

ORIGINAL ARTICLE

Dose–effect relationships between manganese exposure and neurological, neuropsychological and pulmonary function in confined space bridge welders

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Background: Although adverse neuropsychological and neurological health effects are well known among workers with high manganese (Mn) exposures in mining, ore-processing and ferroalloy production, the risks among welders with lower exposures are less well understood.

Methods: Confined space welding in construction of a new span of the San Francisco–Oakland Bay Bridge without adequate protection was studied using a multidisciplinary method to identify the dose–effect relationship between adverse health effects and Mn in air or whole blood. Bridge welders (n = 43) with little or no personal protection equipment and exposed to a welding fume containing Mn, were administered neurological, neuropsychological, neurophysiological and pulmonary tests. Outcome variables were analysed in relation to whole blood Mn (MnB) and a Cumulative Exposure Index (CEI) based on Mn-air, duration and type of welding. Welders performed a mean of 16.5 months of welding on the bridge, were on average 43.8 years of age and had on average 12.6 years of education.

Results: The mean time weighted average of Mn-air ranged from 0.11–0.46 mg/m³ (55% >0.20 mg/m³). MnB >10 µg/l was found in 43% of the workers, but the concentrations of Mn in urine, lead in blood and copper and iron in plasma were normal. Forced expiratory volume at 1 s: forced vital capacity ratios (FEV₁/FVC) were found to be abnormal in 33.3% of the welders after about 1.5 years of welding at the bridge. Mean scores of bradykinesia and Unified Parkinson Disease Rating Scale exceeded 4 and 6, respectively. Computer assisted tremor analysis system hand tremor and body sway tests, and University of Pennsylvania Smell Identification Test showed impairment in 38.5/61.5, 51.4 and 88% of the welders, respectively. Significant inverse dose–effect relationships with CEI and/or MnB were found for IQ (p ≤ 0.05), executive function (p ≤ 0.03), sustaining concentration and sequencing (p ≤ 0.04), verbal learning (p ≤ 0.01), working (p ≤ 0.04) and immediate memory (p ≤ 0.02), even when adjusted for demographics and years of welding before Bay Bridge. Symptoms reported by the welders while working were: tremors (41.9%); numbness (60.5%); excessive fatigue (65.1%); sleep disturbance (79.1%); sexual dysfunction (58.1%); toxic hallucinations (18.6%); depression (53.5%); and anxiety (39.5%). Dose–effect associations between CEI and sexual function (p < 0.05), fatigue (p < 0.05), depression (p < 0.01) and headache (p < 0.05) were statistically significant.

Conclusions: Confined space welding was shown to be associated with neurological, neuropsychological and pulmonary adverse health effects. A careful enquiry of occupational histories is recommended for all welders presenting with neurological or pulmonary complaints, and a more stringent prevention strategy should be considered for Mn exposure due to inhalation of welding fume.

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Manganese (Mn) exposure through welding fume has been reported to cause parkinsonian syndrome, sometimes described as welding fume-related parkinsonism and often misdiagnosed as Parkinson's disease because of similarities in neurological features including tremor, masked facies and generalised bradykinesia.¹ However, important differences in movement disturbance between Mn-induced parkinsonism (also called manganism) and idiopathic Parkinson's disease (IPD) include an awkward high-stepping dystonic gait in manganism, which is in stark contrast with the typical shuffling gait in patients with IPD, and the tendency to lose balance by falling backward in IPD and forward in manganism. Additionally, tremor characteristics are different, usually resting tremor in IPD and postural intention tremor in manganism.¹ Magnetic resonance imaging (MRI) may be used to differentiate IPD from Mn-induced parkinsonism if a patient has had excess Mn exposure within the previous 6 months.²

Positive MRIs can show cerebral Mn²⁺ deposition in both animals and humans, especially in the globus pallidus (possibly in the striatum), by exhibiting a T₁-weighted signal hyperintensity.³ IPD, however, is associated with lesions in the *substantia nigra pars compacta*, and does not exhibit MRI abnormality in the globus pallidus. Two other key features differentiating between Mn-induced parkinsonism and IPD are:

Abbreviations: Cal-OSHA, California Division of Occupational Safety and Health; CATSYS, computer assisted tremor analysis system; CEI, Cumulative Exposure Index; FCAW, Flux Cored Arc Welding; FVC, forced vital capacity; FEV₁, forced expiratory volume at 1 s; IPD, idiopathic Parkinson's disease; Mn-air, manganese air levels; MnB, whole blood manganese; MRI, magnetic resonance imaging; SCL-90-R, Symptom Checklist 90-Revised; SMAW, Shielded Metal Arc Welding; UPDRS, Unified Parkinson Disease Rating Scale; UPSIT, University of Pennsylvania Smell Identification Test; WAIS-III, Wechsler Adult Intelligence Scale; WMS III, Wechsler Memory Scale

(1) a younger age of onset for Mn-exposed workers and (2) little or no response to L-dopa among Mn-induced parkinsonism cases.^{4,5} Case reports of neurological findings in career welders exposed to Mn have shown dystonia bilaterally in the shoulders and four distal limbs, as well as other parkinsonian features—for example, tremor and postural instability.^{5,6}

Welders have been reported to be exposed to “a wide variety of potential respiratory hazards”,^{7,8} although earlier studies did not show increases in chronic bronchitis.⁹ However, shipyard welders have been reported to have a higher standardised mortality ratio for lung cancer, a finding which was also supported by the California Occupational Mortality Survey, after adjustment for smoking and asbestos exposure. Sjögren presented evidence of a causal relationship between exposure to stainless steel welding and lung cancer.¹⁰

Diagnosis of Mn intoxication in workers actively exposed to excessive Mn in welding fumes can be further supported by biomarkers of exposure indicating increased internal Mn concentrations—for example, in whole blood and to a lesser extent in plasma/serum or urine. Sjögren *et al*¹¹ reported a mean concentration of 8.4 µg/l for whole blood Mn (MnB) in welders, whereas in other industrial settings the mean MnB ranged from 8.1 to 25.3 µg/l. No clear cutoff value of MnB is currently agreed upon, but HAR postulates that any values >10 µg/l is of concern.

Mn air levels (Mn-air) as reported in a few welder studies indicate that aerosols in welding operations (external exposure) usually contain <0.5 mg Mn/m³ (total dust), but sometimes they are >1 mg Mn/m³. A paramount feature of welding fume is that most of the airborne particles are in the respirable fraction (particle size <10 µm).¹² It is astonishing that reliable levels of respirable Mn particulate have rarely been reported, given the importance of the pulmonary uptake of Mn via the alveoli and its significance for Mn distribution to and effects on the central nervous system.¹³ It should be pointed out that inhalation exposure to Mn is for most of the jurisdictions regulated on the basis of total (or inhalable) dust: however, in the particular case of welding, a permissible exposure level established on the respirable fraction would enhance health prevention strategies.

