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I, Adrienne Stolfi, hereby submit this original work as part of the requirements for the degree of Doctor of Philosophy in Epidemiology (Environmental Health).

It is entitled:

Modeling the Pathways of Manganese (Mn) Exposure from Air, Soil, and Household Dust to Biomarker Levels in 7-9 Year Old Children Residing Near a Mn Refinery

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Modeling the Pathways of Manganese (Mn) Exposure from Air, Soil, and Household Dust to Biomarker Levels in 7-9 Year Old Children Residing Near a Mn Refinery

A dissertation submitted to the
Graduate School
of the University of Cincinnati
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By
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Abstract

Introduction: Manganese (Mn) is an essential trace element necessary for normal growth and development, that in excess can be neurotoxic. Excess environmental Mn can occur due to industrial emissions, but exposure pathways from environmental sources to biomarker levels, and ultimately to neurological outcomes have not been determined.

Objectives: The objectives of this dissertation are to 1) determine ambient air Mn exposure levels in a population living near the longest operating ferromanganese refinery in North America, using atmospheric dispersion modeling, 2) evaluate associations between modeled ambient air, soil, and indoor dust Mn collected from residences in the exposure area, and 3) determine pathways from environmental measures of Mn to blood, hair, and toenail Mn levels in exposed children using structural equation modeling (SEM).

Methods: Data are from the Communities Actively Researching Exposure Study (CARES), a cross-sectional study conducted from 2008-2013 in the Marietta, Ohio area to investigate neurological effects of Mn exposure in 7-9 year old children. Emissions from the Mn refinery were modeled using the U.S. Environmental Protection Agency (EPA) regulatory air dispersion model AERMOD. Average annual ambient air Mn concentrations were determined for census blocks within 32 km of the refinery, and for CARES participants' homes and schools. Monthly modeled ambient air concentrations for 2009-2010 were compared to concentrations from a stationary air sampler in Marietta to evaluate accuracy of the model. Exposures by census blocks were determined to estimate population sizes exposed to air Mn levels exceeding 50 ng/m^3, the U.S. EPA guideline. SEM was performed to determine pathways of exposure from air, soil, and indoor dust Mn separately for blood, hair, and toenail Mn. Additional data included in the models were heating, ventilation and air conditioning in the home, average hours/week spent outside by the participant, parent education, and child gender.

Results: Median (IQR) ambient air Mn (ng/m^3) ranged from 6.3 (8.1) to 43.1 (38.2) across the years. For monthly air Mn in 2009-2010, the median (IQR) modeled air Mn was 18.4 (7.6) (ng/m^3), and measured air Mn was 20.3 (12.4). All measures of model accuracy were within acceptable limits. Population sizes exposed to >50 ng/m^3 of ambient air Mn ranged from 959 in 2010 to 56,210 in 2008. Given the significantly low emissions in 2010, this year was omitted from the final SEM. In the SEM models, pathways from ambient air Mn to indoor dust Mn, and from indoor dust Mn to hair and toenail Mn were statistically significant. Significant indirect pathways from ambient air and soil Mn to hair and toenail Mn through indoor dust Mn were also observed. No pathways of exposure to blood Mn were observed in the study.

Conclusions: AERMOD modeling can provide a means of estimating ambient air Mn levels in populations exposed to environmental Mn sources. Based on the modeling, residents in the Marietta area are at times exposed to levels that exceed U.S. EPA guidelines. Ambient air Mn, soil Mn, and indoor dust Mn are important exposure pathways leading to increased levels of hair and toenail Mn.

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I would also like to thank Mr. Jeffrey Burkle from CARES for creating and sending all of the data sets that I requested, and Mr. Timothy Hilbert for answering all of my questions about the CARES protocols and data, among other very helpful assistance. Ms. Joelle Strom, during a summer internship as an undergraduate, located the source websites for all of the input data sets required for AERMOD, and created manuals for running AERMOD preprocessors. I am grateful for her assistance. I would also like to thank all of my course professors and classmates, who helped make this journey so enjoyable.

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Chapter 1: Introduction

Introduction and Background

Manganese (Mn) is an essential trace element that occurs naturally in the environment in air, water, soil, crops and other vegetation. Although ubiquitous it can be toxic to humans at high levels, and many studies have found harmful associations between excess occupational or environmental Mn exposure and adverse health outcomes. High exposure to Mn in the workplace can cause manganism, a neurological condition similar to Parkinson's disease (Racette, 2014). Even chronic, low-level occupational exposure can cause detrimental neurologic effects (O'Neal and Zheng, 2015). In adults and children, environmental exposure to Mn through air, soil, dust, or water has been associated with tremor, impaired motor and cognitive functions, postural instability, and lower intelligence (Zoni and Lucchini, 2013; Rodriguez-Barranco et al., 2013; Rugless et al., 2014; Vollet et al., 2016; Haynes et al., 2018). Children may be more susceptible than adults to environmental Mn exposure through ingestion or inhalation due to higher intestinal absorption rates, lower excretion rates, a higher ratio of inhaled air volume per body weight, and higher inhalation rates per body mass unit (Zota et al., 2011; Lucchini et al., 2017).

A significant source of excess environmental Mn exposure in communities is the emissions from nearby ferromanganese alloy plants, mining activities, and other industrial activities. However, pathways of exposure from environmental Mn to biomarker levels and health outcomes are not known and require further study. Issues that impede understanding of the pathways and mechanisms of exposure include a need for feasible methods to measure ambient air Mn exposure from industrial sources for large groups of people, and an adequate statistical approach to characterizing the associations between environmental exposures and biomarker levels in humans. The overall goal of this dissertation research is to advance knowledge in the area of environmental Mn exposure research by addressing several areas needing further study. The objectives are to 1) determine whether air dispersion modeling of ambient air Mn exposure is a feasible and valid means of quantifying exposures in communities living near industrial sources, 2) determine the associations between ambient air Mn, soil Mn, and indoor dust Mn, and explore whether air Mn averaged over 1, 3, 6, or 12 months prior, or during the year of soil and dust sample collection is more strongly associated with soil and dust Mn, and 3) determine exposure pathways among the three environmental measures to three Mn biomarkers of exposure: blood, hair, and toenails in children aged 7-9 years living near a Mn refinery.

