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The association of bone and blood manganese with motor function in Chinese workers

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Abstract

Manganese (Mn) is an essential element. However, Mn overexposure is associated with motor dysfunction. This cross-sectional study assessed the association between bone Mn (BnMn) and whole blood Mn (BMn) with motor function in 59 Chinese workers. BnMn and BMn were measured using a transportable *in vivo* neutron activation analysis system and inductively coupled plasma mass spectrometry, respectively. Motor function (manual coordination, postural sway, postural hand tremor, and fine motor function) was assessed using the Coordination Ability Test

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Declaration of interests
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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System (CATSYS) and the Purdue Pegboard. Relationships between Mn biomarkers and motor test scores were analyzed with linear regression models adjusted for age, education, current employment, and current alcohol consumption. BMn was significantly inversely associated with hand tremor intensity (dominant hand (β=−0.04, 95% confidence interval (CI):−0.07, −0.01; non-dominant hand β=−0.05, 95% CI: −0.08, −0.01) hand tremor center frequency (non-dominant hand β=−1.61, 95% CI: −3.03, −0.19) and positively associated with the Purdue Pegboard Assembly Score (β=4.58, 95% CI:1.08, 8.07). BnMn was significantly inversely associated with finger-tapping performance (non-dominant hand β=−0.02, 95% CI:−0.04,−0.004), mean sway (eyes closed and foam β=−0.68, 95% CI:−1.31,−0.04), and positively associated with hand tremor center frequency (dominant hand, β=0.40, 95% CI:0.002, 0.80). These results suggest BMn is related to better postural hand tremor and fine motor control and BnMn is related to worse motor coordination and postural hand tremor but better (i.e., less) postural sway. The unexpected positive results might be explained by choice of biomarker or confounding by work-related motor activities. Larger, longitudinal studies in this area are recommended.

Keywords

manganese; biomarkers; IVNAA; motor skills; movement disorders; metal workers

1. Introduction

Manganese (Mn) toxicity has been associated with neurotoxic effects including decreased motor function (Martin et al., 2020; O’Neal and Zheng, 2015). Occupational exposure to the metal has resulted in lower psychomotor function (Lucchini et al., 1997), general motor function (Ma et al., 2018), and manual dexterity (Cowan et al., 2009; Wells et al., 2018). Chronic manganese exposure has been associated with increased reaction time, impaired finger-tapping and digit-span performance scores (Wennberg et al., 1991), as well as grooved pegboard scores (Wastensson et al., 2012). The development of manganism, a disease like idiopathic Parkinson’s disease, can occur in cases of high or chronic manganese exposure (Lucchini et al., 2009). Additionally, recent evidence suggests that manganese exposure may be associated with Parkinson’s disease severity (Racette et al., 2021).

One of the most widely used biomarkers of Mn exposure is whole blood Mn (BMn) (Ge et al., 2018; Lucchini et al., 1997; Mirmohammadi et al., 2017). Despite its frequent use, previous research has suggested that the relationship between BMn and Mn exposure can be complex (Baker et al., 2014; Smith et al., 2007). BMn has been shown to reflect recent exposure, generally exposure occurring within days, due to the short half-life of Mn in the blood (Laohaudomchok et al., 2011; O’Neal and Zheng, 2015; Zheng et al., 2011). Idiopathic Mn-induced parkinsonism, also referred to as manganism, is a chronic disease which likely results from cumulative Mn exposure over varying lengths of time (Cersosimo and Koller, 2006). A biomarker reflecting recent exposure may not reflect long-term exposure. Until recently, biomarkers reflecting long-term Mn exposure were not available. Thus, the relationship between chronic Mn exposure and motor dysfunction is still unclear due to the lack of a biomarker for cumulative Mn exposure (Chen et al., 2016).

Bone manganese (BnMn) has previously been suggested as a viable biomarker of cumulative Mn exposure due to ~40% of Mn's body burden being found in bone and a relatively long half-life of the metal in bone, estimated at 8.6 years in human bone (Arnold et al., 2002; O'Neal et al., 2014). BnMn was also associated with Mn concentrations found in the brain, suggesting that BnMn could be reflective of Mn in target tissues of neurologic function (O'Neal et al., 2014). More recently, a lifetime Mn exposure study in rats reported that bone Mn was reflective of recent ongoing exposure but not lifetime exposure (Conley et al., 2021).