Neuropsychological testing methods used over the past two decades have successfully differentiated Mn-exposed welders from unexposed controls.^{4,6,11} There have been 13 reports on welders showing deficits for motor, tremor, memory and neurocognitive domains, as well as for sleep, sexual function and vision. Although not all reports dealt with all of these domains, 11 studies indicated slowing of motor speed/efficiency^{4,6,11,14–21} and tremor^{3,4,6,14–17,19–22}; eight found loss of neurocognitive functioning^{4,6,11,14,16,18,19,21}; and six reported diminished memory function.^{4,6,11,14,18,21} Six studies reported sleep disturbances^{4,6,11,14,15,17} and three sexual problems.^{4,6,14} Vision was assessed in only two studies, and both found loss of colour vision associated with Mn exposure.^{6,14}

Welders exposed to Mn-containing welding fumes and dust have rarely been investigated by clinical neuropsychologists using an epidemiological study design in which actual measurements of internal and external exposure to Mn are studied in relation to outcome variables of a comprehensive test battery (including measures of IQ). Therefore, in the latter part of 2004, we decided to evaluate a welder group with health complaints, identified as employees on the reconstruction project of the San Francisco–Oakland Bay Bridge, which was damaged during the 1989 earthquake. The work on a vulnerable portion of the East span of the bridge began in 2003, requiring confined space welding of 28 anchoring foundations or piers, consisting of steel piles and footing boxes. The welding operations took place below the Bay's surface in

unpressurised cofferdams. During the first 1.5 years of welding on the support piers for the new bridge, welders began to express concerns of ill health feared to be the result of exposure to fumes due to confined space welding. During this period the welders were not required to wear personal protective equipment, and ventilation was minimal or ineffective. After receiving health complaints from almost 90% of the welders employed on the project, workers' compensation evaluations were enacted, which supported their report of adverse health effects. A multidisciplinary study group took advantage of this “natural experiment” for undertaking additional clinical evaluations (1) to assess the extent of neurological, neuropsychological, neurophysiological and pulmonary effects, (2) to explore whether these effects were associated with internal and/or external measures of Mn exposure and (3) to define a tentative permissible exposure level for Mn in welding fume.

METHODS

Study population

The study group consisted of 49 welders (45 men and 4 women), who were engaged in manual Shielded Metal Arc Welding (SMAW) and automated Flux Cored Arc Welding (FCAW) in confined small spaces during the construction of the new Bay Bridge. The four women, too few to analyse as a group, and two male individuals whose scores on a test of memory malingering²³ indicated low effort were evaluated, but excluded from the statistical analysis. All the welders underwent physical examinations before their employment on the bridge and were found to be healthy. The final group of 43 male welders remained for analysis in the current study.

Almost 90% of the welders employed over several months on this project during 2003–4 (based on the employer's confined space entry logs)²⁴ were evaluated for workers' compensation. To determine whether their health complaints could be medically documented, a comprehensive neuropsychological evaluation was conducted. As part of this evaluation, detailed health, lifestyle, work and exposure histories were obtained during individual clinical interviews and during testing. All workers stated that they had previously been in good health and that this was their first experience of confined space welding. None of the welders reported excessive alcohol consumption, which was generally low overall.

Procedures

The participants signed informed consent forms approved by the San Francisco State University's Institutional Review Board, and thereby agreed to use their clinical data from their workers' compensation evaluations, which included Health Insurance Portability and Accountability Act consents.

All tests were double scored using the methods detailed in their respective manuals by specialists of each of the disciplines (neuropsychology, neurology, neurophysiology and pulmonology). Data were then double entered in the SPSS V.13 programme to assure accuracy.

Study design

For the clinical workers' compensation evaluations, RMB, in her role as principal neuropsychologist, conducted clinical history interviews and administered tests of motivation. Five neuropsychologists administered a neuropsychological test battery, which included IQ testing, tests of executive, motor and other cognitive functions; sensory testing including vision and smell; and scales of symptoms, affect and mood.

In January 2005, the welders were also invited for a multidisciplinary investigation, during which they were subjected to neurological examinations and tests for lung function and olfaction. A board certified neurologist (WK) performed

neurological examinations and a PhD candidate (MB), trained in neurotoxicology, administered hand tremor and body sway tests. Two certified pulmonary technicians assessed lung function with spirometry. Psychometrician graduate students in psychology administered smell tests, scales of autonomic nervous system function, and a self-report evaluation of sleep and sexual function. Blood and urine samples were collected by a certified phlebotomist for trace metal analysis. Additional information on exposure histories were recorded by an experienced industrial toxicologist (HAR).

Exposure assessment

Air measurements

Reports of employer-commissioned air sampling at various locations on the bridge project, for California Division of Occupational Safety and Health (Cal-OSHA) compliance purposes, were made available by the Cal-OSHA inspectors. However, the actual sampling in the field was done by independent non-employer-affiliated laboratories, and all analyses were carried out autonomously, independent from employer control.

The results of the analyses for Mn and other metals in the confined space air samples taken at the Bay Bridge during January 2003 to June 2004 were averaged over three time periods (January to June 2003, July to December 2003 and January to June 2004) by type of welding: automated welding (FCAW) and manual stick welding (SMAW). For the period July to December 2004, for which no personal air sampling data were available, levels from the preceding 6-month period were used. A Cumulative Mn Exposure Index (CEI) was calculated for each welder (fig 1) using the self-reported percentage of time a welder performed FCAW or SMAW during his or her employment in the successive 6-month periods. Percentage of time was multiplied by estimated average levels of Mn-air for the two welding types, multiplied by the number of months worked, and then summed over the four time periods.

