Petition to include Parkinson's Disease as a result of exposure to the World Trade Center Collapse

I do hereby petition the Administrator of the WTC Health Program for the addition of a New WTC – Related health Condition for Coverage under the WTC Health Program.

I am enclosing an Abstract of a study on the increased risk of parkinsonism associated with welding exposure.

I, and many others were exposed to the same heavy metals that a welder is 3exposed to.

Yours truly

Enclosures

Studies

Abstract of Study of the Increased risk of parkinsonism associated with welding exposure 9 pages

Inducible nitric oxide synthase gene methylation and parkinsonism in b manganese – exposed welders – 9 pages

Multiple risk factors for Parkinson's disease 2 pages

Occupational exposure to manganese, copper, lead, iron, mercury and zinc and the risk of Parkinson’s disease – 3 pages

Whole-body lifetime occupational lead exposure and risk of Parkinson’s disease 2 pages
I was 2 blocks away from the area called Ground Zero when the building collapsed.

The air quality was so bad no one should have been allowed to go down to that area without a respirator on. Every metal chemical used in the buildings, the computers and furnishings went up in the air. The heat so intense they could not put out the fires until December 2001.

When you called and complained about the smell, you were told it was safe to be in the area. The closest air monitoring station was at the Holland Tunnel over a mile away.

Parkinson's like cancer has no known cause, but statically it has been proven that environmental factors play a big role in determining whether you get Parkinson's or not. The triggers, like heavy exposures to carcinogens in the air that ignited the high rate of cancer among 9-11 victims were also there for Parkinson's. There has been studies showing a higher incidence of Parkinson's among people doing welding when compared to the general population.

There has been not one study done by the CDC or any other organization to analyze the statistics showing how many people, like myself came down with Parkinson's or other neurological diseases. Unfortunately due to the high rate of cancer among 9-11 victims many of the people who may have shown to have had Parkinson's, died of cancer before the symptoms of Parkinson's may have been recognized.

Unlike cancer Parkinson's is a slowly deteriorating disease and may take years before it is recognized. Only spinal taps are conclusive (rarely if ever done) in showing whether you have Parkinson's.

I know from the WTC physician at Bellevue hospital she said she treated numerous 9-11 victims that had Parkinson's as well as other 9-11 recognized illness. She said to me that there had been no study done of the incidence of Parkinson's. She said that from her patients (9-11 victims) there was a higher rate of Parkinson's than normal.
Increased risk of parkinsonism associated with welding exposure

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Abstract

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 ≥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 non-welding-exposed workers and a clinical phenotype that overlaps substantially with PD.

**Keywords:** Parkinsonism, Parkinson disease, Welding, Manganese, Occupational exposures

### 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 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) UPDRS 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 indicator of less than full effort (Demakis, 1999; Kalogija-Sackellas and Sackellaes, 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
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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:

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

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-examiners. 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 ≥ 15 and workers with UPDRS3 ≥ 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 ≥ 20). Mean values of clinical characteristic subscores from the UPDRS3 were derived for each subject and workers with UPDRS3 ≥ 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%).

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

The mean (standard error), adjusted UPDRS3 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 ≥ 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 UPDRS3 scores in the UPDRS3 ≥ 15, UPDRS3 ≥ 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 ≥ 15 performed fewer taps than subjects with UPDRS3 ≥ 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%.

Table 2
Welding exposure in workers from welding job sites.

To investigate the dose–response relations between welding exposure and parkinsonism, we calculated the prevalence of parkinsonism (UPDRS3 ≥ 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 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.

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

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.

Table 4
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 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 ≥ 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 estimate 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
Increased risk of parkinsonism associated with welding exposure

**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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Footnotes

Conflict of interest statement

None.

References

Inducible nitric oxide synthase gene methylation and parkinsonism in manganese-exposed welders

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Abstract

Introduction
Neurologist-assessed parkinsonism signs are prevalent among workers exposed to manganese (Mn)-containing welding fume. Neuroinflammation may possibly play a role. Inducible nitric oxide synthase, coded by NOS2, is involved in inflammation, and particulate exposure increases the gene's expression through methylation of CpG sites in the 5' region.

