Associations of welding and manganese exposure with Parkinson disease : Review and meta-analysis

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Associations of welding and manganese exposure with Parkinson disease

Review and meta-analysis

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ABSTRACT

Objective: To examine associations of welding and manganese exposure with Parkinson disease (PD) using meta-analyses of data from cohort, case-control, and mortality studies.

Methods: Epidemiologic studies related to welding or manganese exposure and PD were identified in a PubMed search, article references, published reviews, and abstracts. Inclusion criteria were 1) cohort, case-control, or mortality study with relative risk (RR), odds ratio (OR), or mortality OR (MOR) and 95% confidence intervals (95% CI); 2) RR, OR, and MOR matched or adjusted for age and sex; 3) valid study design and analysis. When participants of a study were a subgroup of those in a larger study, only results of the larger study were included to assure independence of datasets. Pooled RR/OR estimates and 95% CIs were obtained using random effects models; heterogeneity of study effects were evaluated using the Q statistic and I^2 index in fixed effect models.

Results: Thirteen studies met inclusion criteria for the welding meta-analysis and 3 studies for the manganese exposure meta-analysis. The pooled RR for the association between welding and PD for all study designs was 0.86 (95% CI 0.80–0.92), with absence of between-study heterogeneity ($I^2 = 0.0$). Effect measures for cohort, case-control, and mortality studies were similar (0.91, 0.82, 0.87). For the association between manganese exposure and PD, the pooled OR was 0.76 (95% CI 0.41–1.42).

Conclusions: Welding and manganese exposure are not associated with increased PD risk. Possible explanations for the inverse association between welding and PD include confounding by smoking, healthy worker effect, and hormesis. ***Neurology***® **2012;79:1174–1180**

GLOSSARY

CI = confidence interval; **MOR** = mortality odds ratio; **OR** = odds ratio; **PD** = Parkinson disease; **RR** = relative risk.

Although case reports suggest that exposure to high levels of manganese is associated with the development of an atypical parkinsonism called manganism,[1–5] the association of manganese exposure with the common form of Parkinson disease (PD) is more controversial. Welders are exposed to manganese in the fume, but it is unclear whether the dose provided by this exposure is sufficient to increase PD risk. Expert reviews prior to 2006 concluded that there was little evidence for a causal association between welding and PD.[6,7] However, there has been no published meta-analysis of studies in this area. Since 2005, several large epidemiologic studies of welding and PD have been published, affording an opportunity to revisit this issue more systematically and with greater statistical power.

In this article, we examine the associations between welding and PD and between manganese exposure and PD based on meta-analyses of data from published epidemiologic cohort, case-control, and mortality studies.

Supplemental data at www.neurology.org

Supplemental Data

METHODS **Search strategy.** To identify studies for inclusion, we conducted a PubMed search to find epidemiologic studies related to welding or manganese or occupation and PD from January 1974–December 2011. This search was supplemented by a search of Cochrane Database of Systematic Reviews, and by examining other published reviews, reference lists from published studies,

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and abstracts from scientific meetings. Identified studies were screened to determine those in which welding or manganese exposure was related to clinical diagnoses of PD.

Inclusion and exclusion criteria. Because ecologic studies do not provide individual data suitable for judging causal associations and cross-sectional studies do not provide evidence for a temporal sequence between exposure and outcome, the meta-analysis was restricted to cohort, case-control, and mortality studies. Further, since age is a strong risk factor for PD,[8] studies where age was not matched or controlled were excluded. In addition, in view of the male preponderance of PD,[8] studies in which sex was not matched or controlled also were excluded. To be eligible for inclusion, studies had to report relative risks (RR), odds ratios (OR), or mortality odds ratios (MOR) with 95% confidence intervals (95% CI).

In case-control studies where results were reported for both prevalent and incident PD, the OR associated with incident PD was selected to minimize survival bias. Further, when multiple sources of data existed for exposure determination, the source with the lowest probability of information bias was selected. For example, when exposure determination could be determined either from records obtained at the time of diagnosis or from retrospective recall of an informant, we used the former source because the latter is subject to proxy respondent bias.[9]

In addition, studies were excluded if after evaluation it was determined that invalid study designs or analytic methods were used to generate the risk estimates.