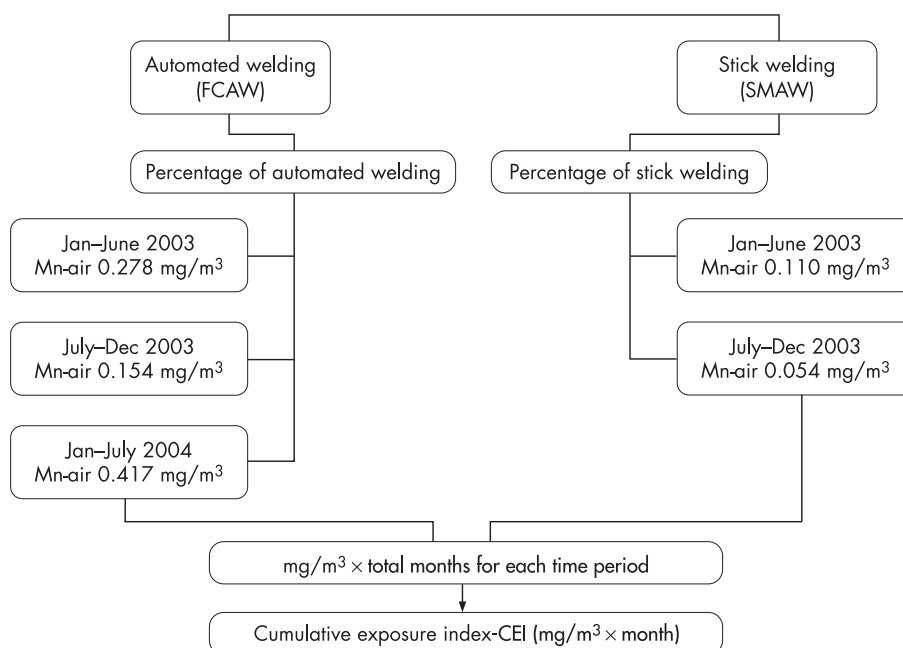


Figure 1 Construction of the Cumulative Exposure Index (CEI) based on type of welding, air measurements and months worked.

Biomarkers

Samples of 4 and 2 ml blood were collected by venipuncture using a 19-gauge butterfly catheter and heparinised tubes (BD#367 734). The 2-ml sample was then centrifuged at 800 *g* for 10 min at room temperature (about 25°C) to separate the plasma. A spot-urine sample (50–200 ml) was collected, from which a 1-ml aliquot was taken for creatinine analysis. Whole blood, plasma and urine were analysed in the trace metal facility at the University of California Santa Cruz (DS). The concentrations of Mn in whole blood, plasma and urine, and the plasma concentrations of copper and iron were determined by high-resolution inductively coupled plasma/mass spectrometry²⁵; Zeeman graphite furnace atomic absorption spectroscopy was used for lead in whole blood.

Neurological and neuropsychological evaluation

Neurological assessment

For the clinical neurological examination, the neurologist used the motor and the activities of daily living scales of the Unified Parkinson Disease Rating Scale (UPDRS).²⁶ The UPDRS is the most widely used instrument for measuring severity of parkinsonian symptoms qualitatively and quantitatively in clinical research and practice. It has high validity, and high inter-rater and intra-rater reliability. Computer assisted tremor analysis system (CATSYS)-2000 (Danish Product Development) was used to determine postural hand tremor intensity and bodily sway according to standardised procedures.²⁷

Neuropsychological testing

The comprehensive neuropsychological examination included the following tests: for IQ, the Wechsler Adult Intelligence Scale (WAIS-III) and Wechsler Memory Scale (WMS III)²⁸; for executive function, Rey-Osterrieth Complex Figure,²⁹ Stroop Colour Word³⁰ and Trail Making Tests A and B²⁹; for verbal function, animal naming, Controlled Oral Word Association Test,²⁹ Wide Range Achievement Test 3 reading subtest²⁹ and the Boston Naming Test²⁹; for motor function, Fingertapping, Dynamometer, Grooved Pegboard and Santa Ana Pegboard Test²⁹; for neuropsychiatric symptomatology, the Beck

Depression Inventories-II and Beck Anxiety Inventories,²⁹ the Symptom Checklist 90-Revised (SCL-90-R),³¹ and Satisfaction with Life Scale and Quality of Life Scale³²; and for malingering, Test of Memory Malingering²³ and the Rey 15-item test.²⁹

Spirometry, olfaction and vision tests

The spirometry test results were evaluated by a board-certified pulmonologist (RPB). Data analysed are forced expiratory volume at 1 s (FEV₁), forced vital capacity (FVC) and the FEV₁:FVC ratio. In total, spirometry testing reports were available for three points in time: after working on the bridge for an average of 1.5 months (time 1), after 10.8 months (time 2) and after an average of 20.9 months (time 3) of work on the bridge (study date in January 2005).

For olfactory function testing, we used the University of Pennsylvania Smell Identification Test (UPSIT), which consists of 40 "scratch and sniff" odorants administered according to standardised instructions.³³ The scores are summed and interpreted using the UPSIT norms to determine normosmia, microsmia and anosmia.

For the visual function, the Snellen Visual Acuity Test, the Lanthony 15-hue Test for colour vision and the Vistech Contrast Sensitivity Test were used.³⁴

Missing data

Analyses computing the IQ scores could not be done for eight participants who did not complete all of the subtests of the WAIS or WMS necessary to compute the summary IQs. These participants were given alternate IQ measures in Spanish.

Impairment definition

The neuropsychological tests were scored according to the test publishers' norms, which are adjusted for age and/or education. Scores of 1 standard deviation (SD; for whites) and 1.25 SD (for non-whites) below the mean of the reported test norms were categorised as impaired.⁶ The normative data used to compute the impairment level for the tremor are from Després *et al.*²⁷ Spirometry was evaluated according to the American Thoracic Society Standards and Guidelines³⁵ for mean predicted values to indicate different levels of lung function (mild, moderate and severe).³⁶ A cut-off of <75 was used to determine abnormality for FEV₁:FVC (%). For the UPSIT, clinical olfactory diagnoses were given according to age-adjusted and sex-adjusted centile norms from the manual.³³ Diagnoses of at least mild microsmia or anosmia were classified as impaired. For the SCL-90-R, T scores, mean (SD) 50 (10), based on sex-adjusted adult norms, were used to derive impairment ratings.

Statistical analyses

Demographic characteristics, biological and exposure results were analysed using descriptive statistics, and for trace metals in whole blood, plasma or urine high normal cut-off values or normal ranges are shown (table 1). Table 2 shows the neuropsychological mean test scores, SDs and prevalence percentage of impairment using the normative data.

Multiple regression analyses were performed to examine dose-effect associations between neuropsychological/neurophysiological test scores or self-reported adverse health symptoms obtained in the clinical interview and MnB or CEI. For spirometry, the ratio percentage changes from T1 to T3 were modelled using smoking and total years of welding before the Bay Bridge as covariates and MnB or CEI as independent variables.