Methods
We assessed DNA methylation at three CpG sites in the NOS2 exon 1 from blood from 201 welders. All were non-Hispanic Caucasian men 25–65 years old who were examined by a neurologist specializing in movement disorders. We categorized the workers according to their Unified Parkinson Disease Rating Scale motor subsection 3 (UPDRS3) scores as parkinsonism cases (UPDRS3 ≥ 15; n = 49), controls (UPDRS3 < 6; n = 103), or intermediate (UPDRS3 ≥ 6 to <15; n = 49).

Results
While accounting for age, examiner and experimental plate, parkinsonism cases had lower mean NOS2 methylation than controls (p-value for trend = 0.04), specifically at CpG site 8329 located in an exonic splicing enhancer of NOS2 (p-value for trend = 0.07). These associations were not observed for the intermediate UPDRS3 group (both p-value for trend ≥ 0.59).
Conclusions

Inflammation mediated by inducible nitric oxide synthase may possibly contribute to the association between welding fume and parkinsonism, but requires verification in a longitudinal study.

Keywords: DNA methylation, inhalation exposure, manganese, nitric oxide synthase type II, occupational exposure, parkinsonian disorders, welding

1. Introduction

Historically, occupational exposure to manganese (Mn) has been associated with parkinsonism among highly exposed workers, such as Mn miners and ore crushers. Modern occupational Mn exposures are substantially lower, but welders are frequently exposed to Mn above current occupational standards [1]. While records-based studies provide little evidence that contemporary welders have an increased risk of Parkinson disease [2], studies that investigate parkinsonism more generally and employ neurologists in the assessment of this broader outcome demonstrate that signs of parkinsonism are prevalent among workers exposed to welding fume [3, 4] and other occupational sources of Mn [5]. Among welders, characteristic signs of this movement disorder are bradykinesia and rigidity [1].

Welders demonstrate increased signal on T1 weighted MRI in the basal ganglia [6], a finding generally believed to indicate Mn accumulation. Basal ganglia dysfunction likely contributes to the association between parkinsonism and Mn-containing welding fume [6–8]. Although the exact pathophysiologic mechanism of Mn neurotoxicity has not been fully elucidated, inflammation may play a role. In contemporary Mn mine workers, Mn exposure is associated with microglia cell density in the globus pallidus [8], the portion of the basal ganglia traditionally considered a target of Mn neurotoxicity. Glial cell activation enhances the uptake of Mn into neurons [9], which in turn may contribute to neuronal death [10]. In addition, activation of glial cells, particularly microglia, might damage adjacent neurons through increased expression of pro-inflammatory mediators [11, 12]. These include nitric oxide, which is produced by nitric oxide synthase [13]. There are three such enzymes in humans, including inducible nitric oxide synthase (iNOS). Inhaled welding fumes, at concentrations consistent with potential workplace exposures, increase levels of messenger RNA for microglial markers and iNOS in the striatum and midbrain of rats [14]. Moreover, mice without the gene coding for iNOS are less susceptible to the neurotoxic effects of Mn [15].

The gene coding for iNOS in humans, NOS2, is primarily regulated at the transcriptional level, at least in part via methylation of CpG dinucleotides [16]. Specifically, hypermethylation of CpG sites in the 5' promoter region of the gene decreases its expression [16, 17] and is associated with lower breath nitric oxide [18] suggesting lower iNOS activity. Conversely, hypomethylation of NOS2 may be associated with greater iNOS activity. Most studies indicate that exposure to fine and coarse particulate, including metal-rich particulate, is associated with lower NOS2 methylation in or near the gene's promoter region [19–23]. Therefore, in a sample of workers from a well-characterized cohort of welders with a relatively high prevalence of parkinsonism [2], we assessed the association between NOS2 methylation and parkinsonism. Our hypothesis was that compared to welders with normal neurological exams, parkinsonian welders would have lower NOS2 methylation (Figure 1).