The data for the dissertation will come from three sources: the Marietta Communities Actively Researching Exposure Study (CARES), the U.S. Environmental Protection Agency (EPA), and the U.S. 2010 Census. CARES is an academic-community partnership between researchers at the University of Cincinnati and members of the Marietta, Ohio community. CARES was undertaken to study environmental and biomarker measures of Mn exposure and the effects on neurological outcomes in children (Haynes et al., 2012). The data collected from 2008-2013 on 323 7-9 year old children, including home and school geolocations, soil and indoor dust levels of Mn, blood, hair, and toenail levels of Mn, and sociodemographic variables will be used in the analysis. Eramet Marietta, Inc., the longest running Mn refinery in the U.S., is in Marietta, Ohio, and is responsible for the majority of Mn emissions in the area (ATSDR, 2009). Emissions data and operating parameters for 2008-2013 were obtained from the U.S. EPA and will be used to model ambient air Mn concentrations over the study period. Concentrations will be determined for U.S. Census blocks in order to estimate population exposures (Chapter 2), and for CARES study participants based on a weighted average of each child's home and school concentrations (Chapter 3).

Specific Aims:

Specific Aim 1 (Chapter 2): Determine ambient air Mn concentrations in the community of Marietta, Ohio and the surrounding area during 2008-2013, using the regulatory air dispersion model AERMOD, and quantify exposures to the population using 2010 census block data.

Specific Aim 2 (Chapter 2): Measure the accuracy of AERMOD results by comparing modeled ambient air Mn to ambient air Mn measured at a stationary monitoring site in Marietta, Ohio from January 2009 through October 2010.

Specific Aim 3 (Chapter 2): Determine whether modeled annual ambient air Mn concentrations averaged over each year are associated with soil and indoor dust Mn concentrations measured during the same years at Marietta and surrounding area sites.

Specific Aim 4 (Chapter 3): Perform structural equation modeling to determine pathways of exposure from ambient air Mn, through soil and dust, to biomarker measures of Mn in children aged 7-9 years living near a Mn refinery in Marietta, Ohio.

Review of Relevant Literature

A literature search was conducted in PubMed of articles that evaluated associations between environmental exposures to Mn, biomarkers of Mn exposure, and health outcomes. Studies were included in the review if they measured ambient air, soil, or indoor dust Mn levels, and at least one association with a biomarker of exposure or a health outcome. Additional inclusion criteria were that all measurements were made at the individual subject level, articles were in English, and were published from 2005-2019. An initial search using the term manganese combined with air, soil, or dust, and then combined with biomarker and health outcome terms, retrieved 496 articles (Figure 1). After exclusion of articles in foreign languages, reviews, non-human studies, studies of occupational exposures, and health risk assessments with no measures in humans, the full texts of 120 articles were retrieved and evaluated. Twenty-six of the 120 articles met all inclusion criteria for the review. The remainder either only measured associations between biomarkers and health outcomes, or conducted comparisons of both exposures and outcomes at the group level. Four additional articles were located through examination of the reference lists of included articles, for a total of 30 articles (Table 1).

The 30 included studies were conducted in 8 different countries (Australia, China, Italy, Mexico, Nigeria, Portugal, Spain, and the U.S.). Twenty-six of the studies were cross-sectional, three were longitudinal, and one was a retrospective cohort study. Sample sizes ranged from 27 to 9920; 15 of the studies were of children, 12 were of adults, and three studies included both children and adults. For 14 of the studies, associations were made between environmental measures and biomarkers, 12 studies assessed associations between environmental measures and health outcomes, and 4 studies determined associations between environmental measures and both biomarkers and health outcomes. The environmental measures included air Mn measured with personal monitors, stationary monitors, or modeled with AERMOD, soil, and both indoor dust and outdoor dust measured as concentrations, loadings, or loading rates. The most common biomarker of exposure was blood, followed by hair, then urine, fingernails or toenails, and saliva. A number of validated neurological tests were the primary health outcomes assessed, including measures of motor function, cognition, memory, and intelligence. Other health outcomes included asthma, medication use, and low birth weight.

Associations between Environmental Measures of Mn Exposure and Mn Biomarkers

Table 2 provides a summary of the correlations between air, soil, or dust Mn and biomarkers of Mn exposure in the reviewed studies. For blood Mn, five studies determined associations between air Mn and blood Mn, nine assessed associations with soil Mn, and ten assessed associations with indoor or outdoor dust Mn. Most of the studies found very small correlations between the environmental measures and blood Mn, with correlation coefficients ranging from -0.16 to 0.22. The highest correlation (0.22) was found by Solis-Vivanco et al. (2009) in a study of 288 adults living in a mining district in Mexico. Air Mn was measured with stationary monitors placed in the communities, and exposure levels were assigned to participants based on the closest monitor to their home. The positive correlation between air and blood Mn was statistically significant. Lucas et al. (2015) collected 24-hour personal PM_{10} air samples in the homes of residents living near ferromanganese alloy plants in Italy. In 376 children aged 11-14 years, air Mn was significantly negatively correlated with blood Mn (r=-0.16). The children resided in three separate areas; one with an active ferromanganese plant, one where ferromanganese plants were historically active, and a control site. The mean blood Mn levels among the three groups were not different. None of the studies reviewed found statistically significant positive correlations between soil, outdoor dust, or indoor dust Mn with blood Mn. The correlations with blood Mn ranged from -0.16 to 0.14. However, three of the studies (Rentschler et al., 2012; Wahlberg et al., 2018; Butler et al., 2019) were part of a large series of studies conducted at the same three sites in Italy as the Lucas et al. (2015) study mentioned above, and had overlapping subjects, exposure measures, and measurement methodologies. For all but one of the studies measuring blood Mn, the upper values of the range of study participant's blood levels were above the reference range of 4.0-15.0 µg/L (Table 1) (ATSDR, 2012).