When there was a choice within a single study, the more specific category of welders and cutters was preferred over a broader definition of occupations that may or may not have involved welding as a task. To assess the effect of this criterion, we conducted a sensitivity analysis in which the broad definition was substituted for the narrower definition of welders and cutters only.

When participants of 1 study were a subgroup of participants of a larger study, only results of the larger study were included to assure independence of datasets.

Statistical analyses. Statistical analyses were conducted using Comprehensive Meta-Analysis, version 2.2.055 (www.Meta-Analysis.com). This software package provides for combination of ORs or RRs from epidemiologic association studies to produce pooled estimates of risk together with their 95% CIs. For rare diseases such as PD, ORs and MORs provide good approximations of the RR; thus reported measures of effect were considered to be equivalent to RRs for all 3 types of studies. For each meta-analysis performed, a pooled RR and 95% CI was obtained. Both fixed and random effects models were estimated. In this article, we present the more conservative random effects estimates for all analyses, although it is recognized that both models lead to similar interpretations.

For fixed effect models, results from studies were weighted by the precision of the individual risk estimates with studies having more precise estimates being weighted more heavily in the determination of the pooled risk estimate. For random effect models, precision of individual studies contributed to the determination of weights. However, because it is assumed that the underlying risk ratio varies from population to population, the influence of smaller studies with divergent estimates can be greater in random effect than in fixed effect model solutions.

Heterogeneity of effects was evaluated using the Q statistic; the I^2 index was used to estimate the percentage of variation across studies due to heterogeneity rather than chance.[10] For measurement of heterogeneity, a fixed effect model was used.

In addition to analyses in which the 3 types of studies were pooled, separate analyses were run for each study design.

RESULTS A total of 105 studies were identified from a PubMed search, and 4 additional studies[11–14] from a review article,[15] a published abstract,[14] and reference lists of articles. Of these 109 studies, 71 were excluded because they did not report results from epidemiologic association studies. Of the 38 articles retrieved, 3 were ecologic studies,[16–18] 3 were cross-sectional studies,[19–21] 13 lacked valid exposure information for welding or manganese (10 case-control studies,[22–31] 1 cohort study,[32] 1 mortality study,[33] and 1 ecologic study[16]), 2 lacked diagnoses of PD (1 cohort study,[34] 1 case-control study[35]), 3 did not report OR, MOR, or RR (3 case-control studies[36–38] and 1 mortality study[12]), 1 study lacked adjustment for age differences in cases and controls,[11] and the RR in 1 study was based on an invalid data analysis.[39] The latter study, an industrial cohort study performed in Korea,[39] was based on 9 patients with PD, only 2 of whom had a history of welding. The relative risk in this study was estimated by a Cox proportional hazards regression analysis, in which exposed and subsets of exposed workers were included as covariates in the same model, invalidating the hazard ratio obtained. Further, the number of welding exposed (n = 2) and unexposed (n = 3) cases was insufficient to apply this model.[40] The remaining 13 studies[13,14,41–51] met inclusion and exclusion criteria for the meta-analysis and are described in tables 1–3.

Association between welding as an occupation and PD. Figure 1 shows the forest plot and pooled RR for cohort, case-control, and mortality studies after excluding studies that utilized datasets that were subsets of or greatly overlapped those employed in other studies. The pooled RR was 0.86 (95% CI 0.80–0.92). Fixed and random effects models produced identical pooled RRs, consistent with an I^2 index = 0.00 indicating absence of heterogeneity. The Q statistic with 8 degrees of freedom was 4.448 (p = 0.82). Conditioned on the null hypothesis that RR = 1.0, the p value associated with the pooled RR of 0.86 was 0.000012.

When a broader definition of welding occupations was employed in the single mortality study included in this meta-analysis,[41] the pooled RR was 0.84 (95% CI 0.80–0.88). As before, there was no heterogeneity.

Pooled RRs for cohort (0.91 [95% CI 0.84–0.99]), case-control (0.82 [95% CI 0.67–1.01]), and mortality (0.87 [95% CI 0.78–0.97]) studies, considered separately, were similar.

