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Increased risk of parkinsonism associated with welding exposure

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ABSTRACT

Objective: Manganese (Mn), an established neurotoxicant, is a common component of welding fume. The neurological phenotype associated with welding exposures has not been well described. Prior epidemiologic evidence linking occupational welding to parkinsonism is mixed, and remains controversial.

Methods: This was a cross-sectional and nested case–control study to investigate the prevalence and phenotype of parkinsonism among 811 shipyard and fabrication welders recruited from trade unions. Two reference groups included 59 non-welder trade workers and 118 newly diagnosed, untreated idiopathic PD patients. Study subjects were examined by a movement disorders specialist using the Unified Parkinson Disease Rating Scale motor subsection 3 (UPDRS3). Parkinsonism cases were defined as welders with UPDRS3 score $\geq$15. Normal was defined as UPDRS3 $<$ 6. Exposure was classified as intensity adjusted, cumulative years of welding. Adjusted prevalence ratios for parkinsonism were calculated in relation to quartiles of welding years.

Results: The overall prevalence estimate of parkinsonism was 15.6% in welding exposed workers compared to 0% in the reference group. Among welders, we observed a U-shaped dose–response relation between weighted welding exposure-years and parkinsonism. UPDRS3 scores for most domains were similar between welders and newly diagnosed idiopathic Parkinson disease (PD) patients, except for greater frequency of rest tremor and asymmetry in PD patients.

Conclusion: This work-site based study among welders demonstrates a high prevalence of parkinsonism compared to nonwelding-exposed workers and a clinical phenotype that overlaps substantially with PD.

1. Introduction

Over one million workers are exposed to manganese (Mn) containing welding fume as part of normal work duties (Antonini, 2003). Mn is an established neurotoxicant that causes a severe, atypical parkinsonian syndrome with high levels of exposure (Couper, 1837; Rodier, 1955). Contemporary exposures are substantially lower, perhaps by an order of magnitude, than historical exposures, from which much of the clinical descriptive literature is derived (Myers et al., 2003; Rodier, 1955; Ruhf, 1978). Studies suggest that 62–72% of welding exposed American workers are overexposed as defined by the American Conference of Governmental Industrial Hygienists (ACGIH) threshold limit value (TLV) for Mn (ACGIH, 1992; Korczynski, 2000; Susi, 2000). As such, occupational welding exposure provides an excellent opportunity to investigate the neurotoxic health effects of environmental Mn exposure.

The association between parkinsonism and exposure to welding fume is controversial. We previously reported an increased prevalence of parkinsonism in welders relative to a non-exposed reference population in a cross-sectional study of parkinsonism in Alabama welders (Racette et al., 2005). However, other studies have found no relations between occupational

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welding exposure and PD in movement disorders clinic based case–control studies (Goldman et al., 2005) or in cohort studies relying on PD hospitalization or mortality as the outcome (Fored et al., 2006; Fryzek et al., 2005). Differing methodologies for determining clinical diagnoses and assessing welding exposures may explain these discrepant findings. This study was designed to investigate the dose–response relation between welding fume and parkinsonism based on standardized clinical evaluations performed by movement disorders experts, and to compare the distinctive parkinsonian features in Mn-exposed workers from welding job sites to those of newly diagnosed, untreated PD patients.

2. Methods

2.1. Informed consent

This study was approved by Human Subjects committees at Washington University in St. Louis, MO and the University of Washington in Seattle, WA. Written informed consent, that included an explanation of the procedures and purpose of the study, was obtained from each subject.

2.2. Subjects and design

Welders were identified from the union membership list, and recruited from employees of two Midwestern US shipyards and one indoor fabrication shop between the years 2006 and 2011. To be included in the list, workers had to have been employed for at least 90 days. No workers were excluded from participation. All subjects were engaged in shipbuilding or repair or heavy equipment fabrication and were recruited by phone and mail. Welders were compared to two reference groups. To compare the prevalence of parkinsonism in welders to a working population, we recruited a group of 59 union workers from the same region as welders but with no welding exposure (defined as less than 100 lifetime welding hours). These workers were recruited by the local trade union directly and we were not provided a membership list. To compare parkinsonian signs in welders to patients with PD, we extracted initial UPDRS3 data from the clinical database on 118 consecutive, newly diagnosed, untreated PD patients from the Movement Disorders Center at Washington University School of Medicine evaluated from 1996 to 2011.