Limited research has assessed the relationship between BnMn and Mn exposure in human populations. When analyzed in a group of welders versus controls, BnMn was higher in the occupationally Mn-exposed welders compared to the non-occupationally exposed controls (Pejović-Milić et al., 2009). To continue assessing BnMn at different field sites, our research team developed a transportable *in vivo* Neutron Activation Analysis (IVNAA) (Liu et al., 2017, 2014, 2013). This transportable IVNAA system was used to assess BnMn in a group of 19 adult males, where BnMn was found to be significantly associated with decreased manual dexterity (Wells et al., 2018).

As part of a continued effort to develop a feasible noninvasive biomarker for assessing the relationship between chronic Mn exposure and motor dysfunction, we applied the transportable IVNAA technology to a larger cross-sectional study. In this study, BnMn was significantly associated with a Mn cumulative exposure index reflecting cumulative occupational Mn exposure over the previous 16 years ($MnCEI_{16}$), but BMn was not associated with the cumulative exposure index (Rolle-McFarland et al., 2018). Here, we assess the relationship between BnMn or BMn with motor dysfunction in the same population with high, chronic occupational Mn exposure.

2. Methods

2.1. Study Design and Population

This cross-sectional study focused on occupational manganese exposure; study procedures have been explained in detail previously (Rolle-McFarland et al., 2019). Participants were adult male workers ≥18 years old. They were recruited from a manufacturing facility (N=30) and a ferroalloy smelting facility (N=31) in Zunyi, China. However, some participants changed jobs frequently, and participants from both facilities reported prior welding (manufacturing: 21/30; ferroalloy (13/31) or working with Mn ore (manufacturing: 6/30; ferroalloy: 21/30). Thus, we relied on Mn biomarkers instead of current employment for estimation of exposure, as biomarkers integrate exposure from multiple sources; and bone Mn can integrate these over time. Two participants were excluded due to missing data for BnMn (N=1) or motor function tests (N=1); thus, the final N=59. Other exclusion criteria included: 1) the self-reported presence of non-manganese related cognitive symptoms, active neurological or psychiatric disease, or movement impairments; and 2) participation in other studies involving the use of radiation within the past year. No participants were excluded from analyses based on these additional exclusion criteria.

Study procedures were explained by local study staff before participants signed informed consent documents. This study was approved by both the Purdue Biomedical Institutional Review Board and the Zunyi Medical University (ZMU) Ethical Review Board. Participants completed a short physical examination, BnMn measurement, a short battery of neurological performance tests, and had a sample of blood collected at the new ZMU campus. A questionnaire was used to collect self-reported demographic information. This questionnaire was administered to participants by study staff during the BnMn assessment. Data collected included age, years of education completed, alcohol consumption and smoking.

2.2. Determination of Blood and Bone Manganese

BnMn was determined using a transportable *in vivo* Neutron Activation Analysis (IVNAA) system developed by this group of investigators (Liu et al., 2017). A cleaning procedure was conducted prior to the BnMn measurement, including participants washing their right hand and arm with soap and water and then wiping the area with a 50% alcohol solution. Once dried, the IVNAA system was used to irradiate participants' right hand for 10 minutes to excite ^{55}Mn atoms in the hand bone to ^{56}Mn. After a 5-minute break, participants had their hands placed in a high purity germanium (HPGe) detection system which collected characteristic Mn γ ray signals (847 keV) over the span of an hour. The detection limit (DL) for a 30 minute measurement with the HPGe detection system was 0.64 μg Mn per g of bone (Liu et al., 2017).

The Mn γ ray counts were used to calculate BnMn concentrations based on a pre-existing calibration curve created from Mn-doped bone-equivalent hand phantoms. To account for variation in counting geometry, neutron flux, and hand-palm beam attenuation, a Mn/Ca γ ray ratio was calculated. Nineteen participants (31.7 %) had BnMn concentrations <DL and N=13 (21.7 %) of these measurements were negative. Similarly to measuring bone lead, negative BnMn values can occur due to the true concentrations being close to zero (Park et al., 2009). BnMn values <DL were retained for analyses, including negative values, to help decrease bias and increase analytical efficiency (Kim et al., 1995; Park et al., 2009).

Using standardized collection protocols, trained study staff collected whole blood samples in trace-metal free vacutainers (Becton-Dickinson, USA). Samples were stored at −20°C prior to being shipped on dry ice to the Chinese Centers for Disease Control and Prevention in Beijing, China, where they were analyzed for Mn using ICP-MS using the same protocols as reported by Zhang *et al.* (Zhang et al., 2015). All 60 blood samples collected and analyzed were above the DL for BMn (0.11 μg/L).