To examine the possibility that the pooled RR may depend on the choice of studies included in the

Table 1 Cohort studies meeting inclusion criteria

Study reference	Study location	Exposure	Outcome	Relative risk (95% CI)	No. exposed	Person-years of follow-up	No. of outcomes in exposed	Covariates adjusted or matched
43[a]	Sweden	Welders or flame cutters in 1960 or 1970 Swedish censuses	First hospitalization with PD	0.89 (0.79–0.99)	49,488	1,436,645	353	Birth year, sex, county of residence, gainful employment
48	Denmark	Self-identified welders in questionnaire administered to industrial cohort	First hospitalization for PD	0.90 (0.40–1.50)	6,163	142,466	11	Age, sex
44[b]	Sweden	Welders or flame cutters in 1960 Swedish census	First hospitalization for PD	0.85 (0.68–1.06)	25,580	Not specified	85	Age, sex, education, region of residence
46[b]	Sweden	Welding fume exposure as judged by industrial hygienists from main occupation	Initial diagnosis of PD in Swedish National Patient Register or Cause of Death Register	0.90 (0.60–1.50)	Not specified	588,577	22	Age, sex, education, smoking

Abbreviations: CI = confidence interval; PD = Parkinson disease.
[a] Study sponsored by industry.
[b] Datasets are subsets or overlap greatly with that of reference 43.

meta-analysis, 2 government-sponsored studies[42,44] were substituted for 2 studies sponsored by the welding industry.[41,43] The pooled RR estimate (0.89 [95% CI 0.83–0.95]) was similar, suggesting that selection of particular studies for inclusion had little effect on the result.

Association between exposure to manganese and PD. Three studies met inclusion criteria for this assessment (table e-1 on the *Neurology*® Web site at www.neurology.org).[45,52,53] The forest plot is shown in figure 2. The pooled RR was 0.76 (95% CI 0.41–1.42). Consistent with the few studies and greater variability in effect sizes, I^2 was 62.22 and the Q statistic with 2 degrees of freedom was 5.29 (p = 0.07), demonstrating moderate heterogeneity.

DISCUSSION The meta-analysis for welding as an occupation produced similar effect sizes across studies with no indication of heterogeneity. The pooled RR of 0.86 (95% CI 0.80–0.92) is incompatible with an increased risk for PD among welders. With this RR, the null hypothesis that RR = 1.0 would be rejected (p = 0.000012) in favor of an inverse association between welding and PD. For any null hypotheses that RR >1.0 (consistent with an increased risk of PD among welders), the p value would be smaller than this value. Meta-analysis of the 3 studies with manganese as the exposure resulted in a pooled RR of 0.76 (95% CI 0.41–1.42), similar to those obtained with welder occupation as the exposure, further adding to the consistency of no increased risk of PD with manganese exposure.

Table 2 Case-control studies meeting inclusion criteria

Study reference	Exposure	Outcome	Odds ratio (95% CI)	No. of cases	No. of controls	No. of exposed cases
51	Welding occupation as abstracted from Medical Record	Parkinson disease	0.14 (0.01–2.74)[b]	202	202	0
50[a]	Ever a welder in any plant	First filed medical insurance claim for PD or secondary parkinsonism within defined time period	0.76 (0.26–2.19)	28	280	5
45	High manganese exposure from job exposure matrix: only found in welders	Parkinson disease (UKPDS Brain Bank criteria)	0.92 (0.64–1.32)	767	1,989	Not specified
47[a]	Self-identified welders in questionnaire	Parkinsonism, but 96.9% of cases fulfilled PD criteria	1.01 (0.61–1.66)	519	511	41
13	Self-reported job: welder or cutter	Newly diagnosed PD cases	0.60 (0.37–1.07)	252	326	25
14	Jobs where welding was a job task as determined by industrial hygienist	Newly diagnosed PD cases	0.76 (0.5–1.1)	496	541	50

Abbreviations: CI = confidence interval; PD = Parkinson disease; UKPDS = UK Parkinson's Disease Society.
[a] Studies sponsored by industry.
[b] Odds ratio (95% CI) obtained after adding 0.5 to all cells.