2.3. Assessments

2.3.1. Clinical assessment

One of two movement disorders trained neurologists performed a neurologic exam that included the Unified Parkinson Disease Rating Motor Scale 3 (UPDRS3) on each subject (Fahn and Elton, 1987) blinded to subjects' exposure history. The UPDRS contains four sections (Part 1 – Mentation Behavior, and Mood; Part 2 – Activities of Daily living; Part 3 – Motor; Part 4 – Complications of Therapy) used to measure the severity of parkinsonism. Subject examinations were videotaped and another fellowship trained movement disorders neurologist, rated the examination (except for rigidity) in a subset of subjects to identify any unintended examiner bias that might result from direct subject contact. All three examiners were validated to the principal investigator's (BAR) UPDRS3 by rating ten PD patient videos prior to the study; intraclass correlation coefficients were all >0.80.

We used a case definition of "parkinsonism" of UPDRS3 score ≥ 15 because most idiopathic PD patients become symptomatic and present for medical attention with UPDRS3 scores ≥ 15 (The Parkinson Study Group, 1989, 1996, 2007). We predicted that this threshold would reflect functionally impairing motor dysfunction and would represent a clinically relevant case-definition. This case definition is based upon severity of clinical signs, in contrast to standard clinical definitions of parkinsonism that use a qualitative interpretation of clinical data to determine the presence or absence of parkinsonian clinical signs (rigidity, bradykinesia, rest tremor, rigidity). Normal was defined as UPDRS3 < 6. Workers with UPDRS3 from 6 to 14 were combined for analysis as an intermediate group. We used standard subcategories of the UPDRS3, to investigate cardinal parkinsonian manifestations, by summing UPDRS3 components: upper limb bradykinesia, upper limb rigidity, lower limb bradykinesia, lower limb rigidity, rest tremor, action/postural tremor, and axial signs. To determine asymmetry of parkinsonism, we calculated the more and less affected side from lateralizing clinical signs for each subject. Subjects were excluded from analyses if they were on dopamine receptor blocking medications or had a co-morbid disease that would confound interpretation of the UPDRS3. Diseases that excluded subjects included: stroke ($n = 4$), encephalitis ($n = 1$), rheumatoid arthritis ($n = 1$), Huntington disease ($n = 1$), brain tumor ($n = 1$).

To exclude less than full effort testing, all subjects performed a timed motor task using a counter with two levers spaced 20 cm apart. Each subject completed three-30 second trials for each hand starting with the dominant side and then alternating between hands. For each trial, subjects were instructed to use the index finger of the indicated hand to alternate tapping between the two levers as many times as possible in the 30 second period. Scores were recorded for each 30 second trial. Mean tapping scores were calculated by averaging the 30 second trial scores. The coefficient of variation was calculated as the quotient of the standard deviation divided by the mean. The coefficient of variation is used to quantify performance variability and inconsistency between trials and has been used as an indication of less than full effort (Demakis, 1999; Kalogjera-Sackellares and Sackellares, 1999; Matheson et al., 1998).

2.3.2. Exposure assessment

All subjects completed a comprehensive welding exposure questionnaire (Hobson et al., 2009) that included detailed work exposure history and questions about common PD confounders (Checkoway et al., 2002). We used weighted exposure-years as the exposure metric, calculated for each participant from information provided on the questionnaire (Hobson et al., 2011). We calculated the duration at all welding related jobs by summing self-reported years at each welding exposed job. To account for time and intensity differences among jobs, we developed a weighted exposure-years metric. From self-reported job title, category, and duties we derived three job categories: full-time welder, part-time welder, and work around welding. Information provided by study participants and union leaders working at these sites regarding typical site-based welding assignments was used to assign hours per week welding or around-welding per job category. Full-time welders were assigned 40 welding hours/week. Part-time welders were assigned 20 welding hours and 20 hours around-welding hours/week. Around-welding participants were assigned 0 hours welding and 20 hours around-welding/week. Differences in exposure intensity were determined from published literature reporting both personal and area sample concentrations for welding and Mn under normal field operations. Based on six studies, mean area sample concentrations for both welding particulate and Mn were 25% of personal sample concentrations (Akbar-Khanzadeh, 1993; Boelter et al., 2009; Karlsen et al., 1994, 1996; Wilson and Stenzel, 1981; Zaidi et al., 2004). A weight of 0.25 was assigned to around-welding hours to reflect this lower intensity of exposure. Based on a 50-week, 2000-hour work year, weighted exposure years were calculated by summing welding

