



Environmental exposure to manganese in air: Associations with tremor and motor function



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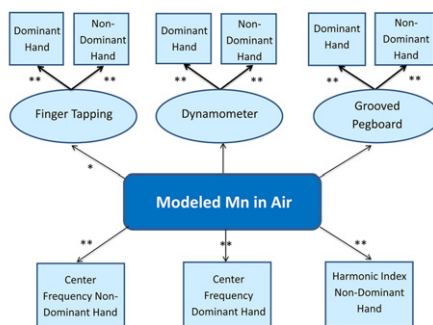
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HIGHLIGHTS

- Adult residents of two towns environmentally exposed to manganese in air
- 10 year modeled air-Mn exposures range from 0.01 to 6.32 $\mu\text{g}/\text{m}^3$
- Air-Mn associated with CATSYS tremor intensity, center frequency, and harmonic index
- Center frequency showed strongest associations with air-Mn exposure.
- Increased air-Mn levels also associated with lower psychomotor speed.

GRAPHICAL ABSTRACT

Structural equation model of motor and tremor tests and modeled Mn in air estimated using Bayesian regression



Significant associations at: * $p < 0.05$; ** $p < 0.0001$;

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ABSTRACT

Background: Manganese (Mn) inhalation has been associated with neuropsychological and neurological sequelae in exposed workers. Few environmental epidemiologic studies have examined the potentially neurotoxic effects of Mn exposure in ambient air on motor function and hand tremor in adult community residents. Mn exposed residents were recruited in two Ohio towns: Marietta, a town near a ferro-manganese smelter, and East Liverpool, a town adjacent to a facility processing, crushing, screening, and packaging Mn products.

Methods: Chronic (≥ 10 years) exposure to ambient air Mn in adult residents and effects on neuropsychological and neurological outcomes were investigated. Participants from Marietta ($n = 100$) and East Liverpool ($n = 86$) were combined for analyses. AERMOD dispersion modeling of fixed-site outdoor air monitoring data estimated Mn inhalation over a ten year period. Adult Mn-exposed residents' psychomotor ability was assessed using Finger Tapping, Hand Dynamometer, Grooved Pegboard, and the Computerized Adaptive Testing System (CATSYS) Tremor system. Bayesian structural equation modeling was used to assess associations between air-Mn and motor function and tremor.

Results: Air-Mn exposure was significantly correlated in bivariate analyses with the tremor test (CATSYS) for intensity, center frequency and harmonic index. The Bayesian path analysis model showed associations of air-Mn

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with the CATSYS non-dominant center frequency and harmonic index; while the Bayesian structural equation model revealed associations between air-Mn and lower Finger Tapping scores. Household income was significantly associated with motor dysfunction but not with tremor.

Conclusion: Tremor and motor function were associated with higher exposure to airborne Mn.

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1. Introduction

Manganese (Mn) is a naturally occurring essential element for living organisms, including humans. Industrial processes using Mn can result in high occupational and environmental Mn exposures from dust particles (Bowler et al., 2007a,b; Mergler et al., 1999; Myers et al., 2003; Solís-Vivanco et al., 2009). Exposure to Mn in the environment may also result from excess Mn in water, soil, and foods (ATSDR, 2012).

Exposure to excessive amounts of Mn may lead to adverse health outcomes (ATSDR, 2012). Neurological and neuropsychological sequelae from Mn overexposure include problems with motor efficiency and speed, tremor, postural sway and rigidity (similar to Parkinson's disease), mood disturbances and cognitive impairment (Bowler et al., 1999; Mergler et al., 1999). Most health studies on Mn overexposure report on occupational exposures to Mn (Meyer-Baron et al., 2013). Few studies on adults have examined adverse effects of environmental exposures to Mn, which tend to be much lower compared to occupational exposures (Bowler et al., 2011; Haynes et al., 2010; Kim et al., 2011; Mergler et al., 1999; Rodriguez-Agudelo et al., 2006; Solís-Vivanco et al., 2009; Baldwin et al., 1999; Menezes-Filho et al., 2011).

The published literature on environmental Mn studies examining motor and tremor function is sparse (Solís-Vivanco et al., 2009; Rodriguez-Agudelo et al., 2006; Baldwin et al., 1999; Kim et al., 2011; Bowler et al., 2012). Solís-Vivanco et al. (2009) investigated eight communities in a Mexican mining district and found an association between attention and air-Mn in 288 adults. In the same sample, Rodriguez-Agudelo et al. (2006) report elevated odds ratios for reduced coordination and declines in motor function with exposure to air-Mn concentrations ranging from 0.003 to 5.86 $\mu\text{g}/\text{m}^3$.