Table 3 Mortality studies meeting inclusion criteria

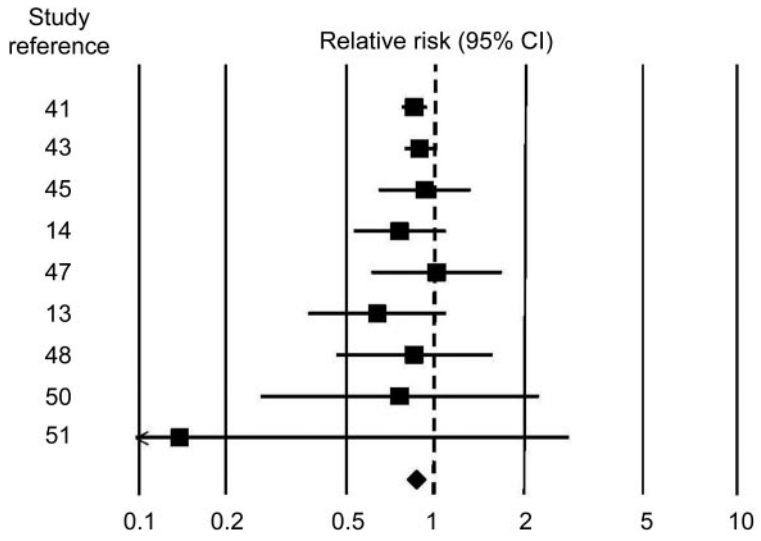
Study reference	Exposure	Outcome	Mortality odds ratio (95% CI)	No. of deaths	No. of deaths with welding occupation on death certificate	No. of exposed cases
49[b]	Welders and cutters	Parkinson disease	2.26 (0.85–6.06)	3,112 men	18	12
42[b]	Broad group of occupations in which welding may be a job task	Parkinson disease	0.87 (0.80–0.95)	1,683,783 men	44,545	540
41[a]	Welders and cutters	Parkinson disease	0.85 (0.77–0.94)	4,252,490 men	42,139	373

Abbreviation: CI = confidence interval.
[a] Study sponsored by industry.
[b] Exposed individuals are subset of workers in the same occupations reported in reference 41.

The consistency among studies regarding the absence of an increased risk of PD among welders is reflected in the lack of heterogeneity, which suggests that differences in risk estimates from study to study can be attributed to chance. Because the findings are based on comparison of the frequency of PD in approximately 100,000 welders and over a million nonwelders, considerable confidence can be placed in the pooled RR, which was significantly less than 1.0. The fact that mortality studies, cohort studies, and case-control studies carried out in different populations yielded similar estimates suggests that the pooled RR accurately reflects the absence of an increased risk of PD among welders.

Cross-sectional and ecologic studies as well as case series and single case reports were excluded from the meta-analysis. Because of the absence of controls, case series and single case reports cannot be used to assess association. Ecologic studies, which lack information on individual exposure and outcomes, rely on associations between characteristics of groups, frequently defined geographically, and measures of disease prevalence and incidence. Such studies are susceptible to the ecologic fallacy in which the association evident at a group level is not present at the level of the individual.[54] This occurs most often because compared groups differ on other uncontrolled factors related to both the exposure and risk of disease. A recently published ecologic study[18] reported an incidence ratio of 1.78 (95% CI 1.54–2.07) representing the incidence rate for new (nongeographically mobile) PD cases in 2003 in counties that were in the highest 75th percentile of all counties for manganese release and lowest 25% percentile for lead and copper release compared to the incidence rate in counties in the lowest 25th percentile for manganese, lead, and copper release, according to the Environmental Protection Agency's Toxic Release Inventory database.[55] Important potential sources of confounding in this study include socioeconomic discrepancies between counties with high and low levels of release of manganese, which could affect both migration and access to diagnosis and were not adjusted for in the analysis. In addition, the exposure measure used in this study reflects neither individual nor county-wide exposure to this metal.[55]

Figure 1 Forest plot for studies in welding–Parkinson disease analysis

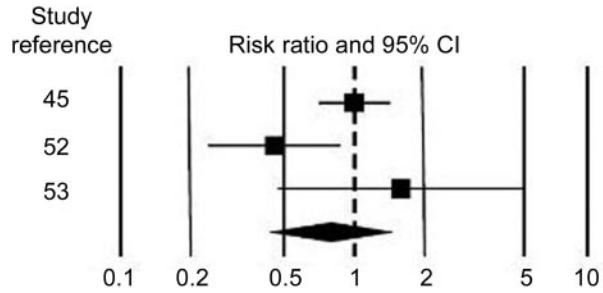


Pooled relative risk (95% confidence interval [CI]) = 0.86 (0.80–0.92) (shown by diamond).