hours and around-welding hours per week at each job and then summed across all jobs, as follows:

$$\text{Weighted welding exposure years}_i = \sum_{j=1}^{J}\left[\frac{\text{welding hours} + (\text{around-welding hours} * 0.25)}{\text{week}}\right]_{ij} \times [\text{weeks in job}]_{ij} \times \frac{\text{years}}{2000\,\text{hours}}$$

2.3.3. Statistical analysis

All analyses were calculated using SAS 9.3 (Cary, NC). We compared demographics and characteristics of welding and non-welding job site workers using a *t*-test for continuous variables, a chi-square test for categorical variables, and Fishers exact test when appropriate. We performed analysis of covariance to evaluate adjusted UPDRS3 scores. Covariates were included if significant ($p < 0.05$) when performing the screening *t*-test or chi-square test. We performed a test for homogeneity between covariates and dependent variables to ensure regression coefficients for each group were not significantly different. As a sensitivity analysis, the video reviewer UPDRS3 scores were analyzed with and without in-person examiner rigidity scores. Dose–response analyses were restricted to welders only to minimize potential confounding from comparisons with non-welders, and because there were no cases of parkinsonism among non-welders. Prevalence ratios (PR) for parkinsonism were calculated with a modified Poisson approach to estimate relative risk using robust error variance (Spiegelman and Hertzmark, 2005; Zou, 2004). Exposure strata were defined such that there was an equal number of welders with UPDRS3 scores <6 (the internal reference group) in each stratum. Models were run to evaluate the prevalence of workers with UPDRS3 $\geq$ 15 and workers with UPDRS3 $\geq$6 to <15 by exposure quartile, using workers with UPDRS3 < 6 as the common reference group. Additional analyses with 5 and 10 year lagged exposures were conducted. A test for trend was performed using median values from each quartile. Covariates considered were age at examination, gender, race, work site, ever smoked cigarettes, examining neurologist, and years since last occupational welding exposure (to account for non-active workers). Race, worksite, and ever smoked cigarettes did not improve the model fit, and therefore were not included in the final model. Since there are no "gold standard" thresholds for defining "parkinsonism" and "normal" using the UPDRS3, we performed sensitivity analyses using stricter UPDRS3 criteria for normal (UPDRS3 < 3) and for parkinsonism (UPDRS3 $\geq$ 20). Mean values of clinical characteristic subscores from the UPDRS3 were derived for each subject and workers with UPDRS3 $\geq$ 15 and were compared to PD patients using a *t*-test for unequal variances. Timed motor tests and coefficient of variation were compared between diagnostic groups using ANOVA, adjusting for age.

3. Results

From an available workforce of 1612 welding-exposed workers, 811 workers agreed to participate in this study, 41 declined participation, 110 could not be contacted due to disconnected phone numbers or address change, and 650 were invited to participate but did not present for evaluation nor decline participation. Welding-exposed workers excluded from the analysis consisted of those with co-morbid disease or confounding medication ($n = 15$), or incomplete data ($n = 12$). We also excluded 68 welding site workers who reported no history of welding exposure from analysis due to inability to characterize exposures. Subject demographics are in Table 1. Two thirds of welders and 58% of non-welder reference workers were smokers. As expected, PD patients had a substantially lower prevalence of ever smoking (32%).