To avoid bias of confounders in the dose-effect analyses, potential confounding factors (age, years of education, ethnicity and total years of welding before the Bay Bridge) were included as covariates in multiple regressions for the

neuropsychological tests when test scores were not previously adjusted for demographic variables in the test publisher norms. Similarly, age, years of education and total years of welding before the Bay Bridge were controlled in multiple logistic regressions examining the association between exposure variables and adverse health symptoms. As smoking among 10 welders ceased at a minimum of ≥ 8 years before the study date, the number of cigarettes smoked currently was included as a possible confounder in the dose-effect analyses for spirometry and olfactory tests. Smoking was not adjusted in other dose-effect analyses as it was found to have neither significant association with neuropsychological test performance or self-reported symptoms, nor significant covariate effects on the relationship between exposure variables and these dependent variables.

RESULTS

Study population characteristics

Table 1 shows the Bay Bridge welder group characteristics of demographics, work and exposure, and biomarkers of trace metals. On average, the welders were 43.8 years old, had 12.6 years of education, had welded already for 14.2 years before the Bay Bridge, and did 16.5 months of confined space welding at the Bay Bridge, where 22 of 43 welders were still active at the end of January 2005. About half of the welder group was composed of whites. As to smoking habits, 25 welders had never smoked and 10 were ex-smokers who reported cessation of smoking at least 8 years before the actual study date.

Exposure

Before April 2004, the welders reported wearing respirators on average 6% of the time, whereas after this date they wore them 82% of the time. On-site Cal-OSHA inspections of the confined spaces in which the welders worked noted deficiencies in orientation and functioning of the ventilation devices and identified overexposure to Mn in welding fumes.

Cal-OSHA data for May and June 2003 at the Bay Bridge reconstruction site and personal exposure monitoring done by the contracted laboratory during 75–80% of the work shifts showed air levels of Mn ranging from 0.11 to 0.46 mg/m³. Table 1 shows the Mn concentration in air, CEI and trace metal concentrations in whole blood (Mn, Pb), serum/plasma (Mn, Fe, Cu) and urine (Mn).

It is interesting to note that 55% of the average Mn-air levels exceeded the Cal-OSHA PEL or ACGIH TLV, which is 0.2 mg/m³ for 8-h time weighted average (total dust). All biomarkers of trace metals are considered normal, except MnB, the level of which exceeded 10 µg/l in 16 of 37 (43%) welders. Moreover, welders still actively welding at the time of the study (n = 21) had a significantly higher mean (SD) MnB than those who had stopped working at the Bridge 1 month or more ago (n = 16)—that is, 10.3 (2.82) v 8.7 (1.74) µg/l ($t_{35} = 2.00$, $p = 0.05$).

Spirometry

Spirometric findings indicated that the welders' lung function decreased from time 1 to time 3 by 7% for FEV₁, by 2% for FVC and by 21.2% for the FEV₁:FVC ratio. By the time of the study (time 3), 33.3% of the welders had an abnormal FEV₁:FVC ratio. This was supported by the result of a paired t test analysis of FEV₁:FVC ratio in non-smokers for times 1 and 3 ($t_{24} = 2.36$, $p < 0.05$). The ratio percentage changes from time 1 to time 3 were regressed with smoking, total years of welding before the Bay Bridge and each exposure variable (MnB or CEI), but no significant dose-effect association was obtained.

Table 1 Demographics, work and exposure characteristics, and biomarkers for trace elements in Bay Bridge welders

	Bay Bridge welders (n = 43)			
	n	Mean (%)	SD	Range
Demographics				
Age (years)	43	43.8	10	23–66
Years of education	43	12.6	2	7–17
Ethnicity				
White	22	51.2		
Non-white	21	48.8		
Smoking habits				
Current smokers	8	18.6		
Ex-smokers	10	23.3		
Work and exposure				
Years of welding before Bay Bridge	43	14.2	11	0–39
Months of welding at Bay Bridge	43	16.5	6	6–28
Active welders at Bay Bridge*				
Yes	22	51.2		
No	21	48.8		
Type of welding (% of time)				
FCAW	40	66.5	28.5	0–100
SMAW	40	28.9	25	0–100
Respirator worn at Bay Bridge (% of time)				
Before April 2004	42	6	19.7	0–100
After April 2004	29	82.2	28.5	0–100
Mn-air average (mg/m ³)	40	0.21	0.08	0.01–0.38
Mn-air CEI (mg/m ³ × month)	40	2.56	1.2	0.07–4.72
Biomarkers for trace metals				
Mn-blood (µg/l)†	37	9.6	2.5	5.13–15.3
Mn-urine (µg/g creatinine)††	36	0.28	0.460	0.00–1.93
Mn-plasma (µg/l)†	33	0.58	0.13	0.22–0.85
Pb-blood (µg/dl)†	37	2.8	1.1	1.24–6.59
Fe-plasma (µg/l)§	33	1127	327	469–2016
Cu-plasma (µg/l)§	33	807	120	601–1114

FCAW, flux cored arc welding; SMAW, shielded metal arc welding.

*Regarded as active welder if the welder left Bay Bridge <1 month before the January 2005 assessment date.

†Cut-off value upper normal: MnB, 10 µg/l; MnU, 2 µg/g creatinine; Mn-plasma, unknown; PbB, 25 µg/dl.

††LOD computed as 0.00003 µg/g creatinine.

§Normal range: Fe, 650–1700 µg/l; Cu, 700–1400 µg/l.³⁷

Neuropsychological testing

Table 2 shows the neuropsychological test results for selected parameters which are frequently affected in parkinsonism, including subtests of the WAIS-III (Letter–Number Sequencing, Working Memory), the WMS-III, the Rey–Osterrieth Complex Figure test, Design Fluency and Free Sorting, Auditory Consonant Trigrams, Stroop, Trailmaking Tests A and B, Grooved Pegboard, Fingertapping, Dynamometer, Santa Ana Pegboard and Parallel Lines Test. Bolded scores indicate the prevalence of welders with impaired performance at least twice as large as expected. DSM-IV clinical diagnoses in the workers' compensation evaluation resulted in classifying 79% with cognitive disorders.

Neurological and sensory examination

UPDRS results indicate that participants had total mean scores of 6.79 (SD 5.08, range 0–19) on the activities of daily living scale and 6.62 (SD 8.16, range 0–24) for the motor scale. In addition, a bradykinesia score was computed by summing scores of fingertaps, hand movements, rapid alternating movements of hands, leg agility, arising from a chair, gait and body bradykinesia/hypokinesia (mean (SD) 4.15 (6.53), range 0–20). Results from the CATSYS Tests showed impairment of hand tremor intensity (Harmonic Index) for 38.5–61.5% and postural sway intensity for 51.4% in the fourth condition (on foam and blinded; table 2).