Cross-sectional studies examine the association of exposures and outcomes measured at the same time. One cross-sectional study[20] compared the prevalence of parkinsonism in Alabama welders with the prevalence of PD in an epidemiologic study that was conducted decades before in the general population. Because the method of ascertainment of cases was different in these studies, the obtained prevalence ratio (10.19) reported in this study is unlikely to be valid. A more recent study by the same investigators[56] showed that utilization of a similar method to that used to assess parkinsonism in Alabama welders generated a very high rate in the general population as well, bringing into question the conclusion from the Alabama welding study that welders have higher risk of PD.

That welding was associated with a significantly decreased risk of PD was surprising. One possible

Figure 2 Forest plot for studies in manganese exposure–Parkinson disease analysis



Pooled relative risk (95% confidence interval [CI]) = 0.76 (0.41–1.42) (shown by diamond).

explanation is that welders may be more likely to smoke and that their increased frequency of smoking could result in a decreased risk of this illness through the well-established inverse association between smoking and PD.[15] However, arguing against this interpretation was the finding that the case-control studies controlled for smoking in their analyses and the associated pooled RR for these studies was the lowest of the 3 study designs. In addition, a recently published cohort study of occupational exposures in the Swedish twin registry[46] where the effects of smoking were adjusted reported a relative risk for exposure to welding fume of 0.9, consistent with the findings of other cohort studies that did not adjust for this potential confounder.

The reduced risk of PD among welders also might be explained by a variant of the healthy worker effect. Welding is a physically challenging occupation and it is possible that individuals developing this disease may stop welding and take another occupation. In 2 of the cohort studies,[43,44] welders were identified from their occupations at the time of censuses conducted every 10 years. A person who became a welder in the period between censuses and then changed occupation before the next census would not have been identified as having been a welder. In addition, mortality studies could identify the last occupation that an individual had and therefore miss an earlier occupation that included welding as a job task. However, these exposure misclassifications would likely be nondifferential, resulting in an attenuation of the inverse effect (moving it closer to 1.0) with the true relative risk being even more inverse. Finally, while a healthy worker effect could be posited for 2 of the cohort studies[44,48] that compared PD incidence with the general population, the largest cohort study,[43] which reported the lowest RR, compared welders to a gainfully employed male population, which should have mitigated this effect. A healthy worker effect also may be expected to be reflected in a more inverse association with increased duration of employment as a welder. However, 1 cohort study[44] compared welders employed as welders at 1, 2, and 3 censuses and did not observe a significant decrease in the risk estimate with longer disease duration.

A third possibility for explaining the decreased PD risk among welders is the biological phenomenon of hormesis, where moderate levels of exposure to agents that cause disease or degeneration can lead to beneficial effects.[57] A well-known example is that of alcohol, where moderate consumption reduces the risk of cardiovascular disease while high consumption leads to cardiomyopathy.[58] High levels of manganese exposure produce manganism, a degenerative neurologic condition with features of parkinsonism.[1–5] It is possible that as with other potential toxicants, moderate exposure to manganese could be beneficial in stimulating protective pathways in the brain. Of course, welders are exposed to moderate levels of other metals, including iron, which may have similar beneficial properties.

The absence of an association of welding or manganese exposure with increased risk for PD is consistent with conclusions reached in previously published reviews.[6,7,15,59] This finding does not preclude the possibility that high manganese exposure as occurs in some miners and workers at manganese processing facilities can lead to a form of parkinsonism called manganism.

AUTHOR CONTRIBUTIONS

Dr. Mortimer was responsible for drafting and revising the manuscript for content, study design, and statistical analysis and interpretation of data. Drs. Borenstein and Nelson contributed to analysis and interpretation of findings, as well as to drafting the manuscript and its revisions.

DISCLOSURE

J. Mortimer received compensation from a consulting agreement with the Welding Industry Defense Group, a group of current and former manufacturers of welding consumables involved in litigation, for his work as an expert witness. This support was used for the initial review of literature on the association between welding or manganese exposure and Parkinson disease. The Welding Industry Defense Group and their attorneys had no role in the initiation, design, or conduct of the meta-analysis; or in preparation, review, or approval of the manuscript. A. Borenstein reports no disclosures. L. Nelson is currently funded by grants from NIH (R21-OH009914, R01 AG034639), Department of Defense (10124005), and the Muscular Dystrophy Association (115267). **Go to Neurology.org for full disclosures.**

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