The mean (standard error), adjusted UDPRS3 score for the workers from welding job sites was 9.7 (0.5) and 3.8 (1.0) for workers from non-welding job sites (*F*-test; $p < 0.05$). Overall prevalence of parkinsonism as defined by UPDRS3 $\geq$ 15 was 15.6% in welding exposed workers and 0% in non-welding reference workers (Fisher's exact test; $p < 0.05$) (Table 1). As a sensitivity analysis, mean UPDRS3 scores from the subset of subjects reviewed by the video rater were also significantly higher for workers from welding job sites as compared to workers from non-welding worksites (data not shown). Mean welding years for welding exposed subjects are given in Table 2. The proportions of welders with UDPRS3 scores in the UPDRS3 $\geq$ 15, UPDRS3 $\geq$6 to <15, and UPDRS3 < 6 was similar between the three job sites studied (Table 2). There was a significant difference in combined mean timed motor score between UPDRS3 categories ($F = 45.08$, $p < 0.001$). A post hoc comparison, controlling for age, indicated that the subjects with UPDRS3 $\geq$ 15 performed fewer taps than subjects with UPDRS3 $\geq$6 to <15 and UPDRS3 < 6 (Tukey's HSD, $F = 34.28$, $p < 0.001$). There was no significant difference between the coefficient of variation between UPDRS3 categories, with all categories falling between 7.2 and 7.5%.

To investigate the dose–response relations between welding exposure and parkinsonism, we calculated the prevalence of parkinsonism (UPDRS3 $\geq$ 15) by quartile of welding exposure using the lowest exposed welders as reference. There was a U-shaped dose–response trend, with a modest increase in the prevalence of parkinsonism for the two middle quartiles of total weighted-welding years (Table 3) The findings only changed minimally in the lagged exposure analysis (data not shown). The prevalence ratios were similar when stricter UPDRS3 criteria were

Table 1
Comparison of workers from welding and non-welding job sites.

	Workers from welding job sites ($n = 716$)	Workers from non-welding job sites ($n = 57$)	Newly diagnosed PD ($n = 118$)
Age, mean (SD)	45.9 (12.3)	51.6 (9.8)[a]	63.8 (14.6)[a]
Gender (male), *n* (%)	680 (95%)	48 (84%)[a]	74 (63%)[a]
Race (non-Hispanic Caucasian), *n* (%)	695 (97%)	57 (100%)	111 (94%)
Smoking (ever), *n* (%)	480 (67%)	33 (58%)	37 (31%)[a]
Education (years), mean (SD)	12.3 (1.1)	12.9 (1.4)[a]	14.4 (2.8)[a]
UPDRS3, mean (SD)	9.0 (6.2)	4.6 (2.6)[a]	22.9 (13.7)[a]
UPDRS3, marginal mean (std error)	9.6 (0.5)	3.6 (0.9)[b]	
UPDRS3 $\geq$ 15, *n* (%)	112 (15.6%)	0 (0%)[c]	85 (72%)[a]

Note: test of significance ($p < 0.05$) compared to workers from welding job sites.
[a] *t*-test for continuous variables, chi-square test for categorical variables.
[b] *F*-test for marginal mean (comparing workers from welding vs. non-welding job sites only) adjusted for age at examination, active status, gender, and examining neurologist.
[c] Fishers exact test.

Table 2
Welding exposure in workers from welding job sites.

	UPDRS3 ≥ 15 (*n* = 112)	UPDRS3 ≥6 to <15 (*n* = 369)	UPDRS3 < 6 (*n* = 235)	All (*n* = 716)
Age, mean (SD)	50.5 (12.6)	47.0 (11.7)	42.0 (12.1)	45.9 (12.3)
Active (yes), *n* (%)	91 (81%)	338 (92%)	223 (95%)	652 (91%)
Days since last occupational welding exposure, mean (SD)	866 (2158)	375 (1535)	211 (1000)	398 (1520)
Site 1, *n* (%; by site)	51 (18%)	149 (52%)	88 (30%)	288
Site 2, *n* (%; by site)	39 (14%)	143 (50%)	104 (36%)	286
Site 3, *n* (%; by site)	22 (16%)	77 (54%)	43 (30%)	142
UPDRS3 total, mean (SD)	19.8 (4.6)	9.6 (2.4)	2.9 (1.7)	9.0 (6.2)
Total job duration (years), mean (SD)	19.0 (13.1)	17.8 (13.0)	13.9 (11.9)	16.7 (12.8)
Weighted welding exposure-years, mean (SD)	9.0 (10.7)	9.6 (10.9)	7.4 (9.9)	8.8 (10.6)
Timed motor task*, mean right and left (SD)	67.5 (12.6)	75.7 (10.2)	79.0 (9.1)	75.5 (11.0)

