and codes for the primary diagnosis at discharge or visit as well as up to 19 auxiliary diagnoses, coded according to the Danish versions of the International Classification of Diseases (ICD), 8th revision up to 1993 and 10th revision thereafter. Only codes representing the primary diagnosis were used in the present study. The diseases (and codes) of interest for this analysis included PD (ICD8 342.0, ICD10 G20), secondary parkinsonism (ICD8 342.1, ICD10 G21), other degenerative diseases of basal ganglia (ICD10 G23), dystonia (ICD10 G24), other extrapyramidal and movement disorders (ICD 10 G25), parkinsonism in diseases classified elsewhere (ICD10 G22), and poisoning caused by manganese and its compounds (ICD10 T57.2).

### Follow-up

Follow-up began on the date first worked or January 1, 1977, whichever occurred later (thus, only original study cohort members<sup>21</sup> alive at the start of 1977 were included in the present study). All individuals in the cohort were followed through 2002 for first-time hospitalization or outpatient visit with one of the neurological diseases of interest as the primary diagnosis. Individuals were censored on the first occurrence of either hospitalization as the result of a primary diagnosis of one of the neurological conditions of interest, death, emigration from Denmark, or end of study (December 31, 2002). Information on emigration and death was obtained through linkage with the files of the Central Population Register. Because information on welders deceased between 1977 (start of follow-up) and 1986 (mailing of questionnaire) could be gathered from their next of kin or long-term colleagues, a supplemental analysis for welders with questionnaire data was conducted with follow-up beginning on September 1, 1986.

## Statistical Analyses

Observed and expected numbers of hospitalizations were determined for the total cohort of iron and metal goods manufacturing employees, for those who worked in welding departments, for questionnaire responders who worked in welding departments, and for those who indicated that they worked specifically as welders. For each specific neurological disease, a standardized disease-specific hospitalization rate ratio (SHR = observed/expected cases of disease) was calculated as a measure of the rate of first-time hospitalization for a given condition (as a primary diagnosis) relative to that of the Danish population. This measure may be interpreted as the relative occurrence of the specific disease under investigation compared with the national average. To calculate the expected number of cases, national hospitalization rates were first constructed by dividing the number of patients in the Register of Patients with a pri-

mary diagnosis of one of the specific diseases by the corresponding average person-years for men in the general population in 5-year age- and calendar-periods. The expected number of cases in each group was then determined by multiplying the age- and calendar-period-specific person-years of follow-up in the cohort by the national rates. Ninety-five percent confidence intervals (95% CI) were calculated around the SHR assuming a Poisson distribution for the observed number of cases.<sup>23,24</sup> Logistic regression analysis was used to assess the significance of the trend in risk of PD associated with smoking.<sup>24</sup> Because previous studies have shown inverse trends with smoking,<sup>25</sup> a one-tailed test was used.

## Results

Characteristics of the entire group of men included in this study ( $n = 27,839$ ), the entire subgroup of welding exposed persons ( $n = 9817$ ),

the total subgroup responding to the questionnaire ( $n = 8190$ ), and the welders ( $n = 6163$ ) are shown in Table 1. There were more than 600,000 person-years of follow-up in the total cohort, with more than 213,000 and 140,000 person-years of follow-up accrued among those employed in the welder department and among those welders defined in the questionnaire data, respectively. Nearly 60% of the workers were born after 1940, with a mean age at entry of follow-up of 37 years. For welders, the mean age at first welding was 22 years. More than 50% of those working in the welding departments or working as welders were current smokers in 1986.

Sixty-nine cases of PD were identified overall, with 25 among those in welding departments and 11 among welders (Table 2). The SHR for PD for the total cohort was 0.9 (95% CI = 0.7–1.2). The SHRs for PD among those who worked in welding departments was 1.0 (95% CI =