Olfactory tests were compared with matched controls (by age, years of education and smoking habits) of a control subject database from the University of Pennsylvania Smell and Taste Center, and showed that 88% of the welders scored below their

individually matched controls.³³ The mean for welders was significantly lower than that for their matched controls ($F_{1,42}$ 23.06, $p < 0.001$).

Mood

Analyses of affect and mood indicated that the levels of clinical depression and anxiety were >2 SDs above the normative mean, indicating high levels of mood disturbance. Figure 2 shows the mean scores and standard errors of the welders' SCL-90-R, which indicate dysphoric mood and affect, signs of withdrawal from life interests, lack of motivation and loss of vital energy in addition to having clinical signs such as nervousness, tension and trembling, with possible panic episodes and feelings of terror. Psychoticism scores also were moderately raised, supporting some of the welders' statements of having hallucinations while welding. The mean (SD) score of the Beck Depression Inventories was 18.9 (10), and 63% of the welders had clinical elevations. The Beck Anxiety Inventories mean score was 22.6 (SD 14.6), with 80.5% clinical elevations. DSM-IV diagnoses indicate 70% anxiety disorders and 61% depression for the welders.

Based on the Behavioural Risk Factor Surveillance System, the average numbers of days reported for poor physical and mental health were 14 and 15 of 30 days, respectively, indicating significantly more poor health days than those reported by the US Center for Disease Control.

Dose–effect relationships

Significant dose–effect relationships between neuropsychological variables and blood Mn or CEI, shown in table 3, resulted

Table 2 Neuropsychological tests by domain of function

	Bay Bridge welders (n = 43)			Prevalence (%) of impairment
	n	Mean	SD	
IQ				
Full IQ	35	95.26	12.93	20
Performance IQ	41	94.49	13.67	17.1
Verbal IQ	35	93.69	14.17	22.9
Cognitive flexibility and executive functioning				
Stroop colour/word T score	42	39.76	13.40	45.2
Rey-Osterreith copy	43	30.60	3.73	69.8
Design fluency—total correct	41	10.24	2.84	9.8
Design fluency—percent design accuracy	41	8.73	2.69	24.4
Design fluency—switching	41	10.61	2.64	4.9
Sorting—Recognition Description score	37	7.65	2.78	43.2
Sorting—recognition v free sorting	37	7.30	3.15	35.1
Information processing speed				
Stroop colour T score	42	38.98	10.59	45.2
Stroop word T score	42	39.10	11.80	40.5
Working memory/attention and concentration/learning				
WAIS-III WMI	40	90.6	13.24	25
Digit span	41	8.44	2.37	26.8
Digit span—longest digits (forward)	41	6.1	1.43	17.5
Digit span—longest digits (backward)	41	4.22	1.01	27.5
Letter—number sequencing	40	8.38	3.04	32.5
WMS-III Auditory Immediate Memory Index	37	90.32	13.59	32.4
Logical memory I	37	7.97	3.14	43.2
Verbal paired associates I	37	8.65	2.19	18.9
Word lists 1 recall	36	7.78	3.34	44.4
Auditory consonant trigrams 3"	43	10.16	3.27	51.2
Auditory consonant trigrams 9"	43	7.86	3.25	55.8
Auditory consonant trigrams 18"	43	6.28	3.31	48.8
Rey-Osterreith immediate recall	43	38.79	13	46.5
Memory				
WMS-III Auditory Delayed Index	36	94.03	12.61	13.9
Verbal paired associates II	37	8.86	2.52	18.9
Word lists 2 recall	35	9.57	3.38	22.9
Rey-Osterreith delayed recall	43	39.02	13.18	60.5
Visuomotor tracking speed				
WAIS-III PSI	42	89.52	11.99	33.3
Digit symbol coding	42	7.79	2.37	31
Trail Making Test A T score	42	44.43	11.78	31
Verbal skills				
WAIS-III VCI	35	95.11	15.53	17.1
WRAT3-reading	34	93.65	13.91	23.5
Comprehension	41	8.78	2.92	24.4
Similarities	35	8.71	3.56	28.6
Vocabulary	37	8.62	3.12	35.1
Information	35	9.94	2.71	17.1
Motor dexterity and strength				
Grooved pegboard T score (dominant hand)	43	53.93	12.27	14
Finger tapping T score (dominant hand)	43	46.42	13.76	23.3
Dynamometer T score (dominant hand)	42	35.33	8.36	52.4
Santa Ana pegboard (dominant hand)	43	21.89	3.83	97.7
Tremor/postural sway				
Parallel Line Test	43	2.12	1.22	90.7
CATSYS Tremor: Harmonic Index (right)	39	0.15	0.11	38.5
CATSYS tremor: Harmonic Index (left)	39	2.32	0.56	61.5
CATSYS sway 4: sway intensity	35	8.84	5.11	51.4

CATSYS, computer assisted tremor analysis system; VCI, Verbal Comprehension Index; WAIS-III, Wechsler Adult Intelligence Scale; WRAT, Wide Range Achievement Test 3; WMS III, Wechsler Memory Scale.

from multiple regression analyses with the covariates of years of welding before Bay Bridge and age, years of education and ethnicity when these covariates were not adjusted in their respective norms. For blood Mn, significant associations were obtained for Full Scale IQ; cognitive flexibility and executive function; working memory, attention and concentration/learning;

and memory. For CEI, significant associations were obtained for verbal IQ, working memory and concentration/learning, memory and verbal skills. The partialled out effects of the potential covariates show that the welding fume exposure on the Bay Bridge remained significantly associated with impaired scores on tests. All coefficients (β values) had negative signs, indicating a

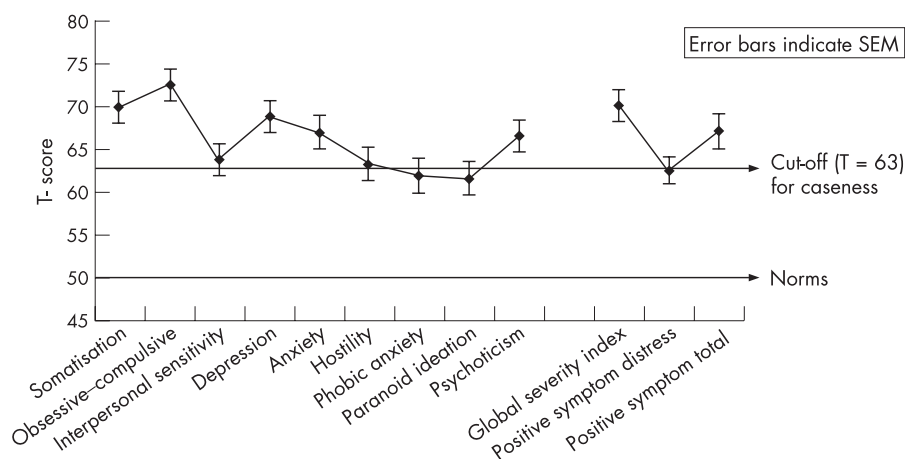


Figure 2 T scores of the Symptom Checklist 90-R (SCL-90-R), mean (SEM), for the nine clinical and three summary scales.