* Unadjusted $F = 45.08$, $p < 0.001$, adjusted for age $F = 34.28$, $p < 0.001$.

Table 3
Prevalence ratios (PRs) for parkinsonism in relation to duration of employment and total welding exposure-years.

	n UPDRS3			PR (95% CI)[a] UPDRS3		PR (95% CI)[b] UPDRS3	
	≥15	≥6 to <15	<6	≥15 vs. <6	≥6 to <15 vs. <6	≥15 vs. <6	≥6 to <15 vs. <6
Total weighted welding exposure-years[c]							
<1.0	14	65	58	Reference	Reference	Reference	Reference
1.0–3.4	28	78	59	1.7 (0.9–2.9)	1.0 (0.9–1.1)	1.4 (0.8–2.4)	1.0 (0.9–1.1)
3.4–8.8	38	97	59	2.0 (1.2–3.4)	1.1 (1.0–1.1)	1.4 (0.9–2.3)	1.0 (0.9–1.1)
≥8.8	32	129	59	1.8 (1.0–3.1)	1.1 (1.0–1.2)	1.0 (0.6–1.6)	1.0 (0.9–1.1)
p-trend						0.08	0.76

[a] Crude estimates.
[b] Adjusted for age at examination, gender, examining neurologist, and days since last occupational welding exposure; analyses restricted to workers from welding worksites.
[c] Weighted by job category and title.

used for normal (UPDRS < 3) and for parkinsonism (UPDRS3 ≥ 20). There was no dose–response trend between weighted welding exposure and the intermediate UPDRS3 category (≥6 to <15). Findings from an analysis restricted to men were only minimally different from those for all study subjects.

To investigate the distinctive parkinsonian features in Mn exposed workers from welding job sites, we compared subcategories of the UPDRS3 in workers from welding sites with UPDRS3 ≥ 15 to a group of newly diagnosed, untreated PD patients. The mean UPDRS3 score was 19.8 for welders with UPDRS3 ≥ 15 and 22.9 for newly diagnosed, untreated PD patients. There were no differences in overall mean upper limb bradykinesia, upper limb rigidity, lower limb bradykinesia or action/postural tremor between welders with UPDRS3 ≥ 15 and PD patients (Table 4). Welders with UPDRS3 ≥ 15 had greater lower extremity rigidity, less rest tremor, fewer axial signs, and greater symmetry of signs than PD patients (Table 4). All 112 welding exposed workers meeting our case definition of UPDRS3 ≥ 15 had bradykinesia, and 109 had rigidity. Absolute differences in frequency of any clinical signs between groups were modest, indicating substantial overlap in clinical phenotypes. The results were similar when analyses were restricted to men.

4. Discussion

In this worksite-based epidemiology study, we found a relatively high prevalence of parkinsonism in welding exposed workers, suggesting an association between exposures to Mn and other welding fume metals and parkinsonism. Advantages of our study methods include selection of a study population with relatively high exposures to Mn, examination of each worker by a movement disorders expert, standardized method of exposure

Table 4
Comparison of parkinsonian signs (mean (SD)) in welders and newly diagnosed, untreated PD patients.