![Figure 1](image)

Hypothesized mechanism for association between welding and parkinsonism

2. Materials and Methods

2.1 Participants and assessment of parkinsonism

Prior to study conduct, we obtained Human Subjects approval from Washington University (St. Louis, MO) and
the University of Washington (Seattle, WA), and written informed consent from each participant. All participants were part of an ongoing study in the U.S. Midwest examining the association between welding and parkinsonism [3]. Recruitment has been detailed previously [24]. Briefly, we used a union membership list to contact employees and retirees from three welding worksites: two shipyards and one heavy equipment fabrication shop. One of two neurologists specializing in movement disorders (B.A.R. and S.R.C.) examined each participant using a standardized neurological exam that included the Unified Parkinson Disease Rating Scale motor subsection 3 (UPDRS3) [3, 22]. At the time of the exam, we asked each participant to complete a structured questionnaire [24] on demographics and work history, and to provide a blood sample. We stored all blood samples at -80°C.

At the time of laboratory analysis, 437 whole blood specimens were potentially available for the present work. We selected a subsample based on demographic characteristics to minimize the potential for confounding. Specifically, most participants in the cohort were non-Hispanic Caucasian men [3], and therefore we focused on this demographic group to avoid confounding by race, ethnicity, and sex. In addition, as expected parkinsonism was very strongly associated with age, so we restricted our study to workers age 25–65 to minimize the potential for confounding by age. This also had the benefit of largely restricting to active workers exposed for a sufficient period of time to have developed parkinsonism. Because this was a pilot study, we then applied to the cohort a design similar to a nested case-control study: We excluded specimens obtained at a repeat exam and selected workers based on UPDRS3 category. In total we included 201 workers from one of three UPDRS3 groups: UPDRS3 score < 6 (n = 103, hereafter controls), UPDRS3 score > 8 to ≤ 12 (n = 49, hereafter intermediate UPDRS3 group), and UPDRS3 ≥ 15 (n = 49, hereafter parkinsonism cases). These categories parallel our previous classification [3] except that we were unable to include all workers in the intermediate category (UPDRS3 ≥ 6 to UPDRS3 < 15), so we only retained workers with UPDRS3 scores most clearly distinct from those of both cases and controls.

2.2 Assessment of NOS2 methylation

We (P.L.S., F.M.F.) collected DNA from whole blood using the QIAamp DNA blood kit (Qiagen, Germantown, MD). We then bisulfite-treated 500 ng of purified DNA using Qiagen’s EpiTect Fast DNA Bisulfite Kit and diluted to a concentration of 10 ng/μl. We assessed NOS2 methylation at the three CpG sites as in a recent study [26] of apprentice welders: sites 8309 (CpG site 1), 8314 (CpG site 2) and 8329 (CpG site 3). These CpG sites are in exon 1 (Genbank: AF017624), bordering the 5’ promoter region and immediately adjacent to a transcription factor binding site and overlapping an exon splicing enhancer.

We designed the assay using Qiagen’s Assay Design Software, and obtained primers from Eurofins MWG Operon (Huntsville, AL). The sequences were ggtgagatataatattttttttgtgtag (forward primer), biotintaacctacttacctcat (reverse primer), and tggtagtggtgtgtgtata (sequencing primer). Each 25 μl PCR reaction consisted of 12.5 μl of a PyroMark PCR Master Mix (Qiagen), 5 pmol forward primer, 5 pmol reverse primer, 15–20 ng of bisulfite-treated DNA, and water. Thermocycling conditions were 15 min at 95°C followed by 40 cycles of 30 seconds at 94°C, 30 seconds at 56°C, and 30 seconds at 72°C, with a final extension of 10 minutes at 72°C. After visual determination of a single band on an agarose gel, 8 μl of the PCR product was used in a Qiagen Q24 Pyrosequencing Assay according to the manufacturer’s protocol. DNA methylation status was determined using a PyroMark Q4 instrument and final results were analyzed using PyroMark Q24 software. We included duplicate sample(s) and positive and negative laboratory controls on each experimental plate. The inter-assay coefficient of variation for mean NOS2 methylation was 2.4% and the intra-assay coefficient of variation was 0.98%.

We ensured that all three UPDRS3 groups were represented on each experimental plate, while maintaining blinding of the lab. Complete methylation data were available for all participants; most had complete data in the initial attempt, but a repeat attempt was required for 4 cases, 5 controls, and 2 in the intermediate UPDRS3 group.