Correlations between environmental measures and hair Mn were stronger than for blood, but still varied widely among the studies. Three studies of 7-9 year old children in Marietta, Ohio exposed to Mn from a Mn refinery (Haynes et al., 2010; Haynes et al., 2012; Fulk et al.; 2017) found no association between hair Mn and air Mn measured with personal monitors. Fulk et al., 2017 also determined associations with soil and indoor dust loadings. The correlation between hair Mn and soil Mn was 0.22 ($P>0.05$), and was 0.39 ($P<0.05$) for hair Mn and indoor dust Mn. Lucas et al. (2015) found that soil Mn was not associated with hair Mn, but both outdoor and indoor dust were associated with hair Mn. However, a study by Butler et al. (2019) using some of the same subjects in the same exposure areas in Italy found that outdoor dust Mn was not associated with hair Mn, and the correlation with indoor dust Mn was small (0.12) but statistically significant. Lucas et al. (2015) and Butler et al. (2019) also determined associations between fingernail and saliva Mn and environmental exposures. The correlations for fingernail Mn with air, soil, outdoor dust and indoor dust were similar between the studies, and ranged from 0.14-0.17 for air Mn, 0.20-0.22 for soil Mn, 0.27-0.36 for outdoor dust Mn, and 0.23-0.24 for indoor dust Mn (Table 2). Correlations were weaker for saliva Mn, except for the correlation with personal air sampling. Only one study found a significant association between urine Mn and soil Mn (Butler et al., 2019), and no studies found an association between urine Mn and air, outdoor dust, or indoor dust Mn.

Based on the studies reviewed, hair and nail Mn are the most consistently associated with environmental measures of Mn in both adults and children, and in general are more strongly associated with outdoor and indoor dust Mn than with air or soil Mn. In a review of biomarkers-based approaches to measuring the impact of Mn exposure on children's neurodevelopment, Coetzee et al. (2016) concluded that in school-aged children hair was the more consistent and valid biomarker of exposure. While the research to date on biomarkers is helpful, Lucchini et al. (2018) in a 2018 editorial concluded that "Research on Mn biomarkers needs to be enhanced, to understand what type of exposure and what exposure window can be better reflected by each candidate biomarkers, including hair, nails, saliva, blood and urine."

Associations between Environmental Measures of Mn Exposure and Health Outcomes

Sixteen of the reviewed studies measured associations between environmental Mn exposures and health outcomes at the individual level, and quantified the associations either with correlation coefficients, multiple regression coefficients, or crude or adjusted odds ratios. Seven of the studies were conducted by Dr. Rosemarie Bowler and colleagues and involved adults residing in Marietta, Mount Vernon, or East Liverpool, Ohio. Marietta is home to EMI, the Mn refinery, and East Liverpool residents are exposed to Mn from a storage and packaging facility. Mount Vernon residents, with no excess environmental Mn exposures, were used as a control group in two of the studies. In all seven studies, AERMOD modeling was used to estimate chronic 10-year ambient air Mn exposure. The first study by Kim et al. (2011) administered the Unified Parkinson's Disease Rating Scale (UPDRS) Activities of Daily Living (ADL), Motor and Bradykinesia scales to 100 Marietta adults aged 30-75 years and 90 adults of the same age range from Mount Vernon. There were no differences between the groups in ADL scores, but within the Marietta group increased modeled air Mn was associated with increased odds of abnormal Motor and Bradykinesia scores. Bowler et al. (2012) studied the same groups and found significantly higher generalized anxiety scores and Medical Symptoms Questionnaire scores in the Marietta group. Bowler et al. (2015), in a follow-up study of the 100 adults in

Marietta recruited 86 adults aged 30-75 years from East Liverpool and administered a neuropsychological battery of 21 tests to all 186 participants. Higher modeled air Mn was associated with lower scores on visuospatial memory, delayed living memory, and verbal reasoning. No other tests were significantly associated with modeled air Mn. Follow-up studies of the same participants assessed motor coordination and tremor (Bowler et al., 2016a), medication use for chronic illnesses (Bowler et al., 2016b), self-reported concentration and memory problems (Bowler et al. 2017), and performed cluster analysis of UPDRS Motor scores, coordination tests, tremor tests, and five tests of executive function measures (Kornblith et al., 2018). Increased modeled air Mn exposure was negatively associated with numerous motor function measures, and positively associated with increased medication use for hypothyroidism, pain, supplements, and total medication use. There was no association with self-reported memory problems (Table 1).

A second series of seven studies was conducted by Dr. Roberto Lucchini and colleagues in three areas of Italy with different levels of exposure to Mn from ferromanganese alloy plants (Lucchini et al., 2012a; Lucchini et al., 2012b; Rentschler et al., 2012; Lucchini et al., 2014; Rosa et al., 2016; Wahlberg et al., 2018; Broberg et al., 2019). One area had an active plant, one area had three historically active plants without current activity, and one area had no ferromanganese alloy plant exposures. Five of the seven studies measured exposures and neurological outcomes in children aged 11-14 years, with sample sizes ranging from approximately 300 children in a 2012 study to over 600 in a 2019 study. Two of the studies measured exposures and outcomes in elderly adults. The environmental measures were 24-hour personal air Mn and residential soil Mn. Neurological outcomes included the Wechsler Intelligence Scale (WISC), Luria Nebraska Motor Battery, Finger Tapping Test, Visual Simple

Reaction Time, Pursuit Aiming Test, Tremor 7.0 (tremor and body sway), Sniffin' Sticks Olfactory Screening Test, Conners-Wells' Adolescent Self-Report Scale-Long Form (CASS-L), and the Conners' Parent Rating Scale (CPRS-R) oppositional problems, cognitive problems/inattention, hyperactivity, and ADHD index. One study of the children assessed parent report of asthma symptoms and asthma medication use. Increases in both personal air Mn and soil Mn were associated with worse outcomes for many of the motor coordination and odor identification tests in the children and adults (Lucchini et al., 2012a; Rentschler et al., 2012). There were no associations with WISC scores (Lucchini et al., 2012b), but increased soil Mn was associated with cognition problems and inattention in the children. Significant U-shaped associations were found between soil Mn and both CASS-L scores and hyperactivity in girls (Broberg et al., 2019). For the parent report of increased asthma and asthma medication use, there were small but statistically significant increased odds with 1 IQR increases in air Mn (Rosa et al., 2016).