consistent direction of effect—that is, the higher the Mn values, the less favourable the neuropsychological outcomes. A substantial amount of variance was uniquely accounted for by MnB shown in table 3 and CEI as shown in table 4 (expressed by sr^2). Partial regression plots (fig 3) illustrate the inverse slopes for the regression lines of the residuals for the age-adjusted neuropsychological tests with MnB—that is, Full Scale IQ, Word List recall total (WMS-III), Letter-number sequencing (WAIS-III) and Design Fluency total correct—and with CEI—that is, Verbal IQ, Verbal Comprehension Index (WAIS-III) Working Memory Index (WAIS-III), and Auditory Immediate Memory Index (WMS-III). Multiple regressions indicate that an MnB increment of 5.0 $\mu\text{g/l}$ results in a decrease in Full Scale IQ of 10 points ($B = -2.0$, $SE = 1$), and a CEI increment of 2.4 $\text{mg/m}^3 \times \text{month}$ in a decrease of 12 points in verbal IQ ($B = -5.2$, $SE = 1.7$) and in a loss of 9 points for Working Memory Index ($B = -3.8$, $SE = 1.8$).

Logistic regression analyses for symptoms while working were performed to examine their relationship with MnB or CEI,

by controlling possible confounders such as age, years of education and years of welding before the Bay Bridge. A unit increase in MnB showed a significant association with depression ($OR = 1.5$, $p < 0.05$, 95% CI 1.0 to 2.2). There were also significant associations between the CEI and sexual dysfunction ($OR = 2.6$, $p < 0.05$, 95% CI 1.2 to 5.5), headache ($OR = 2.0$, $p < 0.05$, 95% CI 1 to 4), depression ($OR = 2.8$, $p < 0.01$, 95% CI 1.3 to 6) and fatigue ($OR = 2.7$, $p < 0.05$, 95% CI 1.3 to 5.9). No significant association was obtained for hallucination, sleep disturbance, tremors, anxiety and numbness. Bonferroni adjustments were not made as each symptom is considered its own domain.

DISCUSSION

Although there is a large body of literature on the association between occupational Mn exposure and ill health, a controversy remains whether Mn exposure in welders produces welding-related symptoms and associated specific deficits in

Table 3 Multiple regression analyses on neuropsychological test scores and using Mn in blood as a predictor

	Mn in blood ($\mu\text{g/l}$)			sr^2 Control variables			
	β	sr^2 (95% CI of sr^2)	p Value	Age	Edu	Eth	Yr W
IQ							
Full IQ	-0.34	0.09 (0-0.28)	0.053	-	0.10	0.05	0.01
Verbal IQ	-0.31	0.08 (0-0.25)	0.061	-	0.18	0.06	0
Cognitive flexibility and executive functioning							
Design fluency—total correct	-0.51	0.22 (0-0.44)	0.004	-	0.02	0.04	0.01
Design fluency—percentage design accuracy	-0.43	0.15 (0-0.36)	0.012	-	0.05	0.01	0.04
Design fluency—switching	-0.39	0.13 (0-0.32)	0.027	-	0.01	0.09	0.01
Working memory/attention and concentration/learning							
WAIS-III WMI	-0.29	0.07 (0-0.23)	0.095	-	0.11	0.14	0
Letter-number sequencing	-0.38	0.12 (0-0.32)	0.035	-	0.09	0.00	0.01
Word lists 1 recall	-0.29	0.07 (0-0.23)	0.042	-	0.41	0.01	0.01
Memory							
WMS-III WMI	-0.36	0.11 (0-0.3)	0.061	-	0.02	0	0.02
WMS-III Auditory Delayed Index	-0.3	0.08 (0-0.25)	0.093	-	0.07	0.04	0.09
Verbal Paired Associates II	-0.40	0.14 (0-0.35)	0.041	-	0.01	0.01	0.01
Verbal skills							
WAIS-III VCI	-0.27	0.06 (0-0.21)	0.094	-	0.18	0.08	0

Edu, education; Eth, ethnicity; sr^2 , squared semi-partial correlation; VCI, Verbal Comprehension Index WAIS-III, Wechsler Adult Intelligence Scale; WMS III, Wechsler Memory Scale; Yr W, years of prior welding. —demographic variable (age) was not entered in multiple regressions.

Table 4 Multiple regression analyses on neuropsychological test scores using Mn in Cumulative Exposure Index (CEI) as a predictor

	CEI (mg Mn/m ³ × month)			sr ² control variables			
	β	sr ² (95% CI of sr ²)	p Value	Age	Edu	Eth	Yr W
IQ							
Verbal IQ	-0.44	0.16 (0-0.37)	0.004	-	0.16	0.03	0
Cognitive flexibility and executive functioning							
Stroop colour-word T score	-0.30	0.07 (0-0.22)	0.097	-	0.04	0.01	0.01
Working memory/attention and concentration/learning							
WAIS-III WMI	-0.35	0.1 (0-0.26)	0.041	-	0.08	0.02	0.01
Digit span (forward)	-0.30	0.07 (0-0.21)	0.081	-	0.06	0.06	0.02
Letter-number sequencing	-0.39	0.12 (0-0.3)	0.036	-	0.05	0	0.02
WMS-III Auditory Immediate Memory Index	-0.42	0.14 (0-0.34)	0.017	-	0.03	0.05	0.06
Verbal Paired Associates I	-0.5	0.2 (0-0.42)	0.007	-	0.01	0.01	0.08
Auditory consonant trigrams total score	-0.34	0.09 (0-0.24)	0.071	0.05	0.02	0	0.05
Memory							
WMS-III WMI	-0.38	0.11 (0-0.29)	0.052	-	0	0	0.01
Logical memory I	-0.31	0.08 (0-0.24)	0.09	-	0.03	0.08	0.03
Verbal skills							
WAIS-III VCI	-0.35	0.1 (0-0.28)	0.026	-	0.19	0.05	0
Comprehension	-0.51	0.2 (0-0.41)	0.003	-	0.06	0	0
Similarities	-0.34	0.09 (0-0.27)	0.053	-	0.09	0.06	0
Vocabulary	-0.43	0.15 (0-0.35)	0.006	-	0.13	0.03	0