2.3 Statistical analysis

All statistical analyses were conducted in Stata Version 11 (College Station, TX). We constructed logistic
regression models to separately compare two groups – parkinsonism cases and the intermediate UPDRS3 group – to controls with regard to percent NOS2 methylation. In our primary analysis, we defined percent NOS2 methylation as mean percent methylation across the three CpG sites [26]. In a secondary analysis, we considered percent methylation at individual CpG sites [20], as these sites have been observed to be differentially methylated in the brain despite their close proximity [27]. We modeled NOS2 methylation linearly, but to verify the appropriateness of this approach, we also constructed tertiles of NOS2 methylation. We calculated p-values for trend based on the former.

We adjusted a priori for age because of its association with both NOS2 methylation [28] and UPDRS3 score [3]. We also adjusted a priori for experimental plate for pyrosequencing reactions [20, 22], specifically conditional logistic regression while grouping on experimental plate. We examined whether inclusion of any of the following factors in the model further altered odds ratios (ORs) or 95% confidence intervals (CIs) by > 10%: age squared; examiner; current and former tobacco smoking; consumption of caffeine, coffee and alcohol; body mass index and timing of blood collection. This included year, day of the week, season and heating degree days in the study region on the day blood was collected. We accordingly adjusted all models for examiner in addition to age and experimental plate. Other considered factors, including smoking, did not alter results and therefore were not included in models. We also did not adjust for welding exposure because our hypothesis was that DNA methylation is in the causal pathway between welding fume exposure and parkinsonism (Figure 1), and therefore is inappropriate to include in the model as a potential confounder. We repeated all analyses while excluding workers who had been retired for > 1 year because NOS2 methylation appears to change relatively rapidly [26, 29, 30], and the presence of parkinsonism could affect a worker’s ability to work in a welding related job. Results from the larger cohort study [3] were consistent with such a potential healthy worker effect. In addition, we verified results were similar when we excluded all participants with co-morbidities associated with vascular parkinsonism (stroke, hypertension, heart disease and/or diabetes). Specifically, participants with a history of stroke were excluded from the original cohort [3], and then we conducted sensitivity analyses here in which we excluded participants with any of the other three conditions.

We also explored whether, as hypothesized (Figure 1), welding fume exposure was associated with NOS2 methylation. Using the workers’ self-reported work histories, we calculated cumulative duration (years) of occupational exposure to welding fume. This exposure metric is the one most strongly associated with parkinsonism among this cohort [3] and thus was our primary exposure of interest. We also considered the current job classification (welder, welder helper, around welding, not around welding) and retirement status to explore the influence of intensity and recentness of exposure on NOS2 methylation.

3. Results

3.1 Participants

On average, participants with DNA methylation data had worked nearly 20 years in a job with exposure to welding fume (mean 19.8 years, standard deviation 13.8 years). Parkinsonism cases were older than controls and were less likely than participants in the intermediate UPDRS3 group to be a welder at the current or most recent job (Table 1). Proportionally more controls had ever smoked tobacco regularly compared to the other UPDRS3 groups.

![Table 1](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4512640/)

3.2 NOS2 methylation and parkinsonism
The NOS2 CpG sites we assessed were highly methylated; all controls had > 90% methylation at each of the three CpG sites, and the overall mean NOS2 methylation was 95.5% (standard deviation 1.3%). Methylation appeared similar in cases (mean 95.4%, standard deviation 1.5%) as compared to the other groups (each with mean 95.5%, standard deviation 1.2–1.3%). However, after accounting for age, examiner and especially experimental plate, there was a clear inverse association between NOS2 methylation and parkinsonism (p-value for trend = 0.04, Table 2). Compared to the lowest tertile of NOS2 methylation, the prevalence of parkinsonism was 59% lower in the middle tertile of NOS2 methylation and 76% lower in the upper tertile of NOS2 methylation. A weaker inverse association was suggested when comparing the intermediate UPDRS3 group to controls, but there was no evidence of a dose-response association (p-value for trend = 0.59).