Two additional studies determined associations between air or soil Mn and health outcomes. Solis-Vivanco et al. (2009) found a significant association between air Mn and worse performance on the Digit Span test in 288 adults aged 20-87 years, but no other associations between air Mn and a battery of neurological tests (Table 1). Finally, McDermott et al. (2014) performed a retrospective study of 9920 pregnant women from 10 areas of South Carolina and found no association between soil Mn and low birth weight.

Significance and Relevance to Environmental Health

The overall objectives of this study are to quantify the exposure to ambient air Mn in Marietta, Ohio and surrounding communities using AERMOD modeling, and determine pathways of exposure from environmental sources (air, soil, and dust) to biomarkers of exposure.

Communities near industrial sources of pollution are at risk of adverse health outcomes, and methods are needed to monitor ambient air exposures that are feasible as well as accurate. Personal air monitoring is expensive and labor-intensive, and monitoring at stationary sites may not adequately capture exposures to individuals at relatively short distances from the monitor. Most commonly, distance from the industrial source is used as a surrogate measure of exposure. Air dispersion modeling may provide a useful means of monitoring ambient air Mn exposures from industrial sources. As part of this study, AERMOD modeling will be performed to determine ambient air Mn exposure over a six-year period in Marietta. For just under two of the years modeled, the modeled air Mn concentrations will be compared to Mn concentrations obtained by stationary sampling to determine accuracy of the modeling. This study will add to the small body of literature available on air dispersion modeling of ambient air Mn exposures from industrial sources.

In addition to the need for establishing methods to monitor environmental Mn exposures, further research is needed on the pathways of exposure from industrial emissions to biomarkers of exposure in humans. Mn from industrial emissions is deposited in soil and dust, providing additional sources of environmental Mn exposure. While a number of studies have determined associations between environmental sources of Mn and biomarkers (Tables 1 and 2), only two have assessed pathways of exposure (Gulson et al., 2014, Fulk et al., 2017). Gulson et al. studied pathways from soil, indoor dust, outdoor dust, and diet to blood Mn in children, but did not include a measure of ambient air Mn. Fulk et al. determined the pathway from modeled ambient air, soil, and indoor dust to hair Mn in children, but the sample size was small (n=88) and only hair was assessed. In the current study, a sample size of 323 is available for determining pathways of exposure that will include modeled ambient air, soil, and indoor dust, leading to blood, hair, and toenail levels in 7-9 year old children.

Institutional Review Board Approval

Human subjects data used in this study were collected under the University of Cincinnati Institutional Review Board Study ID Number 2011-2542, "Communities Actively Researching Exposure Study." Adrienne Stolfi was added to the protocol as an investigator on September 17, 2018.

Overview of Dissertation Approach

The dissertation consists of three chapters. Two of the chapters (Chapters 2 and 3) will be submitted to journals for publication as original research articles. Chapter 1 is an introduction to the dissertation and includes specific aims, significance and relevance to environmental health, and a review of relevant literature. Although direct associations between environmental Mn exposures and health outcomes are not addressed in this dissertation, articles measuring these associations are included in the literature review. These studies provide evidence linking ambient air, soil, and dust Mn levels with adverse health outcomes, supporting the need for studies examining initial pathways of exposure from environmental sources to biomarkers that may potentially reflect the body burden of excess Mn.

Chapter 2 covers AERMOD modeling of ambient air Mn exposures in Marietta, Ohio and surrounding communities from 2008-2013, using reported Mn emissions from EMI. Residential soil, indoor dust, and data from a stationary air sampler collected as part of the Marietta Communities Actively Researching Exposure Study (CARES) will be used in this study. Average annual ambient air Mn will be modeled for census blocks in the study area, and U.S.

2010 Census population data will be used to estimate the number of individuals exposed to different ambient air Mn levels. Ambient air Mn will also be modeled at the site of a stationary air sampler and all locations where soil and indoor dust samples were collected. Next, the modeled air Mn will be compared to ambient air Mn measured at the stationary site in Marietta from 2009-October 2010. Measures of model fit will be applied to determine accuracy of the modeled ambient air estimates. Associations between modeled ambient air Mn, soil Mn, and indoor dust Mn will then be determined with Pearson correlation coefficients. The modeled air Mn levels will be average for the year of soil and indoor dust sample collection, and then for the 1, 3, 6, and 12 months prior to sample collection to assess whether different averaged time periods for air Mn result in higher correlations with soil and indoor dust Mn.

Chapter 3 will cover structural equation modeling (SEM) of pathways from environmental sources of Mn (modeled ambient air, soil, and indoor dust) to blood, hair, and toenail levels of Mn. The data to be used are from the CARES study, in which 323 children aged 7-9 years were enrolled to determine neurological outcomes and associations with biomarkers of exposure. Three separate SEM models (one for each biomarker) will be evaluated. Factors that will be included in each model are child's gender, number of hours the child spent outside in an average week, parent education, and a heating-ventilation-air conditioning score. Modeled ambient air Mn exposure for each child will be based on a weighted average of 70% for the ambient air Mn concentration at the child's residence and 30% for the concentration measured at the child's school.