2.3. Motor Function Assessment

Trained research assistants facilitated completion of all motor assessments. These assessments were selected to evaluate participants' manual coordination, postural stability, postural tremor, and fine motor function. Participants completed both the computerized CATSYS 2000 system (Snekkersten, Denmark) as well as the Purdue Pegboard test (Lafayette Instruments, Lafayette, IN, USA). The CATSYS system has been standardized for motor function assessment (Allen et al., 2008; Després et al., 2000; Papapetropoulos et al., 2010) and has been used in prior studies of manganese exposure (Ellingsen et al., 2015).

Manual coordination was assessed using protonation/supination (P/S) and finger-tapping (F-tap) CATSYS tests. A recording drum with an internal microphone measured hand coordination and controlled movement. For P/S tests, participants were asked to hit the drum palm up and then palm down in tune with the provided metronome beep for 20 seconds. A slow-paced test and then a fast-paced beep test were completed for each hand. The F-Tap tests followed the same pattern as the P/S tests except participants used their index finger instead of their entire palm. The outcomes reported in this study were slow P/S (dominant and non-dominant hand), fast P/S (dominant and non-dominant hand), slow F-Tap (dominant and non-dominant hand), and fast P/S (dominant and non-dominant hand). Precision values for these manual coordination tests were reported as negative values. Decreases in values indicate decreases in P/S and F-tap precision (worse performance).

The CATSYS postural stability test uses a force plate visually similar to a scale (sway tests). While participants stood on the scale with their shoes off, four (4) one-minute long balance tests were completed: Sway (1) eyes open on plate; Sway (2) eyes closed on plate; Sway (3) eyes open on plate with ~ 1cm polystyrene foam placed on top of plate; and Sway (4) eyes closed with ~ 1cm polystyrene foam placed on top of plate. Mean sway from each condition were reported in this study. Increases in sway values suggest increased postural swaying (worse performance).

Postural tremor was also assessed using CATSYS. Participants held a tremor-sensitive stylus as still as possible about a hand-length in front of their waist. This was completed while sitting in a chair. Six tremor values were reported in this study: tremor intensity (m/s^2) (dominant and non-dominant hand), central frequency, central frequency dispersion (Hz) (dominant and non-dominant hand), and harmonic index (dominant and non-dominant hand). Increases in tremor intensity demonstrate a more intense tremor (worse performance); a typical resting parkinsonian tremor is between 4 and 6 Hz (Crawford and Zimmerman, 2011). Increases in central frequency dispersion values indicates an abnormal tremor with an increasing frequency band (worse performance). Decreases in harmonic index values are associated with frequent, irregular oscillations in a tremor (worse performance) (Després et al., 2000; Papapetropoulos et al., 2010).

Participants' fine motor function, specifically manual dexterity and bimanual coordination was assessed using the Purdue Pegboard. This validated test (Amirjani et al., 2011; Buddenberg and Davis, 2000; Lee et al., 2013) has also been used in several prior studies of manganese exposure (Cowan et al., 2009; Long et al., 2014; Stewart et al., 2002). The Purdue Pegboard battery consists of 4 tests that focus on the dexterity and coordination of 1) the right hand; 2) the left hand; 3) both hands; and 4) an assembly task. For the first test, participants must place as many pegs down the right side of the board as they can in 30 seconds using just their right hand. This is repeated for the second test using just their left hand down the left side of the board. For the third test, participants use both hands to place as many pegs down both sides as they can in 30 seconds. For the fourth test, participants are required to construct as many assemblies as they can in 1 minute. An assembly is made from multiple components: pins, washers, and collars. The assembly test was repeated twice, and the average score was used in analyses. Decreases in any of these scores demonstrates decreased fine motor function (worse performance).

2.4. Statistical Analyses

All statistical analyses were done using Stata 16.1 (College Station, Texas). A *p*-value ≤ 0.05 was considered statistically significant. The distributions of BMn and BnMn are both lognormal and some values of BnMn were negative. A constant of 5.99 μg/g was added to all BnMn measurements to allow using natural log transformations in statistical analyses; while this does affect the concentration amount it does not affect the correlation or association of BnMn with other variables (Rolle-McFarland et al., 2019). To account for the skewed distribution, geometric means are used in descriptive statistics, and natural-log transformations of Mn biomarkers are used in regression analyses. Descriptive statistics of Mn biomarkers, motor tests, and additional covariates were reported for the entire study population. Both dominant and non-dominant hand results were reported for the CATSYS (P/S, F-Tap, tremor) and the Purdue Pegboard systems. One participant did not complete the CATSYS test so N=59 for those results.