Table 2
Parkinsonism and inducible nitric oxide synthase (NOS2) methylation, a
Midwestern U.S. Welders Cohort, 2006–2013

The association between parkinsonism and NOS2 methylation was most evident for the third CpG site (8329). This association was not attenuated when we excluded retirees (Table 2, p-value for trend = 0.01), or conducted a variety of sensitivity analyses (exclusion of participants with co-morbidities associated with vascular parkinsonism, exclusion of samples for which the assay failed initially, application of the smooth function to the continuous methylation data, or adjustment for methylation at the other CpG sites in NOS2, data not shown in tables). Among the non-retired workers, each absolute increase of 1% of the CpG site 8329 was associated with a 33% (95% CI 8% to 51%) lower prevalence of parkinsonism.

3.3 Welding exposure and NOS2 methylation
Because results for the third CpG site (8329) were particularly robust, and methylation of this CpG site is perhaps the most plausibly related to NOS2 expression given its location in the gene, we explored whether welding exposure was associated with methylation at this CpG site. In linear regression models accounting for age and experimental plate, workers with recent exposure to welding fume had somewhat lower NOS2 8329 methylation than workers who had been retired for > 1 year (0.72% lower absolute methylation) or who were still at the worksite but not exposed to welding fume (0.51% lower absolute methylation), although confidence intervals were wide because most workers remained exposed (Table 3). Locally-weighted scatterplot smoothing revealed an inverse association between total duration of welding fume exposure and NOS2 8329 methylation among workers with < 10 years of cumulative exposure, but no association otherwise. Accordingly, likelihood ratio test (p-value = 0.02) indicated that we must include a spline at 10 years duration (in addition to a linear term for duration) to adequately capture the association between duration of welding fume exposure and NOS2 8329 methylation. Therefore we stratified by duration of exposure, and observed 0.16% (95% CI 0.02% to 0.29%) lower methylation of NOS2 8329 per year of exposure among workers with < 10 years of exposure (p-value for trend = 0.03) and no association among workers who had already experienced ≥ 10 years of exposure (0.004%, 95% CI -0.03% to 0.04%, p-value for trend = 0.81).

Table 3
Welding occupations and methylation of NOS2 CpG Site 8329, Midwestern U.S. Welders Cohort, 2006–2013

4. Discussion
In workers from welding worksites subject to contemporary guidelines for workplace exposures, we observed greater UPDRS3 scores in relation to lower NOS2 methylation. Interestingly, when we focused on participants who were employed at the welding worksite at the time of blood collection, this association was particularly evident for the third CpG site (8329), which is located in an exonic splicing enhancer of NOS2. This short motif is
involved in the splicing of hetero-nuclear RNA or pre-mRNA into messenger RNA. It is also adjacent to the 5' promoter region. Because lower NOS2 methylation in the promoter is associated with greater NOS2 expression [16, 17] and perhaps greater iNOS activity [18], these results are consistent with the hypothesis that parkinsonism associated with exposure to welding fume could be mediated, in part, through the nitric oxide pathway (Figure 1). Moreover, our results suggest that at least in the initial years of exposure, methylation at the NOS2 CpG site continually drops with each additional year of on-the-job welding fume exposure. Although this contrasts with results in 38 welding school apprentices [26], our study adds to the mounting evidence [19–23] that particulate exposure reduces promoter region NOS2 methylation in humans. This would be expected if NOS2 methylation contributes to the occurrence of parkinsonism in workers exposed to welding fume (Figure 1). Thus, insofar as our results are not due to chance, inflammation, and iNOS in particular, may play a role in the high prevalence of parkinsonism among welders. As detailed above, experimental and animal studies support the hypothesis that iNOS plays a role in Mn neurotoxicity [11, 12] [14, 15].

In the present study we were not able to assess NOS2 methylation in brain tissue, nor did we assess NOS2 expression, iNOS activity or nitric oxide levels. However, we hypothesize that these are correlated with NOS2 methylation in blood (Figure 1). Blood DNA methylation may be a good surrogate for DNA methylation in the brain [27], and methylation of NOS2 is associated with NOS2 expression [16, 17]. Therefore, it is intriguing that using DNA obtained from blood we observed an association in the hypothesized direction even though this association may have been attenuated by the use of DNA from blood rather than brain, and the use of DNA methylation as a surrogate for gene expression.