Table 1. Studies of Associations between Environmental Manganese and Biomarkers of Manganese or Health Outcomes

First author (year), country	Source of exposure	Study type and population	Covariates	Environmental Mn measures	Mn biomarkers	Health outcomes	Study results
Gulson (2006), Australia[c]	Introduction of methylcyclopentadienyl manganese tricarbonyl (MMT) to motor vehicle fuel	Longitudinal; 113 children aged 0.29-2.4 yrs living at varying proximity to roadways, measured at 3 6-month intervals	Time since first data collection, category of traffic proximity, gender, location within house for indoor dust samples	Indoor dust: median 16.2, range 0.2-196 μg/m^2/30 days, n=201; Handwipes: prior to playing outdoors: median 1.2, range 0.1-24.0 μg/handwipe, n=128 females; median 1.6, range 0.0-25.0, n=157 males; after playing outdoors: median 1.6, range 0.1-27.0, n=76 females; median 2.6, range 0.2-53.0, n=92 males	Blood: median 11.0, range 4.1-31.0 μg/L, n=117 females; median 11.0, range 1.8-45.0, n=137 males	na	No associations between indoor dust Mn and blood Mn; handwipe concentration of Mn prior to playing outdoors was significantly associated with blood Mn in a full mixed model analysis but not in a final reduced model
Solis-Vivanco (2009), Mexico	Mn mining, extraction, and processing	Cross-sectional; 288 adults aged 20-87 yrs	Age, gender, education, tobacco and alcohol consumption, blood lead	Air: median 0.10, range 0.00-5.86 μg/m^3 (81 measurements from 28 stationary monitors, assigned to subjects based on closest monitor to residence)	Blood: median 9.5, range 5.0-31.0 μg/L	Mini Mental State Examination Scale (MMSE), Digit Span Forward and Backward, Word Association Test, Clock Test, Word List Test, Semicomplex Design Test, Beck Depression Inventory (BDI), Geriatric Depression Inventory	Significant correlation between air Mn and blood Mn (r=0.220, P<0.05). Significant association between air Mn >median and worse performance on Digit Span Test (AOR 1.75, 95% CI 1.01, 3.06). No other associations between air Mn and cognitive outcomes. No associations between blood Mn and cognitive outcomes

First author (year), country	Source of exposure	Study type and population	Covariates	Environmental Mn measures	Mn biomarkers	Health outcomes	Study results
Haynes (2010), USA	Mn refinery	Cross-sectional; 141 subjects aged 2-81 yrs	Gender, hair color, distance from refinery, *HFE* and *Tf* genetic variants	Modeled average annual air: mean 0.13, range 0.01-18.13 µg/m^3	Blood: median 8.7, range 1.8-22.0 µg/L, n=135; Hair: median 3.57, range 0.64-41.00 µg/g, n=73	na	No correlation between ln blood (r=0.05, P>0.05) or ln hair Mn (r=0.17, P>0.05) with ln air Mn for all subjects combined. Significant associations between ln hair Mn and ln air Mn for genotype *HFE H63D* (r=0.30, P<0.05, n=56), genotype *HFE C282Y* (r=0.29, P<0.05, n=56), genotype *Tf P570S* (r=0.40, P<0.05, n=58)
Kim (2011), USA[b]	Mn refinery	Cross-sectional; 100 adults aged 30-75 yrs from Marietta, OH (exposed) and 90 adults aged 30-75 yrs from Mount Vernon, OH (control)	Age, gender, diabetes, education, health insurance status, psychiatric medication use	Modeled air: median 0.16, range 0.04-0.96 µg/m^3 (exposed); Cumulative exposure index (CEI, Mn-air x yrs in residence): median 5.53, range 0.89-41.22 µg/m^3 x yr	Blood: exposed: median 9.2, range 4.9-24.6 µg/L; control: median 8.8, range 3.8-18.9 µg/L	Unified Parkinson's Disease Rating Scale (UPDRS) Activities of Daily Living (ADL), Motor, and Bradykinesia scores, Postural Sway (mean sway, transversal sway, sagittal sway, sway area, sway intensity, and sway velocity in conditions of eyes open and no foam, and eyes open with foam under feet)	No difference in blood Mn between exposure groups; no association between exposure group and UPDRS ADL scores; significantly increased odds of abnormal UPDRS Motor and Bradykinesia in exposed group; significantly higher sway parameters in 8 of 12 sway measures in exposed group
Bowler (2012), USA[b]	Mn refinery	Cross-sectional; 100 adults aged 30-75 yrs from Marietta, OH (exposed) and 90 adults aged 30-75 yrs from Mount	Age, gender, ethnicity, education, diabetes, psychiatric medication use	Modeled air: median 0.16, range 0.04-0.96 µg/m^3 (exposed); Cumulative exposure index (CEI, Mn-air x yrs in residence):	Blood: exposed: median 9.2, range 4.9-24.6 µg/L; control: median 8.8, range 3.8-18.9 µg/L	Symptom Checklist-90-Revised (SCL-90-R), Environmental Worry Scale (EWS), Health-Related Quality of Life (HRQOL) Scale,	No difference in blood Mn between exposure groups; significantly higher generalized anxiety T scores in exposed group (P=0.035); significantly higher scores in

First author (year), country	Source of exposure	Study type and population	Covariates	Environmental Mn measures	Mn biomarkers	Health outcomes	Study results
		Vernon, OH (control)		median 5.53, range 0.89-41.22 μg/m^3 x yr		Medical Symptoms Questionnaire (MSQ), Unified Parkinson's Disease Rating Scale (UPDRS), Fingertapping, Grooved Pegboard, Grip Strength (Dynamometer), WAIS-III Similarities subtest, Rey 15-Item Test, Victoria Symptom Validity	exposed group for UPDRS Motor (P=0.034) and Bradykinesia (P=0.048) subscales; higher proportion of adults with all MSQ measures in exposed group (P values 0.001-0.04)
Callan (2012), Australia	Proximity to shipping port	Cross-sectional; 39 children aged 1-12 yrs living at varying distances from port	Age, gender, smoker at property, distance from port, consumption of home-grown produce	Soil: median 15.8, range 4.1-29.6 μg/g, n=37; Indoor dust: median 98, range 3.8-252 μg/g, n=35	Hair: median <LOD, range <LOD-0.21 μg/g, n=22; Urine: median <LOD, range <LOD-550 μg/L, n=37	na	No associations between any environmental measures and hair or urine Mn levels
Haynes (2012), USA[d]	Mn refinery	Cross-sectional; 38 children aged 7-9 yrs	Age, gender, daily dietary Mn intake	Stationary air: GM 11.0 ng/m^3; 48-hour personal air: GM 8.1 ng/m^3	Blood: mean (SD) 9.5 (2.4) μg/L, n=33; Hair: mean (SD) 0.47 (0.30) μg/g	na	No associations between ln personal air Mn and blood Mn or hair Mn; ln stationary Mn was significantly associated with ln personal air Mn (P=0.04)
Lucchini (2012a), Italy[a]	FeMn alloy plants	Cross-sectional; children aged 11-14 yrs from 1 of 2 areas: an area with 3 historically active FeMn plants (n=154), and an area with no	Age, gender, parent education, SES, family size, parity order, hemoglobin, alcohol and smoking habits, body mass index	24-hour personal air: median (IQR) 29.4 (31.8) ng/m^3, n=189; Soil: median (IQR) 579 (483) ppm, n=58	Blood: median (IQR) 10.9 (4.1) μg/L, n=299; Hair: median (IQR) 0.11 (0.13) μg/g, n=258;	Luria Nebraska Motor Battery, Finger Tapping Test, Visual Simple Reaction Time, Pursuit Aiming Test, Tremor 7.0 (tremor and body sway), Sniffin' Sticks	Soil Mn levels significantly negatively associated with Luria-Nebraska motor coordination test (P<0.001), Aiming Pursuit hand steadiness Test (P=0.012), and Sniffin' Sticks odor