Both unadjusted and adjusted linear regression models were used to determine the relationship Mn biomarkers with motor test results. Regression models were adjusted for age (continuous), years of completed education (continuous), current factory of employment (ferroalloy/manufacturing), and current alcohol consumption (yes/no). These covariates were chosen a priori due to their influence on cumulative Mn exposure and demonstrated associations with the exposure or outcome in preliminary analysis. Data on employment history, body mass index, and smoking history were evaluated for inclusion, but ultimately not incorporated into regression models. Model coefficients (β) and 95% confidence intervals (CIs) were reported.

3. Results

3.1 Demographics

Geometric mean BMn in this population was 14.0 μg/L (95% confidence interval (CI):13.1, 15.1) and geometric mean BnMn was 9.2 μg/g (95% CI: 7.4, 11.3). There was no significant correlation of BMn with BnMn (Spearman's $\rho = 0.19$, *p*-value = 0.16).

Geometric mean Mn concentrations stratified by demographic characteristics are presented in Table 1. Participants were, on average, 47.3 years [95% CI: 45.3, 49.4] and completed an average of 10.0 years of education (95% CI: 9.0, 11.0). On average, those reporting current alcohol consumption had higher BnMn concentration; however, this relationship was not significant (*p*-value = 0.21).

Participants were employed at the ferroalloy facility on average for 8.4 years and had significantly higher levels of BMn (*p*-value = 0.01) compared to those that worked at the manufacturing facility (employed on average 9.5 years). Average BnMn was higher among ferroalloy workers than manufacturing workers, however, the difference did not reach the statistical significance (*p*-value = 0.12). Several manufacturing workers did report previous employment at the ferroalloy facility.

3.2 Manual Coordination (protonation/supination; finger tapping)

Mean scores for motor tests are listed in Table 2. There was no substantial difference in CATSYS protonation/supination or finger-tapping scores among those in the highest tertile of BMn or BnMn versus not. Regression model results for Mn biomarkers with motor tests were reported in Table 3. Neither BMn nor BnMn were significantly associated with any changes in manual coordination scores in unadjusted models. However, in adjusted regression models higher BnMn was associated with lower fast finger tapping precision scores for the non-dominant hand ($\beta = -0.02$ s, 95% CI = −0.04, −0.004).

3.3 Postural Stability (sway)

None of the mean sway scores were significantly different among those in the highest tertile of BMn or BnMn versus not (Table 2). In adjusted regression models (Table 3), higher BnMn was significantly associated with lower sway in the test with closed eyes and using foam ($\beta = -0.68$ mm, 95% CI = −1.31, −0.04).

3.4 Postural Tremor

On average, standard deviation of tremor in both the dominant and non-dominant hand was lower among those in the highest tertile of BnMn (Table 2); the unadjusted regression analysis of BnMn with the standard deviation of tremor in the non-dominant hand approached statistical significance (p-value = 0.10) (Table 3). Higher BMn was significantly associated with lower tremor intensity in both the dominant and non-dominant hand as well as center frequency in the non-dominant hand (Table 3). In contrast, higher BnMn was significantly associated with higher center frequency in the dominant hand (Table 3), consistent with the presence of an abnormal tremor.

3.5 Fine Motor Function (Purdue Pegboard)

Purdue Pegboard scores were not substantially different among those in the highest tertile of BMn or BnMn versus not (Table 2). In adjusted regression models (Table 3), higher BMn was associated with higher scores on the Purdue Pegboard assembly task ($\beta = 4.58$, 95% CI = 1.08, 8.07), consistent with improved performance among those with higher BMn.

4. Discussion

This study assessed whether BMn or BnMn were associated with decreasing motor function in a group of Chinese workers. In adjusted models, there were significant associations of BMn with postural tremor (both hands) and fine motor dexterity (Purdue Pegboard), suggesting an association of higher BMn with better performance on these motor assessments. These were unexpected findings. Another unexpected finding was significant associations in adjusted models of BnMn with better performance in postural stability (sway). However, we did observe BnMn was associated with worse performance in postural tremor (dominant hand tremor) and motor coordination (finger-tapping), as hypothesized. Interestingly, while higher BMn was significantly associated with better performance in the fine motor dexterity task, higher BnMn was associated with worse performance in the fine motor dexterity task, although this did not reach statistical significance.

BMn concentrations in this population (geometric mean=14.0 μg/L) is within the range of BMn concentrations reported in prior studies of populations with occupational Mn exposure from a variety of industries (Baker et al., 2014). Average BnMn concentrations in this study are higher than prior studies among welders and controls in the United States (Wells et al., 2018) or Canada (Pejović-Milić et al., 2009) as well as environmentally exposed older adults from Italy (Conley et al., 2021). The higher BnMn in this population is likely in part due to our inclusion of ferroalloy factory workers; differences with Conley et al may also reflect differences in BnMn assessment methods.