We also note there are limitations to the cross-sectional study design. NOS2 methylation appears to change rather rapidly [26, 29, 30]. While this lends support to our results that suggest that NOS2 methylation may be noticeably altered with relatively recent changes in welding fume exposure, it also means that we cannot be certain that NOS2 methylation contributed to parkinsonism, or rather the reverse occurred. Greater UPDRS3 scores could be associated with reduced mobility, and we cannot rule out the possibility that mobility affects NOS2 methylation. In particular, it is known that exercise can affect methylation of a variety of genes in humans [31]. Another consideration when interpreting the results of the present work is that the results may have been influenced by a healthy worker effect, as evidenced by a U-shaped dose-response association between welding and parkinsonism [3], which would be expected since tremor and bradykinesia associated with parkinsonism would make highly demanding fine motor tasks difficult to perform. However, similar to the overall study findings [2], we would anticipate that any healthy worker effect may have attenuated the associations, here between NOS2 methylation and parkinsonism, and between duration of exposure and NOS2 methylation. Finally, we assessed DNA methylation from whole blood and it is possible that the differences we observed could be due to different proportions of blood cell types across UPDRS3 groups, but we have no reason to believe that blood cell types would differ according to UPDRS3 score.

Since parkinsonism in Mn neurotoxicity is presumably mediated through neuropathologic changes, studying DNA methylation of NOS2 in human brain tissue of welders and other Mn-exposed workers would provide the most definitive data. This type of specimen is not widely available in working populations in the U.S. since neuropathologic tissue can only be obtained at death. Future studies of parkinsonism and methylation of NOS2 and other potentially relevant genes, such as inflammatory and metal transporter genes, might benefit from the inclusion of DNA from both blood and brain. Only the former can be collected longitudinally, and a longitudinal assessment of NOS2 methylation will be required to strengthen our findings and those from any future studies utilizing brain tissue. While our study was focused on parkinsonism in welders, such studies might also be of interest in population-based studies of Parkinson's disease. Parkinson's disease shares some features of parkinsonism among Mn-exposed workers [3], and ambient Mn exposure may increase risk of Parkinson's disease [32]. NOS2 has received considerable attention with regard to Parkinson's disease, but results of numerous human studies, which considered NOS2 genotype but not methylation, have been inconclusive. One reason for that could have been a failure to well assess NOS2 expression by genotype alone, as might be expected, given that


methylation of the gene clearly contributes to its expression [16, 17].

5. Conclusions

Lower methylation of the gene coding for iNOS was associated with greater signs of parkinsonism among workers from welding worksites, suggesting that inflammation mediated by iNOS may possibly contribute to the high prevalence of parkinsonism observed previously in workers exposed to welding fume.

Highlights

- We assess methylation of NOS2 in 201 workers exposed to welding fume
- Exposure to manganese-containing welding fume is associated with NOS2 methylation
- NOS2 methylation is associated with parkinsonism among welders
- Inducible nitric oxide synthase may play a role in parkinsonism in welders

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Footnotes

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Author roles

Searles Nielsen: Research project execution, statistical analysis design and execution; writing of the first manuscript draft; Checkoway: Research project conception and organization, review and critique of manuscript; Criswell: Research project execution including data acquisition; review and critique of manuscript; Farin: Research project execution including data acquisition; review and critique of manuscript; Stapleton: Research project execution including data acquisition; review and critique of manuscript; Sheppard: Statistical analysis design and critique; and manuscript review and critique; Racette: Research project conception, organization and execution including data acquisition, and review and revision of the manuscript. All authors reviewed and approved the final manuscript.

Conflict of interest

The authors declare that they have no conflict of interest.

References


Multiple risk factors for Parkinson's disease.
Gorell JM, Peterson EL, Rybicki BA, Johnson CC.

Abstract

OBJECTIVE: To determine the relative contribution of various risk factors to the development of Parkinson's disease (PD).

METHODS: Ten variables that were independently associated with PD in a health system population-based case-control study of epidemiological risk factors for the disease were jointly assessed. Stepwise logistic regression, adjusted for sex, race and age was used to develop a multiple variate model that best predicted the presence of PD. The population attributable risk was estimated for each variable in the final model, as well as for all factors together.