First author (year), country	Source of exposure	Study type and population	Covariates	Environmental Mn measures	Mn biomarkers	Health outcomes	Study results
		history of plant activity (n=157)	(BMI), blood lead		Urine: median (IQR) 0.10 (0.00) µg/L, n=301	Olfactory Screening Test	identification task (P=0.003), with poorer scores associated with higher soil levels. Hair (P=0.011) and blood Mn (P=0.005) significantly associated with tremor in dominant hand
Lucchini (2012b), Italy[a]	FeMn alloy plants	Cross-sectional; children aged 11-14 yrs from 1 of 2 areas: an area with historically active FeMn plants (n=151), and area with no history of plant activity (n=148)	Age, gender, parent education, SES, family size, parity order, hemoglobin, alcohol and smoking habits, body mass index (BMI), blood lead	24-hour personal air: median (IQR) 29.4 (31.8) ng/m^3, n=189; Soil: median (IQR) 722 (483) ppm	Blood: median (IQR) 10.9 (4.1) µg/L; Hair: median (IQR) 0.10 (0.12) µg/g, n=186	Wechsler Intelligence Scale (WISC), Conners-Wells' Adolescent Self-Report Scale-Long Form (CASS-L)	No significant main effects of environmental Mn measures or biomarkers of Mn on WISC scores or scores on any of the 10 CASS-L subscores. No interaction effects between Mn measures and blood lead on any of the outcomes
Rentschler (2012), Italy[a]	FeMn alloy plants	Cross-sectional; adults aged 63-80 yrs (n=255) and children aged 11-14 yrs (n=311) from 1 of 2 areas: an area with historically active FeMn plants, and area with no history of plant activity	Age, gender, smoking and alcohol habits, genotype frequencies for *ATP13A2* and *SPCA1,*	Soil: adults: median 786, range 313-1724 ppm; children: median 529, range 160-1730 ppm	Blood: adults: median 9.0, range 3.6-22.0 µg/L; children: median 11.0, range 4.0-24.0 µg/L; Urine: adults: median 0.14, range 0.06-12.0 µg/L; children: median 0.08, range 0.05-5.4 µg/L	Luria Nebraska Motor Battery, Sniffin' Sticks Olfactory Screening Test, Tremor 7.0 Test (tremor and body sway)	Adults: soil Mn was associated with blood Mn ($r_{s=}$-0.136, P=0.036); no association with urine Mn; for children, no associations between soil Mn and blood or urine Mn. Statistically significant associations between soil Mn and motor coordination for adults ($r_{s=}$ -0.130, P<0.05) and children ($r_{s=}$-0.200, P<0.001), and between soil Mn and odor identification in children ($r_{s=}$-0.170,

First author (year), country	Source of exposure	Study type and population	Covariates	Environmental Mn measures	Mn biomarkers	Health outcomes	Study results
							$P<0.05$); genotypes of 2 *ATP13A2* polymorphisms modified association between soil Mn and motor coordination in adults
Callan (2013), Australia	No specific source	Cross-sectional; 173 non-smoking pregnant women aged >18 yrs	First pregnancy, home location, use of iron or folic acid supplements, dietary habits, hobbies, home >50 yrs old	Soil: GM 21.8, range <0.2-443 µg/g, n=158; Indoor dust: GM 53.2, range <0.2-1474 µg/g, n=156	Blood: median 6.8, range <0.1-53.1 µg/L, n=172; Urine: median 0.33, range 0.1-7.0 µg/L	na	Positive association between soil Mn and dust Mn (r_{s}=0.335, $P<0.001$). No associations between environmental Mn measures and blood or urine Mn levels
Gulson (2014), Australia[c]	Introduction of methylcyclo-pentadienyl manganese tricarbonyl (MMT) to motor vehicle fuel in 2001 and cessation in 2004	Longitudinal; 108 children aged 0.5-2.0 yrs at baseline living at varying proximity to roadways, measured at 3 6-month intervals over a 5-year period	Time since first data collection, category of traffic proximity, age, gender, location within house for indoor dust samples	Soil: mean (SD) 220 (190), range 17-1635 µg/g (n=329); Exterior dust sweepings: mean (SD) 222 (245), range 8-2850 µg/g (n=329); Interior handwipes mean (SD) 4.8 (6.4), range 0.03-25 µg/handwipe; Indoor dust, child care dust, exterior handwipes	Blood: median 12.0, range 1.8-45.0 µg/L, n=146 at age 0.5-2.0 yrs; median 9.9, range 1.0-20.0, n=134 at age 5-7 yrs	na	Blood Mn was significantly associated with interior handwipes (r=0.262, P=0.006); no associations between blood Mn and soil, indoor dust, exterior dust sweepings, exterior handwipes, or child care dust Mn
Lucchini (2014), Italy[a]	FeMn alloy plants	Cross-sectional; adults aged 65-75 yrs from 1 of 2 areas: an area with historically active FeMn	Age, gender, smoking and alcohol habits, distance from FeMn source, blood lead	24-hour personal air: median 21.2, range 2.0-103.0 ng/m^3, n=254;	Blood: median 8.5, range 3.6-21.6 µg/L, n=238; Urine: median 0.1, range 0.1-	Mini-Mental State Examination, Story Recall Test, Raven's Colored Progressive Matrices (CPM) Test, Trail Making Test,	Significant negative association between log air Mn and Luria Nebraska motor coordination score (P=0.024); increased