Several other studies have reported that Mn exposure, in particular chronic Mn exposure, is associated with lower performance on motor coordination assessments. Blond and Netterstrom report a decrease in manual coordination over an 8 year period among 60 steel workers; specifically, seniority was associated with a decrease in precision of the protonation/supination test (Blond and Netterstrom, 2007). Ellingsen et al. reported an association of air Mn concentrations with lower scores on finger-tapping assessments among Russian workers (Ellingsen et al., 2008). A longitudinal assessment of this cohort also found this association, but only among welders with elevated carbohydrate-deficient transferrin (CDT), a measure of chronic alcohol exposure (Ellingsen et al., 2015). Two studies using models to estimate chronic manganese exposure also reported a significant association of higher manganese exposure with lower scores in finger-tapping assessments among retired German workers (Pesch et al., 2017) and adults from Ohio, USA (Bowler et al., 2016). In contrast, long-term manganese exposure, determined by a cumulative exposure index, was not associated with performance on finger-tapping assessments in a study of former ship welders (Wastensson et al., 2012). The finding in this study that BnMn (also a measure of chronic exposure) is associated with worse finger-tapping performance is consistent with these prior reports.

In our study, we observed a significant association between increased BnMn and increased postural stability, specifically decreased sway measured when using foam with closed eyes. This is in contrast to two cross-sectional studies of environmental (Kim et al., 2011) and occupational manganese exposure (Bowler et al., 2007), both of which report associations of manganese with increased sway. However, our results are somewhat consistent with the report by Ellingsen et al. where a longitudinal study finds a lower, but not significant, mean sway among welders compared to controls (Ellingsen et al., 2015).

In this study, we found significant associations of BMn with lower tremor intensity and center frequency; however, we found significant associations of BnMn with higher center frequency. The literature related to measurements related to postural hand tremor is also mixed. Associations have been reported between air manganese and increased tremor among welders (Bowler et al., 2007), chronic air manganese exposure with increased harmonic index among US adults (Bowler et al., 2016), and increased frequency dispersion among Russian manganese alloy plant workers (Bast-Pettersen et al., 2004). While no significant difference in CATSYS tremor scores based on occupation was reported in Ellingsen’s longitudinal study of Russian welders, they did report that welders had worse performance in a Static Steadiness test which also evaluates hand tremor (Ellingsen et al., 2015). In contrast, active and retired German welders (Lotz et al., 2021) as well as former ship welders (Wastensson et al., 2012) were reported to perform better in assessments requiring hand steadiness compared to the reference groups.

Our results for fine motor coordination were also mixed: we found improved Purdue Pegboard scores among those with higher BMn and worse scores (but not significant) among those with higher BnMn. Prior studies from members of our team found that poorer performance on the Purdue Pegboard was significantly associated with a different measure of BMn not utilized in this study; a blood manganese-iron ratio (Cowan et al., 2009). Our group has also previously seen poorer performance on the Purdue Pegboard significantly associated with BnMn (Wells et al., 2018). Other work has used a similar assessment, the Grooved Pegboard test. Ellingson et al's study of Russian welders (Ellingsen et al., 2015) as well as a recent study by Racette et al among adults in South Africa (Racette et al., 2021), both reported that manganese exposure was associated with lower performance in the grooved pegboard assessment. Thus, our results in this study for BnMn (chronic exposure) are similar to what has been reported previously (which mostly use estimates of chronic exposure), while our results for BMn (recent exposure) is not.

It is notable that despite the substantial evidence that manganese is a neurotoxin that affects motor function (Aschner, 2000; Martin et al., 2020; Meyer-Baron et al., 2009; O'Neal and Zheng, 2015), several occupational studies, including this report, present at least some data suggesting that workers with higher manganese exposure have somewhat better performance on some motor function tasks compared to controls (Dlamini et al., 2020; Lotz et al., 2021; Pesch et al., 2017). There are a few possibilities for these results. It is possible that the healthy worker effect, where participants who remain in positions with high manganese exposure may be, on average, healthier than others (Dlamini et al., 2020; Lotz et al., 2021). Another possibility is that workers with high manganese exposure are more likely to engage in motor-related tasks through their job responsibilities, and thus have more practice with this type of assessment (Lotz et al., 2021; Wastensson et al., 2012). It is also possible that differences between the different study populations such as genetics, other factors such as iron (Cowan et al., 2009; Pesch et al., 2017), or exposure characteristics (concentration and assessment of chronic versus recent exposure) might explain these divergent results. More investigation would be needed to definitively address this question.