**TABLE 1**  
Characteristics of the Cohort of Workers Employed for a Minimum of 12 Months

	Employees in Welding Companies		Workers in Welding Departments		Questionnaire Responders			
	N	(%)	N	(%)	Total		Welders	
	N	(%)	N	(%)	N	(%)	N	(%)
Follow-up of cohorts (N and person-years (p-y))	27,839	626,561 p-y	9,817	213,431 p-y	8,190	183,003 p-y	6,163	142,466 p-y
Mean years of follow-up (range)	22.5	(0–26)	21.7	(0–26)	23.3	(0–26)	24.1	(0–26)
Vital Status								
Alive	20,077	(72)	7,340	(73)	6,061	(74)	4,872	(79)
Dead	7,309	(26)	2,561	(26)	2,038	(25)	1,222	(20)
Emigrated	428	(2)	148	(2)	82	(1)	63	(1)
Unknown	25	(0)	10	(0)	9	(0)	6	(0)
Year of Birth								
<1920	2,912	(10)	1,092	(11)	775	(9)	350	(6)
1920–1929	3,593	(13)	1,283	(13)	1,069	(13)	635	(10)
1930–1939	4,955	(18)	1,837	(18)	1,515	(19)	1,166	(19)
1940–1949	8,467	(30)	2,978	(30)	2,445	(30)	2,048	(33)
1950–1959	5,809	(21)	2,178	(22)	1,811	(22)	1,465	(24)
1960+	2,103	(8)	691	(7)	575	(7)	499	(8)
Smoking Status (as of questionnaire in 1986)								
Current	—	—	—	—	4,747	(58)	3,563	(58)
Former	—	—	—	—	1,958	(24)	1,469	(24)
Never	—	—	—	—	1,381	(17)	1,089	(17)
Missing	—	—	—	—	104	(1)	42	(1)

CI = Confidence interval.

TABLE 2

Observed (Obs) Number of Hospitalizations, Standardized Disease Ratios (SHR) and 95% Confidence Interval (CI) for Parkinson's Disease and Other Neurological Conditions Among the Total Cohort, and Those who Worked in Welding Departments by Response Group

Disease category	Workers in welding departments									
	Employees in welding companies (N = 27,839)		All welding exposed workers (n = 9,817)		Questionnaire response status					
	Obs	SHR (95% CI)	Obs	SHR (95% CI)	Welders (n = 6,163)		Metal workers (n = 2,027)		Non-responders (n = 1,627)	
	Obs	SHR (95% CI)	Obs	SHR (95% CI)	Obs	SHR (95% CI)	Obs	SHR (95% CI)	Obs	SHR (95% CI)
Parkinson's disease	69	0.9 (0.7-1.2)	25	1.0 (0.7-1.5)	11	0.9 (0.4-1.5)	8	0.9 (0.4-1.8)	6	1.5 (0.6-3.4)
Secondary parkinsonism*	6	0.5 (0.3-2.0)	2	1.0 (0.1-3.5)	1	0.7 (0.0-4.1)	0	0.0 (0.0-6.0)	1	1.4 (0.0-7.5)
Parkinsonism in diseases classified elsewhere*	0	0.0 (0.00-4.0)	0	0.0 (0.0-12.6)	0	0.0 (0.0-19.4)	0	0.0 (0.0-41.0)	0	0.0 (0.0-369)
Other degenerative diseases of basal ganglia*	1	0.3 (0.0-1.8)	0	0.0 (0.0-3.8)	0	0.0 (0.0-5.7)	0	0.0 (0.0-13.7)	0	0.0 (0.0-73.8)
Dystonia*	10	1.0 (0.5-1.8)	2	0.6 (0.1-2.2)	2	0.8 (0.0-2.9)	0	0.0 (0.0-5.4)	0	0.0 (0.0-28.4)
Other extrapyramidal and movement disorders*	7	0.6 (0.2-1.2)	2	0.5 (0.1-1.9)	2	0.6 (0.0-2.7)	0	0.0 (0.0-4.1)	0	0.0 (0.0-16)

\*1994-2002 (ICD-10).

0.7-1.5), and for the subgroups of welders, other welding exposed metal workers, and nonresponders were 0.9 (95% CI = 0.4-1.5), 0.9 (95% CI = 0.4-1.8), and 1.5 (95% CI = 0.6-3.4), respectively. When follow-up was restricted to begin in 1986 (the year the questionnaire was completed), the SHR for PD among welders ( $n = 11$ ) did not change materially (SHR = 0.9, 95% CI = 0.4-1.7). The mean age at onset of PD among the 11 welders was 67 years (95% CI = 61-71), not different than the mean age of 68 years (95% CI = 64-72) among the workers in welding departments and of 70 years (95% CI = 68-72) among the workers in the total 79 companies with welding activities.

In addition to PD, 24 cases of other neurological diseases were found in the total group of employees in the welding companies. These included 6 cases of secondary parkinsonism (1 among welders), 1 of other degenerative diseases of basal ganglia, 10 of dystonia (2 among welders), and 7 cases of other extrapyramidal and movement disorders (2 among welders). No cases of poi-

soning attributable to manganese were reported in the cohort. The observed numbers of hospitalizations for these conditions were, although based on small numbers, all similar to those expected based on national rates of hospitalization among Danish men of similar age (Table 2).