CEI, Cumulative Exposure Index; sr², squared semi-partial correlation; WAIS-III, Wechsler Adult Intelligence Scale; WMS III, Wechsler Memory Scale; VCI, Verbal Comprehension Index.
 -demographic variable (age) was not entered in multiple regressions.

neuropsychological and neurological function. Many of the previous welder studies did not report/measure air Mn, did not have the type of extensive exposure (air Mn) and biomarker measurements (blood, plasma and urine), or lacked the multidisciplinary methods (neurological, neuropsychological and respiratory assessment) used in the present study. There are as yet no reports of groups of confined space welders working in poor ventilation conditions without adequate

personal protection equipment who underwent full clinical neuropsychological and neurological examinations. The Bay Bridge welders afforded a unique opportunity to study health effects in the context of a “natural experiment” for this type of welding fume exposures. Although respiratory protection should have been required according to Cal-OSHA regulations and NIOSH guidelines, this was not done.²⁴ This group of middle age welders, who were pre-screened during a

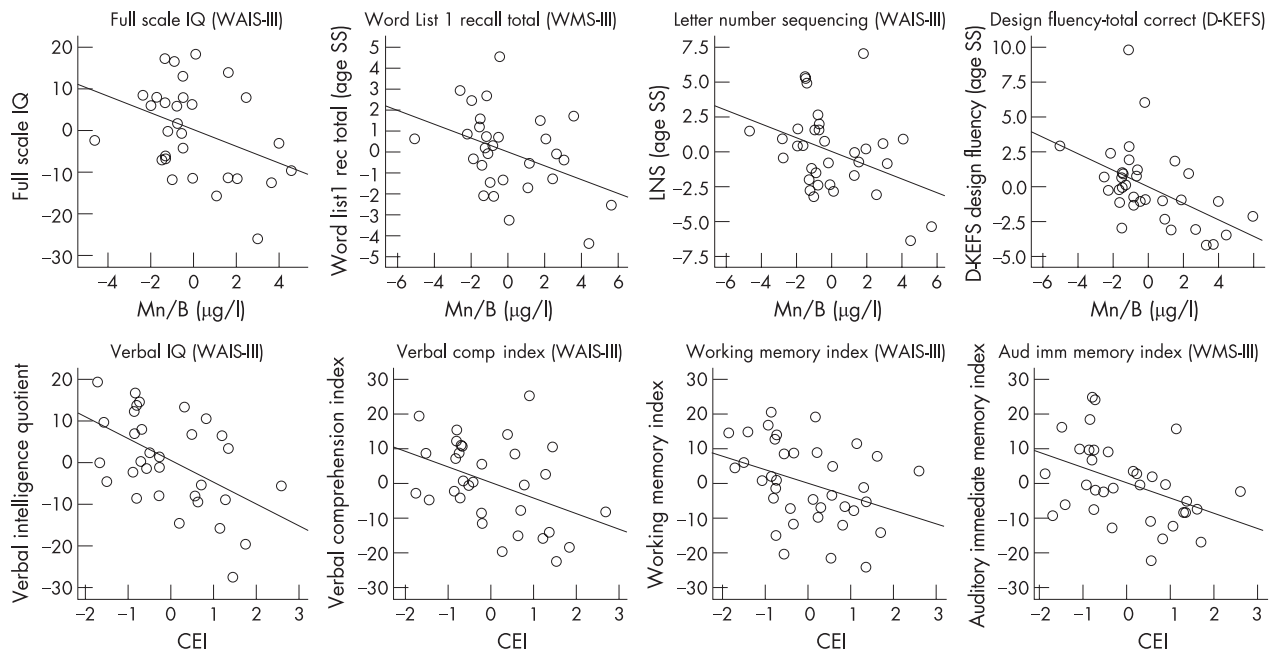


Figure 3 Graphic representation of partial regression graphs for selected tests and manganese in blood (Mn/B) and Cumulative Exposure Index (CEI).

competitive hiring process to assure good health and fitness, were highly skilled, competent and physically fit at the beginning of their employment on the bridge.

A major asset of the study is that the neurological effects identified in the Bay Bridge welders were detected by a neurologist using UPDRS examination, a reliable clinical tool widely used for assessing parkinsonian syndromes. Abnormal mean scores for UPDRS and bradykinesia were found in the welder group. Another important result is the detection of increased hand tremor and body sway with the CATSYS instrument, which allows objective measurements based on physics. Tremor, a hallmark of parkinsonism, was found to be present 39–90% of the time on three different methods of tremor testing. Motor dexterity and speed also was impaired 52–95% of the time on various neuropsychological measures. Welders, by the nature of their job, are required to have good speed and efficient motor performance, and are expected to have scored above average before their confined space welding period. The present results may underestimate the true effects size—this could be answered in a longitudinal study beginning with apprentice welders.

The study also showed strong suggestive evidence that as the welders continued to be exposed to Mn in welding fumes on the bridge, their intelligence level may have declined by as much as 10–12 IQ points, although some uncertainty cannot be ruled out because of the small sample size, lack of baseline and longitudinal data. Although lead has been acknowledged as a neurotoxicant lowering IQ in children, this is the first report of adults having IQ decrements associated with occupational Mn exposure. Recently, Wright *et al*³⁸ reported findings of an association between Mn in hair and lowered IQ in 32 children from Ottawa County in northeastern Oklahoma who lived at the Tar Creek Superfund clean-up site, slated for clean-up by the US Environmental Protection Agency. Wasserman *et al*³⁹ reported that exposures to Mn in tube-well water in Araihaazar, Bangladesh, produced similar decrements as those reported here in welders—that is, Mn exposure correlated with Full Scale IQ, performance and verbal IQ raw scores. This scientific convergence of findings suggests a detrimental effect of Mn on cognitive function resembling the negative effects of lead in children (blood lead levels were negligible in the welders)—regardless of the route of exposure (inhalation or oral). The finding of a dose–effect association between increased internal Mn exposure (moderate elevations of MnB) and lower IQ in a group of welders is of concern and should be followed up with larger observational studies of welding in confined spaces and other occupational settings with Mn exposure. Although the level of impairment for the neuropsychological test results is relatively small compared with more extreme findings of long-term welders reported previously,^{6, 14} the inverse dose–effect relationships between Mn exposure and IQ or other cognitive functions obtained in the present study suggest an increased population-attributable risk and represent a change, albeit small, in the distribution of IQ scores above some threshold of Mn exposure.