First author (year), country	Source of exposure	Study type and population	Covariates	Environmental Mn measures	Mn biomarkers	Health outcomes	Study results
		plants (n=153), and area with no history of plant activity (n=102)		Soil: median 786, range 313-1724 ppm	9.4 µg/L, n=239	Digit Span Test, Luria Nebraska Motor Battery, Finger Tapping Test, Visual Simple Reaction Time, Pursuit Aiming Test, Tremor 7.0 Test, Sniffin' Sticks Olfactory Screening Test	log air (P<0.001), soil (P<0.001), and blood Mn (P=0.010) significantly associated with worse Sniffin' Stick Test score
McDermott (2014), USA	No specific source	Retrospective cohort; 9920 pregnant women from 10 residential study areas in South Carolina	Infant gender and gestation; maternal age, race, parity, alcohol and tobacco use; density per square mile in area of residence, median age of housing	Soil metals measured in 10 areas, kriging methods used to estimate levels at participants' homes. Soil Mn: median (IQR) 179.8 (195.8) mg/kg in low birth weight infant residences, 180.5 (195.8) in normal weight infant residences	na	Low birth weight: <2500 g (n=1146) vs. ≥2500 g (n=8774)	Crude odds ratio for soil Mn and low birth weight: 1.00 (95% CI 1.00, 1.00) for 1 IQR change in soil Mn. No association between soil Mn and low birth weight in multivariable generalized additive model
Pena-Fernandez (2014), Spain	No specific source	Cross-sectional; 117 children aged 6-9 yrs	Gender	Soil: GM 90, range 18-188 µg/g, n=97	Hair: GM 0.25, range 0.11-1.00 µg/g	na	No differences in hair Mn levels between boys and girls; no correlation between log transformed soil Mn and hair Mn (*r*=-0.076, P=0.479)
Bowler (2015), USA[*b*]	Mn refinery or open-air Mn storage and packaging facility	Cross-sectional; 100 adults aged 30-75 yrs living near Mn refinery (Marietta, OH) and 86 adults	Town of residence, education	Modeled air: mean (SD) 0.2 (0.2) µg/m^3 in Marietta, OH; mean (SD) 0.9 (1.2) µg/m^3 in	Blood: specific values not reported	Neuropsychological test battery (cognitive) including 21 tests of cognitive flexibility and executive functioning, verbal	Higher modeled air-Mn predicted lower scores on visuospatial memory (immediate daily living memory P=0.035, delayed living memory

First author (year), country	Source of exposure	Study type and population	Covariates	Environmental Mn measures	Mn biomarkers	Health outcomes	Study results
		aged 30-75 yrs living near storage/packaging facility (East Liverpool, OH)		East Liverpool, OH		skills, information processing speed, memory, working memory/ attention & concentration/learning, visuospatial memory, visuomotor tracking speed, coding	P=0.035), and verbal reasoning similarities (P=0.012). No other statistically significant associations (P values from 0.09 to 0.926)
Lucas (2015), Italy[a]	FeMn alloy plants	Cross-sectional; children aged 11-14 yrs and households from 1 of 3 areas: 1) area with an active ferromanganese plant (n=178), 2) area with 3 historically active plants (n=166), and 3) area with no history of plant activity (n=99)	None	24-hour personal air: specific values not reported; Soil: specific values not reported; Outdoor dust (µg/g): median, range: 1) 4620, 487-183000, n=142; 2) 876, 407-8240, n=81; 3) 407, 258-7240, n=68; Indoor dust (µg/g): median, range: 1) 599, 129-18500, n=147; 2) 308, 60-2110, n=85; 3) 185, 21-2000, n=67	Blood: median 10.8, range 4.0-34.3 ng/ml, n=546; Hair: median 0.10, range 0.01-1.13 µg/g, n=501; Fingernails: median 0.18, range 0.01-8.28 µg/g, n=207; Saliva: median 8.5, range 0.16-305 µg/L, n=249	na	Indoor dust Mn was significantly associated with hair Mn (*r*=0.280, P<0.001) and fingernail Mn (*r*=0.235, P<0.01); outdoor dust Mn was associated with hair Mn (*r*=0.261, P<0.001), blood Mn (*r*=-0.160, P<0.05), saliva Mn (*r*=0.147, P<0.05), and nail Mn (*r*=0.363, P<0.001); soil Mn was associated with nail Mn (*r*=0.204, P<0.01) and saliva Mn (*r*=0.135, P<0.05); air Mn was associated with Mn in hair (*r*=0.126, P<0.05), blood (*r*=-0.155, P<0.01), and saliva (*r*=0.204, P<0.01)
Massaquoi (2015), China	Prior wastewater irrigation of farmlands	Cross-sectional; farmers from areas with prior wastewater irrigation (n=40) and areas without	Gender	Soil: mean 600, range 528-698 mg/kg for wastewater areas; mean 448, range 387-492 mg/kg	Hair: mean 3.09, range 0.00-11.70 mg/kg for wastewater areas; mean 0.65, range	na	Overall, no significant association between soil Mn and hair Mn (*r*=0.08, P=0.62); correlation for males (n=55) was -0.15, P=0.45; correlation for