Table 3 shows stratified SHR analyses performed among the sub group of self-defined welders by calendar time period (1977 to 1992 vs. 1993 to 2002), attained age (<65 vs. 65+ years), duration of time spent welding (less than 10 years, 10 to 20 years, and greater than 20 years) and three levels of smoking (none, light, and heavy). The differences between the occupational categories tended to be small, with SHRs showing no significant deviations from unity, indicating no association between PD and calendar time, attained age, and duration of welding. We saw an inverse association between smoking habits and PD, with a nearly fourfold higher risk among nonsmokers compared with that of heavy smokers. Finally, nonsignificant differences were observed between the SHRs for PD for those who ever worked in

stainless-steel welding (SHR = 0.8; 95% CI = 0.3-1.7) and mild steel welding (SHR = 0.9; 95% CI = 0.5-1.6).

## Discussion

To our knowledge, this epidemiologic cohort study of Parkinson's disease and other neurodegenerative disorders is the first undertaken among men employed as welders. The rates of hospitalization for PD and other neurological illnesses were examined in approximately 6,000 Danish welders with more than 140,000 person-years of observation. The rates of these conditions were compatible with those of the general population of Denmark. Also, examination of the rates of PD by various occupational characteristics among welders was unremarkable. Moreover, the average age of first hospitalization for PD was not different among welders, all workers in welding departments, and all employees in iron and metal goods-manufacturing companies.

Few well-designed epidemiologic studies have evaluated risk of neurological disease among metal welders.

TABLE 3

Observed Number of Cases, Expected Number of Cases, Standardized Disease Ratios (SHR) and 95% Confidence Intervals (CI) for Parkinson's Disease for Welders (n = 6,163) for Various Occupational and Lifestyle Characteristics

	Person-years	Observed Cases of PD	Expected Cases of PD	SHR	95% CI
Calendar Time					
1977-1992	89,022	4	5.01	0.80	(0.21-2.04)
1993-2002	53,443	7	7.91	0.88	(0.35-1.82)
Attained Age					
Less than 65 years old	129,838	5	4.43	1.13	(0.36-2.63)
65 years or older	12,626	6	8.50	0.71	(0.26-1.54)
Duration of time spent welding*					
Less than 10 years	67,268	4	4.48	0.89	(0.24-2.28)
10 to 20 years	41,912	3	2.73	1.10	(0.22-3.21)
More than 20 years	31,781	4	5.16	0.77	(0.21-1.98)
Smoking†					
Non-Smokers	26,276	3	1.58	1.90	(0.38-5.54)
Former/Light Smokers‡	57,718	6	7.30	0.82	(0.30-1.79)
Heavy Smokers§	58,024	2	3.97	0.50	(0.06-1.82)
one-tailed categorical trend:					p = 0.07

\*110 people had missing information for duration of welding.

†42 people had missing smoking information.

‡Former smokers and current smokers who smoke less than 10 cigarettes a day.

§Current smokers who smoke 10 or more cigarettes per day.

A report from India<sup>5</sup> noted the occurrence of manganese poisoning among welders, but the numbers involved were small and selection criteria for the groups compared were not well defined. A case-control study of PD involving 144 cases in the Detroit area in the United States found that slightly more cases than controls reported occupational exposures to manganese for 20 years or more, leading to an elevated odds ratio (OR) of 10.61 (95% CI = 1.06-105.83) for PD; none of the cases had worked as a welder.<sup>6-8</sup> In a recent re-analysis of these data, no significant link between occupational exposure to manganese and PD was found.<sup>16</sup> A small pilot study in Seattle, Washington, reported that 3 of 16 male cases of PD but none of 9 other neurology clinic control patients had a history of employment as a welder.<sup>17</sup> Case-control studies involving 130 cases of PD in Canada<sup>18</sup> and 380 in Germany<sup>19</sup> reported no association between PD and occupational exposure to manganese. In a comparison of serum and urinary manganese levels, no significant differences were seen between 29 PD cases and 27 matched controls in Spain.<sup>26</sup> In a review of occupational

histories among twins discordant for PD, no association (OR = 1.0) between work as a welder and risk of PD was found.<sup>27</sup> Preliminary results from a recent cross-sectional survey involving screening of more than 2000 welders found that nearly 25% were said to have definite or probable PD using a "liberal" classification of the disease and the prevalence was said to be four times greater than expected based on the prevalence of the US population.<sup>28</sup> The very high percentage with PD, however, suggests that the unusual criteria were used for diagnosis of PD in the study group and the lack of control group hinders an informative interpretation of the reported prevalence ratios. In South Korea, interviews with 105 PD patients and 230 controls revealed no significant association between PD and self-reported occupational exposure to manganese.<sup>20</sup>

In a chart review of 15 patients with PD who identified themselves as welders, Racette et al<sup>9</sup> reported that the average age at onset for these patients was 46 years, whereas the average age at onset in other PD patients was 63 years. The authors raised the possibility that welding may lead to an earlier age at onset of

PD, but this study appears systematically biased by differences in the age structure of the patients who were welders versus patients who were not.<sup>29</sup> The ages at first hospitalization for PD among Danish welders in our study were typically in the 1960s and 1970s, with an average age of 67 years and a lower age range of 56 years. Similarly, Goldman et al,<sup>30</sup> in a medical record review of PD cases, failed to find a younger age at onset among welders or other occupational groups.