A limitation of our study was the possibly reduced statistical power due to the relatively small sample size. On the other hand, this population had relatively high levels of Mn exposure; thus, a smaller sample size is sufficient to identify significant associations. This study population was limited to Chinese men with higher occupational Mn exposures that are typically reported within the United States; thus, another potential limitation is that our study population somewhat limits the generalizability of our results. As this is a cross-sectional study, there are limits to our ability to establish temporality. However, this is somewhat allayed by the fact that BnMn reflects exposure over multiple years (O'Neal et al., 2014; Rolle-McFarland et al., 2018), although does not appear to represent lifelong cumulative exposure (Conley et al., 2021; Rolle-McFarland et al., 2018). Thus, although the data were collected at one point in time, we are confident that our BnMn measurements represent long-term exposure.

Strengths of this study include the utilization of well-established motor tests that have been successfully used before in non-English speaking populations (Cowan et al., 2009; Iwata et al., 2007). The design was also strengthened by utilizing bilingual English and Mandarin research assistants. The use of the IVNAA system to measure BnMn was also a strength of this study. This is a novel technology only available to a few research groups; this allowed us to obtain quantitative estimate of BnMn, which reflects cumulative exposure. In contrast, alternative methods to assess long-term Mn exposure typically rely at least in part on qualitative and/or self-reported data.

In summary, we describe the relationship between BMn and BnMn with selected measures of motor function from a cross-sectional study of 60 male Chinese workers. The results presented in this study suggest increased concentrations of BnMn are associated with decreases in select motor outcomes. This study not only verifies the practical utility of the newly developed transportable IVNAA system, but more importantly provides critical information on whether BnMn is associated with subtle motor dysfunction as a result of chronic Mn exposure among smelters. When considered along with prior research, our results highlight the importance of incorporating a useful measure of chronic Mn exposure when assessing chronic outcome measures. It is recommended that future work in this area continue to explore the utility of BnMn as a biomarker and should include longitudinal studies of more diverse populations.

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Highlights

- Blood Mn, bone Mn, and motor function were assessed in 59 Chinese workers
- Higher blood Mn was associated with better postural tremor, fine motor function
- Higher bone Mn was associated with better postural sway
- Higher bone Mn was associated with worse manual coordination, postural tremor

Table 1:

Geometric mean (95% confidence interval) for blood and bone manganese by demographic characteristics

Characteristic	N	BMn (μg/L)	BnMn (μg/g)
Entire population	59	14.0 (13.0, 15.1)	9.2 (7.4, 11.3)
Age (years)			
≤ 44	21	13.3 (11.6, 15.1)	8.0 (6.2, 10.5)
44 to 52	24	14.7 (13.7, 15.8)	9.9 (6.8, 14.5)
≥ 53	14	14.0 (11.1, 17.6)	9.8 (5.7, 16.9)
Education (years)			
≥ 9	29	14.7 (13.1, 16.6)	9.5 (6.9, 13.1)
10 to 12	13	13.2 (11.4, 15.3)	8.6 (7.2, 10.3)
≤ 13	17	13.4 (11.8, 15.3)	9.1 (5.4, 15.3)
Current alcohol consumption			
No	16	14.2 (12.3, 16.4)	7.4 (4.6, 11.8)
Yes	43	13.9 (12.8, 15.2)	9.9 (7.9, 12.6)
Current employer			
Manufacturing	30	12.8 (11.7, 14.1) [a]	7.8 (6.0, 10.1)
Ferroalloy	29	15.3 (13.8, 17.1) [a]	10.8 (7.7, 15.2)

BMn = whole blood manganese; BnMn=bone manganese.

[a.] p<0.05, likelihood ratio test.

Table 2:

Mean (95% confidence interval) of motor function tests

Motor test		Entire population (N=59)	Highest tertile of BMn (N=19) [a]	Highest tertile of BnMn (N=19) [b]
CATSYS: Protonation/supination	Slow (s), dominant hand	−0.10 (−0.12, −0.07)	−0.10 (−0.13, −0.07)	−0.10 (−0.14, −0.06)
	Slow (s), non-dominant hand	−0.10 (−0.12,−0.08)	−0.11 (−0.14, −0.09)	−0.12 (−0.15, −0.08)
	Fast (s), dominant hand	−0.05 (−0.07, −0.04)	−0.06 (−0.09, −0.03)	−0.05 (−0.08, −0.03)
	Fast (s), non-dominant hand	−0.06 (−0.07, −0.04)	−0.06 (−0.09, −0.03)	−0.07 (−0.10, −0.04)
CATSYS: Finger-tapping	Slow (s), dominant hand	−0.08 (−0.10, −0.06)	−0.11 (−0.14, −0.08)	−0.10 (−0.14, −0.07)
	Slow (s), non-dominant hand	−0.07 (−0.10, −0.05)	−0.11 (−0.14, −0.09)	−0.10 (−0.14, −0.05)
	Fast (s), dominant hand	−0.09 (−0.11, −0.08)	−0.11 (−0.13, −0.08)	−0.09 (−0.12, −0.06)
	Fast (s), non-dominant hand	−0.08 (−0.10, −0.07)	−0.09 (−0.12, −0.06)	−0.09 (−0.12, −0.07)
CATSYS: Sway	Mean sway (mm), eyes open	4.53 (4.18, 4.88)	4.31 (3.83, 4.78)	4.55 (3.77, 5.34)
	Mean sway(mm), eyes closed	4.83 (4.42, 5.23)	5.04 (4.26, 5.81)	4.87 (4.00, 5.75)
	Mean sway(mm), eyes open and foam	5.29 (4.83, 5.75)	5.40 (4.29, 6.51)	5.61 (4.53, 6.69)
	Mean sway (mm), eyes closed and foam	6.32 (5.83, 6.82)	6.19 (5.18, 7.21)	6.21 (5.21, 7.20)
CATSYS: Tremor	Intensity (m/s^2), dominant hand	0.10 (0.09, 0.11)	0.09 (0.08, 0.10)	0.10 (0.09, 0.12)
	Intensity (m/s^2), non-dominant hand	0.10 (0.09, 0.11)	0.09 (0.08, 0.11)	0.10 (0.09, 0.12)
	Center frequency (Hz), dominant hand	7.59 (7.27, 7.91)	7.27 (6.77, 7.78)	7.75 (7.29, 8.21)
	Center frequency (Hz), non-dominant hand	8.05 (7.68, 8.42)	7.61 (7.05, 8.17)	7.63 (7.07, 8.18)
	Standard deviation (Hz), dominant hand	3.03 (2.83, 3.23)	2.95 (2.60, 3.30)	2.71 (2.36, 3.07)
	Standard deviation (Hz), non-dominant hand	3.39 (3.20, 3.57)	3.26 (2.87, 3.66)	3.06 (2.66, 3.46)
	Harmonic index (HI), dominant hand	0.91 (0.90, 0.92)	0.92 (0.90, 0.94)	0.92 (0.90, 0.94)
	Harmonic index (HI), non-dominant hand	0.89 (0.88, 0.90)	0.89 (0.86, 0.91)	0.90 (0.88, 0.92)
Purdue Pegboard	Dominant hand (N)	12.56 (12.08, 13.04)	13.16 (12.40, 13.92)	12.37 (11.55, 13.19)
	Non-dominant hand (N)	11.97 (11.56, 12.38)	12.26 (11.42, 13.11)	11.74 (11.09, 12.40)
	Both hands (N)	9.71 (9.32, 10.11)	9.74 (8.99, 10.49)	9.63 (9.05, 10.22)
	Assembly (N)	21.50 (20.48, 22.52)	22.05 (20.017, 24.09)	21.42 (19.36, 23.48)

BMn = whole blood manganese; BnMn = bone manganese

[a] Highest tertile of BMn = 15.5 to 39.7 μg/L

[b] Highest tertile of BnMn= 11.46 to 49.01 μg/g

Table 3:

β (95% confidence interval) for the association of motor function score with manganese, N=59