In Canada, low Mn concentrations in the range of 0.009–0.035 $\mu\text{g}/\text{m}^3$ (based on TSP air sampling near a ferro-alloy and silico-alloy plant) were associated with nervous system dysfunction (Baldwin et al., 1999). We reported previously on motor function and tremor in adults by comparing two communities: one with elevated air-Mn due to ferro-alloy smelting operations at a large metals refinery, and a demographically similar town lacking such industry (Kim et al., 2011; ATSDR, 2007, 2009). We found an increased risk in the exposed town for abnormal Unified Parkinson's Disease Rating Scale (UPDRS) motor findings for bradykinesia and the Computerized Adaptive Testing System (CATSYS) postural sway performance in comparison to the unexposed residents. We concluded that the UPDRS and CATSYS findings may indicate sub-clinical effects of Mn exposure. Using the same exposed study population, we used modeled air-Mn ($M = 0.18 \mu\text{g}/\text{m}^3$; $SD = 0.13$), blood Mn ($M = 9.65 \mu\text{g}/\text{L}$; $SD = 3.21$), distance from the smelter ($M = 4.75$ miles; $SD = 1.64$) and length of residence ($M = 36.1$ years; $SD = 15.8$), and found significant clinically-elevated generalized anxiety (Bowler et al., 2012). Higher scores on anxiety were related to poorer performances on UPDRS motor function and bradykinesia.

Building on the previous study conducted in Marietta, OH, this present report presents additional data collected in East Liverpool, OH, a town with previously documented elevated air concentrations of Mn (ATSDR, 2010). Air-Mn concentrations for 24-h samples had a range as high as 0.02 to 25.0 $\mu\text{g}/\text{m}^3$ and average of 1.50 (AM) and 0.56 $\mu\text{g}/\text{m}^3$ (GM). Both East Liverpool and Marietta were identified in U.S. EPA's School Air Toxics (SAT) initiative as having increased potential for non-cancer health effects from exposure to Mn (U.S. EPA, 2010a, b).

Given the need for further clarification of the effects of environmental Mn exposure, this study evaluated chronic (≥ 10 years) air-Mn

exposure and associations between tremor and motor function. Motor and neurological functions were assessed with established and sensitive clinical tests. The two objectives of this study were to examine the relationship between: 1) motor function as measured by psychomotor speed, strength and tactile manipulative function and Mn-air exposure and 2) measurable tremor and Mn-air exposure.

2. Methods

2.1. Study design and participants

A cross-sectional design was used. Data were collected from residents in two towns, East Liverpool and Marietta, OH. Participant selection for the Marietta sample was described elsewhere (Bowler et al., 2012; Kim et al., 2011).

The same methods of selection/recruitment, inclusion and exclusion criteria were followed for East Liverpool residents and they were administered the same neurological and neuropsychological evaluations using identical procedures.

The Marietta study took place in 2009 and residents were randomly selected based on residential parcel records in a defined exposure zone (within 12 air miles from the smelter Mn source). In 2011, East Liverpool residents, similarly to Marietta, were sent invitation letters whose addresses were located within two air miles downwind of the Mn source (vendor address lists were cross-checked with East Liverpool parcel maps and the Columbiana County 9-1-1 Emergency Response mapping system database). The difference in using recruitment zones for Marietta (within 12 air miles) and East Liverpool (2 air miles) was supported by different particle size fractions of Mn in the two towns; East Liverpool had larger particle sizes, and Mn was dispersed over a shorter distance. Single family units, multifamily units, and trailer addresses were included and resulted in a total of 3041 IRB-approved recruitment letters mailed (1732 in Marietta and 1309 in East Liverpool). In both towns, up to two participants per household could take part in the study. Residents who returned post cards and/or were reached by telephone (269 in Marietta and 436 in East Liverpool) were screened for eligibility (122 were interested and eligible in Marietta and 123 in East Liverpool) and scheduled for testing appointments. Subsequently, the number of eligible residents tested in Marietta was 100 (in 76 households) and 86 in East Liverpool (72 households) (14 "no shows" in East Liverpool due to personal or work scheduling conflicts).

Study inclusion criteria comprised the following: a minimum of 10 years residency and ages between 30 and 75 years. Exclusions included major physical or psychiatric illness, a degenerative disorder, significant prior chemical exposure(s) requiring medical treatment, and/or having worked at either the Mn smelter in Marietta or the Mn plant in East Liverpool. Each participant's self-reported medical history was reviewed for meeting the inclusion/exclusion criteria in clinical interviews conducted by the P.I. (RMB) and was additionally reviewed by the collaborating physician (YK).

After all other study procedures were completed, questionnaires and test folders were reviewed for completeness and a gift card for \$50.00 from a local store was given to each participant.

IRB approval was obtained for both towns from San Francisco State University, the Ohio Department of Health (ODH), and for the U.S. EPA, the University of North Carolina at Chapel Hill.

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