Overall, the skilled welder group, when interviewed by the clinical neuropsychologists, reported good mental health before welding on the bridge. After employment at the bridge, 63% and 81% scored clinically depressed and anxious, respectively. Mood effects have been described in many studies of Mn exposure.^{4, 6, 14, 40} Sleep and sexual disturbance, such as loss of libido and decreased potency, were reported by all but one welder. About 70% of welders who had workers' compensation evaluation were referred for clinical psychotherapeutic interventions.

Good or adequate olfactory ability contributes significantly to the enjoyment of life, and olfactory changes serve as an early

warning system for the detection of overexposure to chemicals, fire, gas, spoiled foods or dangerous levels of air contamination.³³ Olfactory loss has been associated with Parkinson's disease and head trauma,⁴¹ but inhalation exposure to manganese fume/dust may also entail olfactory changes as reported in a study of Mn-exposed ferromanganese-alloy workers.⁴² Recent studies in rats strongly suggest olfactory nerve transport as a significant route for central nervous system uptake of manganese from inhaled fine⁴³ (mass median aerodynamic diameter 1.3 μm) or ultrafine⁴⁴ (count median diameter 0.031 μm) Mn-oxide aerosols. Inhalation exposure of fine (6 h/day, 15 days; 3 mg/m^3) and ultrafine (6 h/day, 12 days; 0.5 mg/m^3) particles resulted in, respectively, 1.7 and 3.5 higher Mn concentrations in olfactory bulbs of exposed rats compared with controls. For ultrafine Mn-oxide aerosol exposure, an increased gene expression was found for tumour necrosis factor α in the olfactory bulb, frontal cortex, midbrain and striatum. For the olfactory bulb, at least a twofold increase over controls was shown for expression of other genes involved in stress response and inflammation.⁴⁴ Elder *et al*⁴⁴ stated that, as the olfactory neuronal translocation pathway was also shown in non-human primates, it is likely to be operative in humans as well. These experimental findings offer a strong basis for a causal association between the Bay Bridge welders' changes in smell identification and inhalation exposure to Mn from confined space welding generating fine/ultrafine particle aerosols. With more than three quarters of the welders showing impaired sense of smell, this loss leaves them deprived of olfaction as a sensory warning sign making them potentially more vulnerable to future injuries.

Most of the welders reported having developed respiratory symptoms (93%). The evolution of pulmonary abnormalities suggests that the longer they welded in the confined spaces on the Bay Bridge, the more the air flow obstruction developed. One third of the welder group presented with a mild obstructive syndrome at an average of 20.9 months after they began working on the bridge. They were referred for further pulmonary follow-up. The spirometric results suggest that further testing is indicated, such as inhaled bronchial challenge or clinical exercise testing. Those welders who continue to exhibit welding-related respiratory symptoms should also be considered candidates for additional pulmonary testing.³⁶

Both the raised MnB levels and the increase in Mn levels in the air of the Bay Bridge welders' working environment suggest that the measurable exposure to Mn is the likely cause of their ill physical and mental health. However, MnB analyses are useful only if they are done within <1 month of cessation of welding. A follow-up is needed to determine if the welders' condition has improved since leaving this work site. The confined space welding and simultaneous unprotected Mn exposure on the bridge were relatively brief (on average 16.5 months), which may make reversibility of their symptoms and deficits possible.

Both neurological and neuropsychological methods were found to be complementary in the diagnosis of welding-associated parkinsonism and, moreover, neuropsychological testing is shown to contribute significantly to the clinical neurological and pulmonary definition of a comprehensive portrait for health effects in Mn-exposed welders. A more complete portrait includes also tremor, IQ and other cognitive deficits, mood disturbance, sleep and sexual perturbations, changes in smell, and surprisingly early lung function effects as well, most probably linked to the size of welding fume particulate being predominantly in the respirable range.

A limitation of this study is the lack of a matched control group for comparison. However, as can be seen in the welders' demographic characteristics, they are similar to the

Policy implications

- Welders should undergo medical/occupational screening for symptoms related to manganese (Mn) exposure, at minimum once per year.
- Appropriate regulatory agencies (OSHA) should monitor welders for safe working conditions, wearing personal protective equipment should be supervised, and air measurements of Mn and other toxic metals should be performed and reviewed on a regular basis (at a minimum of once per month).
- The adverse health effects from Mn exposure in the welders described here occurred at average exposure levels at or slightly above 0.2 mg/m³. Therefore, the current permissible exposure level of California Division of Occupational Safety and Health for Mn exposure (total dust) should be reconsidered for welders, because welding fume aerosol falls nearly completely within the respirable fraction allowing very fine particulate a greater absorption rate of manganese via deposition in the alveolar region of the lung.

standardisation samples of the neuropsychological tests used. This similarity suggests that comparisons with the standardised age norms of the tests used are likely appropriate. Although the welders were not drawn at random, a selection bias is not likely because, according to several foremen, most (90%) of the welders worrying about health effects from welding fume exposure on the Bay Bridge have been included in our sample and are thus likely representative of the overall group. Significant dose-effect associations in this relatively small group support and strengthen the finding of multiple adverse health effects in these welders, despite the conservative approach used by taking into account up to four possible covariates in the multiple regression models. Although this may have had some influence in obtaining statistical significance, the remaining "explained" variance after adjustment for the covariates still supports inverse associations between MnB or CEI and several test performances. As the sample size was not under the investigator's control, replication using a larger sample of welders would be desirable to confirm these findings.

It is highly recommended for occupational physicians and other health professionals, who may evaluate or treat a welder, to consider exposure to Mn fumes as a possible cause of their ill health. The evaluating physician should refer such welders to neuropsychologists and neurologists for further assessments, which will assist in diagnostic considerations. Clearly, the loss of almost 1 SD of IQ, if this loss persists, will affect the welders' lives permanently, lowering their potential to earn a good living and their learning of new information which is required for work and for independent living skills. It is a high cost to society, as aptly stated by Weiss⁴⁵: "That cost is the decline in functional capacity. If the disease is a gradually progressive one, the ability of its victims to function effectively and efficiently will be impaired at stages of the disease far earlier than its eventual detection." Given these findings, enforcing protection by agencies such as NIOSH and Cal-OSHA is essential, and ongoing inspections to ascertain compliance can yield significant benefit to welders and to the society.

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