Motor test		BMn, μg/L		BnMn, μg/g	
		Unadjusted	Adjusted [a]	Unadjusted	Adjusted [a]
CATSYS: Protonation / supination	Slow (s), dominant hand	−0.02 (−0.11, 0.06)	−0.05 (−0.15, 0.04)	−0.01 (−0.04, 0.02)	−0.01 (−0.04, 0.02)
	Slow (s), non-dominant hand	−0.02 (−0.09, 0.05)	−0.06 (−0.14, 0.01)	−0.02 (−0.04, 0.008)	−0.02 (−0.05, 0.01)
	Fast (s), dominant hand	−0.01 (−0.06, 0.04)	−0.03 (−0.08, 0.02)	−0.001 (−0.02, 0.02)	−0.01 (−0.02, 0.01)
	Fast (s), non-dominant hand	−0.01 (−0.06, 0.04)	−0.03 (−0.08, 0.02)	−0.001 (−0.02, 0.02)	−0.01 (−0.02, 0.01)
CATSYS: Finger-tapping	Slow (s), dominant hand	−0.07 (−0.15, 0.02)	−0.07 (−0.17, 0.02)	−0.01 (−0.04, 0.01)	−0.01 (−0.04, 0.02)
	Slow (s), non-dominant hand	−0.06 (−0.14, 0.02)	*−0.09 (−0.17, 0.003)*	−0.01 (−0.04, 0.01)	−0.01 (−0.04, 0.02)
	Fast (s), dominant hand	−0.02 (−0.07, 0.03)	−0.03 (−0.09, 0.02)	−0.004 (−0.02, 0.01)	−0.01 (−0.03, 0.01)
	Fast (s), non-dominant hand	0.0002 (−0.05, 0.05)	−0.002 (−0.06, 0.06)	*−0.02 (−0.04, 0.001)*	**−0.02 (−0.04, −0.004)**
CATSYS: Sway	Mean sway (mm), eyes open	−0.34 (−1.61, 0.94)	0.30 (−1.03, 1.63)	−0.26 (−0.70, 0.18)	−0.17 (−0.61, 0.28)
	Mean sway(mm), eyes closed	0.92 (−0.53, 2.37)	1.06 (−0.54, 2.67)	−0.37 (−0.87, 0.13)	*−0.45 (−0.98, 0.08)*
	Mean sway(mm), eyes open and foam	0.02 (−1.66, 1.69)	0.19 (−1.68, 2.05)	−0.34 (−0.92, 0.23)	−0.27 (−0.89, 0.35)
	Mean sway (mm), eyes closed and foam	−0.84 (−2.64, 0.95)	−0.43 (−2.41, 1.55)	−0.50 (−1.12, 0.11)	**−0.68 (−1.31, −0.04)**
CATSYS: Tremor	Intensity (m/s^2), dominant hand	**−0.04 (−0.06, −0.01)**	**−0.04 (−0.07, −0.01)**	0.01 (−0.004, 0.02)	0.003 (−0.01, 0.01)
	Intensity (m/s^2), non-dominant hand	**−0.04 (−0.07, −0.01)**	**−0.05 (−0.08, −0.01)**	0.004 (−0.01, 0.02)	0.003 (−0.01, 0.01)
	Center frequency (Hz), dominant hand	−0.80 (−1.96, 0.36)	−0.51 (−1.75, 0.73)	**0.40 (0.005, 0.79)**	**0.40 (0.002, 0.80)**
	Center frequency (Hz), non-dominant hand	**−1.49 (−2.77, −0.22)**	**−1.61 (−3.03, −0.19)**	−0.23 (−0.69, 0.23)	−0.18 (−0.67, 0.32)
	Standard deviation (Hz), dominant hand	0.02 (−0.71, 0.75)	0.40 (−0.37, 1.18)	−0.15 (−0.40, 0.11)	−0.13 (−0.39, 0.13)
	Standard deviation (Hz), non-dominant hand	−0.14 (−0.81, 0.53)	−0.06 (−0.78, 0.67)	*−0.19 (−0.42, 0.04)*	−0.19 (−0.43, 0.04)
	Harmonic index (HI), dominant hand	0.02 (−0.02, 0.06)	0.01 (−0.04, 0.05)	0.01 (−0.01, 0.02)	0.01 (−0.01, 0.02)
	Harmonic index (HI), non-dominant hand	−0.01 (−0.05, 0.03)	−0.02 (−0.06, 0.03)	0.01 (−0.004, 0.02)	0.01 (−0.01, 0.02)
Purdue Pegboard	Dominant hand (N)	0.48 (−1.26, 2.23)	*1.67 (−0.07, 3.40)*	−0.08 (−0.69, 0.52)	0.16 (−0.44, 0.76)
	Non-dominant hand (N)	0.56 (−0.93, 2.05)	*1.38 (−0.13, 2.89)*	−0.33 (−0.84, 0.18)	−0.14 (−0.65, 0.38)
	Both hands (N)	−0.39 (−1.83, 1.05)	0.15 (−1.36, 1.66)	−0.03 (−0.53, 0.47)	0.15 (−0.35, 0.65)
	Assembly (N)	1.38 (−2.31, 5.07)	**4.58 (1.08, 8.07)**	−0.60 (−1.88, 0.68)	−0.17 (−1.41, 1.07)

BMn = whole blood manganese; BnMn = bone manganese. Bolded results are statistically significant (p value <= 0.05).

[a] Adjusted for age, education, employer and current alcohol consumption.