Clinical feature	Parkinsonian welders (*n* = 112)			Idiopathic Parkinson disease patients (*n* = 118)		
	Total	More affected side	Less affected side	Total	More affected side	Less affected side
Upper limb bradykinesia	7.7 (2.6)	4.3 (1.3)	3.4 (1.4)[c]	6.9 (4.2)	4.4 (2.2)	2.5 (2.2)
Upper limb rigidity	1.9 (1.4)	1.1 (0.7)[c]	0.8 (0.7)	2.1 (1.3)	1.4 (0.7)	0.7 (0.7)
Lower limb bradykinesia	2.0 (1.4)	1.3 (0.7)	0.7 (0.8)	2.2 (1.8)	1.4 (1.0)	0.8 (0.9)
Lower limb rigidity	2.2 (1.4)[c]	1.2 (0.7)	1.0 (0.7)[c]	1.6 (1.7)	1.0 (0.9)	0.6 (0.8)
Rest tremor	0.3 (0.8)[c]	0.2 (0.5)[c]	0.2 (0.4)[c]	1.9 (2.2)	1.6 (1.5)	0.5 (1.1)
Action/postural tremor	0.9 (1.2)	0.5 (0.6)	0.4 (0.6)	0.9 (1.1)	0.7 (0.7)	0.3 (0.5)
Axial signs[a]	4.3 (2.5)[c]	–	–	6.3 (4.9)	–	–
Mean (SD) of sum of affected side[b]		8.6 (1.9)[c,d]	6.5 (2.1)[c]		10.4 (4.8)[d]	5.5 (4.6)
UPDRS3 score, mean (SD)	19.8 (4.6)			22.9 (13.7)		

[a] Includes neck rigidity, facial masking, arising from chair, posture, gait, postural instability, body bradykinesia.
[b] The mean value for clinical feature scores for the more and less affected side summed per individual.
[c] *t*-test for unequal variances comparing the parkinsonian welders and idiopathic Parkinson's disease patients, $p < 0.05$.
[d] *t*-test for unequal variances comparing the more affected side to the less affected side, $p < 0.05$.

assessment (Hobson et al., 2011), independent support of the research, and assessment for "less than full effort" testing. This study did not address the possible relationship between welding exposure and PD, since our cohort consisted of workers in their 40s in whom the prevalence of PD was expected to be low. Nevertheless, this study provides critical data to inform future studies into the risk of PD in Mn exposed welders.

This study was designed to investigate the dose–response relation between cumulative welding fume exposure and parkinsonism. We found a marked difference in UPDRS3 scores and prevalence of parkinsonism (UPDRS3 $\geq$ 15) in welding exposed workers compared to non-welder reference subjects, suggesting an association between welding exposure and parkinsonism. However, we did not find a simple, monotonic dose–response relationship between the prevalence of parkinsonism and welding exposure. The modest increase in prevalence of parkinsonism between welders in the lowest exposed quartile and those in higher exposed quartiles may have underestimated the actual relation between welding exposure and parkinsonism, since our reference group was exposed to welding fume. Since there were no cases of parkinsonism in non-exposed workers, we were not able to calculate the prevalence ratio of parkinsonism in welding-exposed workers relative to non-exposed reference subjects. There are several possible interpretations of the observed U-shaped dose–response relation among welders. The lower prevalence of parkinsonism in the most exposed group may suggest a healthy worker survival effect, whereby symptomatic workers retire or move to another trade. However, some workers may be manifesting parkinsonian effects with even short term exposures, suggesting a possible "acute" effect that may blunt the dose–response relationship. We attempted to minimize healthy worker effect bias by adjusting for time since last worked as a welder, but this may not have been a complete control. Alternatively, the relationship between welding exposure and parkinsonism may not be linear. Several studies suggest that cognitive dysfunction, particularly executive function, may be impaired early in the course of Mn neurotoxicity (Criswell et al., 2011; Harris et al., 2011). In future studies, a combined cognitive and motor outcome variable may prove to be a better measure of the neurotoxic effects of Mn containing welding fume.