The one notable association in our study was the inverse relationship between cigarette smoking and PD, with a nearly fourfold lower rate of the disease among heavy smokers compared with nonsmokers, although a test for trend was marginally significant ( $P = 0.07$ ). The finding supports the collective scientific data available from other studies, in which smoking is consistently linked to reduced PD risk.<sup>31</sup> Thus, a higher prevalence of smoking among welders compared with the general population could contribute to our observation of a slightly reduced risk of PD among welders. However, according to the 1986 questionnaire, 58% of the welders

currently smoked. This was in agreement with the 53% prevalence of smokers for those that were age 20 to 59 reported in the general population of Denmark during the mid-1980s.<sup>32,33</sup> In addition, the risk of PD in welders ( $n = 6163$ ; SHR = 0.9; 95% CI = 0.4–1.5) was similar to the risk of PD in the other metal workers with equivalent smoking prevalences who worked in welding departments but were not welders ( $n = 2027$ ; SHR = 0.9; 95% CI = 0.4–1.8).

It has been reported that the proportion of misclassified patients with a PD diagnosis may be as high as 25%.<sup>34</sup> To examine the extent of a false positive diagnosis of PD in the files of the Danish National Register of Patients, the original medical records were requested for a random sample of 125 patients identified as having PD through the hospital registries, representatively distributed at hospitals throughout Denmark and diagnosed with PD between 1977 and 2000. A total of 94 (75%) of the requested medical records were received from hospitals and regional archives. On the basis of a careful examination of available information in the medical records, 75 (80%) of the records confirmed the PD diagnosis, 16% had an uncertain PD diagnosis, and 4% had an apparent incorrect PD diagnosis. Although based on small numbers, no major geographical differences were indicated between different regions in Denmark regarding uncertain and misclassified PD patients. Our small survey indicated that the proportion of false-positive diagnoses of PD in the files of the Danish National Patient register is likely to be less than 25%. If such misclassification is nondifferential, the reported SHRs may be slightly biased toward unity. However, the rates of PD are generally somewhat higher in the rural areas than in cities, and the investigated workers lived primarily in the cities, which to some extent may tend to underestimate the estimated SHRs of PD.<sup>35</sup>

This study does have some limitations. Because cases were identified only if recorded in the Register of Patients since 1977, with the inclusion of out-patient visits beginning in 1995, only cases of PD or other neurological conditions serious enough to require hospitalization before 1996 were ascertained. However, PD typically is associated with regular hospital visits and therefore workers with manifest PD would likely have a hospitalization sometime during follow-up for their neurological or other illness. The study questionnaire was administered in 1986; therefore, job exposures after this time period were not collected, and specific cumulative exposure information could not be established. In addition, the rather small number of cases among welders precludes additional analyses of risk related to welding characteristics that may influence the level of exposure to manganese and other metals, such as method of welding, work in confined spaces and use of exhaust ventilation. Nevertheless, the available information was sufficient to identify and classify welding company employees, and ascertain those who had worked as welders, including those welding for an extended period of time.

Although the levels of exposure to metal fumes, including manganese and other agents, are not known for the study subjects, a survey based on more than one thousand measurements of welding fume particulates in the Danish industry during 1971 to 1981 showed a time-weighted median total dust concentration in the breathing zone ranging between 0.9 and 5.2 mg/m<sup>3</sup> depending on type of steel and welding methods.<sup>36</sup> Exposure levels in the Danish industry may have been higher in the 1950s and 1960s. The welders in our cohort may have been less exposed because exposure levels are lower in stainless-steel welding<sup>36</sup> and high-level exposure environments like shipyards were left out of the cohort. Therefore, rates for PD found for

welders in the present study may not necessarily be representative for welders exposed to higher levels of welding fumes and during occupational conditions different from those in Denmark.

## Conclusions

The major strengths of this study include a well-defined study population with long-term follow-up. The population and hospital registries used covered the entire population of Denmark with systematic ascertainment of PD and other neurologic disorders. The upper confidence limit of the SHR for PD among welders was 1.5, suggesting that effects of this magnitude or larger can be ruled out, anticipating no bias and confounding. In conclusion, this cohort of Danish welders with more than 20 years of systematic follow-up had rates of PD and other neurological conditions consistent with those of the general population of Denmark.

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