RESULTS: The 10 initial variables included >20 years occupational exposure to manganese or to copper, individually; >20 years joint occupational exposure to either lead and copper, copper and iron, or lead and iron; a positive family history of PD in first- or second-degree relatives; occupational exposure to insecticides or herbicides; occupational exposure to farming; and smoking. Logistic regression resulted in a final model that included >20 years joint occupational exposure to lead and copper (p=0.009; population attributable risk [PAR]=3.9%), occupational exposure to insecticides (p=0.002; PAR=8.1%), a positive family history of PD in first- and second-degree relatives (p=0.001; PAR=12.4%), and smoking <30 pack-years or not smoking (p=0.005; PAR=41.4%). All four variables combined had a PAR=54.1%.

CONCLUSIONS: Our final model of PD risk suggests that occupational, environmental lifestyle and, likely, genetic factors, individually and collectively, play a significant role in the etiology of the disease. Clearly, additional risk factors remain to be determined through future research.

Comment in
Toxic exposure and Parkinson's disease. [J Neurol Sci. 2006]

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Occupational exposure to manganese, copper, lead, iron, mercury and zinc and the risk of Parkinson's disease.

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Author information

Abstract
A population-based case-control study was conducted in the Henry Ford Health System (HFHS) in metropolitan Detroit to assess occupational exposures to manganese, copper, lead, iron, mercury and zinc as risk factors for Parkinson's disease (PD). Non-demented men and women 50 years of age who were receiving primary medical care at HFHS were recruited, and concurrently enrolled cases (n = 144) and controls (n = 464) were frequency-matched for sex, race and age (+/- 5 years). A risk factor questionnaire, administered by trained interviewers, inquired about every job held by each subject for 6 months from age 18 onward, including a detailed assessment of actual job tasks, tools and environment. An experienced industrial hygienist, blinded to subjects' case-control status, used these data to rate every job as exposed or not exposed to one or more of the metals of interest. Adjusting for sex, race, age and smoking status, 20 years of occupational exposure to any metal was not associated with PD. However, more than 20 years exposure to manganese (Odds Ratio [OR] = 10.61, 95% Confidence Interval [CI] = 1.06, 105.83) or copper (OR = 2.49, 95% CI = 1.06,5.89) was associated with PD. Occupational exposure for > 20 years to combinations of lead-copper (OR = 5.24, 95% CI = 1.59, 17.21), lead-iron (OR = 2.83, 95% CI = 1.07,7.50), and iron-copper (OR = 3.69, 95% CI = 1.40,9.71) was also associated with the disease. No association of occupational exposure to iron, mercury or zinc with PD was found. A lack of statistical power precluded analyses of metal combinations for those with a low prevalence of exposure (i.e., manganese, mercury and zinc). Our findings suggest that chronic occupational exposure to manganese or copper, individually, or to dual combinations of lead, iron and copper, is associated with PD.

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Whole-body lifetime occupational lead exposure and risk of Parkinson’s disease.


Author information

Abstract

BACKGROUND: Several epidemiologic studies have suggested an association between Parkinson’s disease (PD) and exposure to heavy metals using subjective exposure measurements.

OBJECTIVES: We investigated the association between objective chronic occupational lead exposure and the risk of PD.

METHODS: We enrolled 121 PD patients and 414 age, sex, and race, frequency-matched controls in a case-control study. As an indicator of chronic Pb exposure, we measured concentrations of tibial and calcaneal bone Pb stores using 109Cadmium excited K-series X-ray fluorescence. As an indicator of recent exposure, we measured blood Pb concentration. We collected occupational data on participants from 18 years of age until the age at enrollment, and an industrial hygienist determined the duration and intensity of environmental Pb exposure. We employed physiologically based pharmacokinetic modeling to combine these data, and we estimated wholebody lifetime Pb exposures for each individual. Logistic regression analysis produced estimates of PD risk by quartile of lifetime Pb exposure.

RESULTS: Risk of PD was elevated by > 2-fold [odds ratio = 2.27 (95% confidence interval, 1.13-4.55); p = 0.021] for individuals in the highest quartile for lifetime lead exposure relative to the lowest quartile, adjusting for age, sex, race, smoking history, and coffee and alcohol consumption. The associated risk of PD for the second and third quartiles were elevated but not statistically significant at the alpha = 0.05 level.

CONCLUSIONS: These results provide an objective measure of chronic Pb exposure and confirm our earlier findings that occupational exposure to Pb is a risk factor for PD.