The clinical implication of the high prevalence of parkinsonism in these welders is unclear. Welding is a physically and technically demanding trade and parkinsonism would be expected to impair workers' ability to perform their work duties. In a previous study we demonstrated reductions in PD specific quality of life in shipyard welders meeting our definition of parkinsonism, suggesting that these motor abnormalities are associated with impairments in daily activities (Harris et al., 2011). Although beyond the scope of this study, investigating the effects of parkinsonism on changes in job grade, absenteeism, work injuries, and work productivity may provide further insight into the consequences of Mn containing welding fume exposure on worker health and safety. In addition, two recent imaging studies using structural and molecular imaging demonstrate neurotoxic injury to the basal ganglia in a subset of these workers with minimal neurologic abnormalities (Criswell et al., 2011, 2012). Using the radiotracer FDOPA, we have demonstrated that workers with very mild parkinsonian signs have evidence of dopaminergic dysfunction in the caudate nucleus with positron emission tomography. These same workers demonstrate abnormalities in diffusion weighted imaging in the putamen and caudate consistent with tissue injury in these regions. The quality of life and imaging data providing further evidence of the neurotoxic effects of welding fume.

The workers evaluated in this study were relatively young so comorbid neurodegenerative disease is unlikely to confound our results. However, it is possible that mild pyramidal system (i.e., stroke) signs or joint diseases could be mistaken for parkinsonian signs, which are specific to the extrapyramidal system. We did exclude subjects with known neurologic and medical disorders that could confound the examination and all evaluations were performed by clinicians with extensive experience with distinguishing parkinsonism from other medical and neurologic disorders. In addition we established a threshold value for the UDPRS3 ($\geq$15) that we believe improves the specificity of our case definition. The sensitivity analyses with more stringent UPDRS3 definitions for "normal" and "parkinsonism" yielded similar results suggesting that our choice of case definitions did not produce a clear bias. It should be noted that including mildly parkinsonian workers in the "normal" category and workers with secondary causes of parkinsonism in the "parkinsonism" category would be expected to bias results toward the null.

The clinical phenotype of welders with parkinsonism may provide insight into the pathophysiology of welding-associated neurotoxicity. The severity of bradykinesia and rigidity in welding exposed workers was comparable to newly diagnosed PD patients. Although there were slight but significant differences in lower extremity rigidity (worse in welders) and axial signs (worse in PD patients), these differences were not sufficiently different to distinguish parkinsonism in welders from PD patients. Rest tremor and asymmetry were more common in PD patients than welders with parkinsonism. Nevertheless, the broad phenotypic range of PD includes patients who have no tremor and symmetric disease. Postural instability was extremely uncommon in welders with parkinsonism, possibly reflecting the young age of these workers. This study provides a direct comparison of the clinical motor phenotype associated with welding-related Mn exposures and PD. Insofar as Mn is the best characterized neurotoxicant in welding fume, these clinical features likely reflect the clinical phenotype of manganism associated with chronic Mn exposures.

There are several limitations to this study. Exposure misclassification due to reliance on self-reported work histories and literature-based exposure weighting estimates may under-estimate the exposure-response relation. Individual exposure measurements may have improved the accuracy of our exposure metrics; however, only limited historic monitoring records were available from workplaces we studied. Ideally, routine exposure monitoring would be used to derive cumulative exposures. Although OSHA and other regulatory organizations have established permissible exposure limits for occupational Mn, there are no requirements for employers to monitor workers, so historical monitoring data from these worksites is sparse. Since we recruited our subjects through the union and all evaluations were done during worker free time, we were not able to assess the entire workforce. Thus, our prevalence estimates are subject to some uncertainty. Finally, we used the UPDRS3 as a standardized examination for these workers, yet the UPDRS3 was developed to assess PD motor progression (Fahn and Elton, 1987). The UPDRS3 has the advantage of quantifying cardinal parkinsonian manifestations, retaining the necessary elements to diagnose PD. Nevertheless, we believe that use of the UPDRS3 provides the best option for quantifying parkinsonian effects in a non-clinical setting, especially in a mostly actively employed workforce. Despite these caveats, we believe that this study adds to the knowledge of the health effects associated with welding fume and may inform future studies on the etiology of parkinsonism.

5. Conclusions

This study demonstrates a relatively high prevalence of parkinsonism in welding exposed workers with a U-shaped dose–response relation. The parkinsonian phenotype in these welders overlapped substantially with the phenotype of newly diagnosed,

untreated PD patients. Welders' exposures to Mn and other neurotoxicants in welding fume may contribute to parkinsonism risk.

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Conflict of interest statement

None.

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