First author (year), country	Source of exposure	Study type and population	Covariates	Environmental Mn measures	Mn biomarkers	Health outcomes	Study results
		wastewater irrigation (n=40)		for clean water areas	0.00-1.46 mg/kg for clean water areas		females (n=25) was 0.57, P=0.05
Reis (2015), Portugal	Small city near an industrial complex	Cross-sectional; 19 households and 27 residents (21 adults, 6 children; 10 females, 17 males)	Age, gender, homegrown foodstuff consumption, smoking habits, general conditions of the home	Indoor dust: median 173, range 98-304 mg/kg; bioaccessible fraction (BAF) in a subset of 11 samples was from 46%-69%, average 61%	Toenails: adults: median 0.24, range 0.09-1.00 mg/kg; children: median 0.32, range 0.14-2.25 mg/kg; females: median 0.19, range 0.09-1.00 mg/kg; males: median 0.40, range 0.12-0.17 mg/kg	na	In a subset of 11 subjects with data on indoor dust BAF), the correlation (*r*) between total Mn and toenail Mn was 0.67, P=0.024; *r* for BAF Mn was 0.48, P=0.135. For females (n=5) correlations were -0.36, P=0.55 total Mn; *r*=0.99, P=0.001 BAF Mn. For males (n=6) correlations were 0.74, P=0.09 total Mn; r=-0.03, P=0.955
Bowler (2016a), USA[*b*]	Mn refinery or open-air Mn storage and packaging facility	Cross-sectional; 100 adults aged 30-75 yrs living near Mn refinery (Marietta, OH) and 86 adults aged 30-75 yrs living near storage/packaging facility (East Liverpool, OH)	Household income	Modeled air: mean 0.21, range 0.03-1.61 μg/m^3 in Marietta, OH; mean 0.88, range 0.01-6.32 μg/m^3 in East Liverpool, OH	na	Fingertapping Test, Grooved Pegboard, Hand Dynamometer, Coordination Ability Test System (CATSYS) tremor test (center frequency, intensity, harmonic index). All tests performed bilaterally	Significant positive associations between air Mn and center frequency (both hands, P<0.001); significant negative association between air Mn and harmonic index (non-dominant hand, P<0.001). Significant negative association between air Mn and fingertapping speed (both hands,, P=0.014)
Bowler (2016b), USA[*b*]	Mn refinery or open-air Mn	Cross-sectional; 100 adults aged 30-75 yrs living	Age, education, income	Modeled air: mean 0.21, range 0.03-1.61 μg/m^3	Blood: mean (SD) 10.0 (3.5) μg/L in	Medication use in the following categories:	Exposure was significantly associated with medication use for

First author (year), country	Source of exposure	Study type and population	Covariates	Environmental Mn measures	Mn biomarkers	Health outcomes	Study results
	storage and packaging facility	near Mn refinery (Marietta, OH), 86 adults aged 30-75 yrs living near storage/ packaging facility (East Liverpool, OH), and 90 adults aged 30-75 yrs from unexposed town		in Marietta, OH; mean 0.88, range 0.01-6.32 μg/m^3 in East Liverpool, OH	exposed group (n=186); mean (SD) 9.5 (3.2) in unexposed group (n=90)	anti-anxiety, antidepressant, arthritis/osteoporosis, blood pressure, cardiac cholesterol, diabetes gastrointestinal, hypothyroid, pain, respiratory, sleep, supplements	hypothyroid (AOR 8.1, 95% CI 1.8, 36.2), pain (AOR 2.4, 95% CI 1.3, 4.7), supplements (AOR 3.4, 95% CI 1.5, 7.5), and total medications (AOR 2.3, 95% CI 1.2, 4.5). Within exposure group, AOR (95% CI) for a 1-unit increase in air Mn was 1.6 (1.0, 2.3)
Rosa (2016), Italy[a]	FeMn alloy plants	Cross-sectional; children aged 11-14 yrs and households from 1 of 3 areas: 1) area with an active FeMn plant (n=145), 2) area with 3 historically active plants (n=80), and 3) area with no history of plant activity (n=55)	Age, gender, maternal asthma, parent education and occupation (SES), study site	24-hour personal air: area 1) median (IQR) 33.4 (72.1) ng/m^3; 2) median (IQR) 22.9 (33.4) ng/m^3; 3) median (IQR) 14.7 (21.3) ng/m^3	na	Parent report of asthma, asthma medication use in past 12 months, wheeze in past 12 months, nasal allergies/hay fever in past 12 months	Risk ratios (95% confidence intervals) for 1 IQR increase in air Mn: asthma, 1.09 (1.00-1.18); asthma medication use in past 12 months, 1.13 (1.00-1.23); wheeze in past 12 months, 1.09 (0.92-1.29); nasal allergies/hay fever in past 12 months, 0.96 (0.85-1.09)
Zota (2016), USA	Tar Creek Superfund Site	Longitudinal; 53 infants measured at 2 time points: ages 0-6 and 6-12 months	Age, gender, race/ethnicity, breastfeeding duration, mother's age at delivery, maternal smoking	Indoor PM2.5 Mn: time 1: median 0.6 ng/m^3 (n=49); time 2: median 0.6 ng/m^3, n=46 Soil: total: median 341 μg/g, bioaccessible 117 μg/g, n=48	Blood: umbilical cord: GM (GSD) 3.6 (1.6) μg/dL; 12 months: GM (GSD) 1.5 (1.4) μg/dL, n=43; 24 months: GM (GSD) 1.2	na	Blood Mn levels were not associated with PM2.5 Mn, indoor dust or soil Mn levels in adjusted analyses. Hair Mn was associated with indoor dust loadings at times 1 and 2, and indoor dust concentrations at time 2

First author (year), country	Source of exposure	Study type and population	Covariates	Environmental Mn measures	Mn biomarkers	Health outcomes	Study results
				Indoor dust ($\mu g/m^2$): time 1: median 46.0, n=47; time 2: median 57.6, n=46 Indoor dust (µg/g): time 1: median 121, time 2: median 117	(1.3) µg/dL, n=22; Hair: 12 months: GM (GSD) 0.50 (2.30) µg/g, n=39		
Akinwunmi (2017), Nigeria	No specific source	Cross-sectional; 253 children aged 2-15 yrs from 6 urban and 2 semi-rural primary schools	Age, gender	Playground soil and classroom dust: estimated from graphs: soil (mg/kg): mean 95 urban and semi-rural; dust (mg/kg) mean 95 urban, 105 semi-rural	Blood: concentrations estimated from graphs: mean 0.08 µg/ml urban, 0.05 semi-rural	na	Playground soil and dust Mn did not differ between urban and semi-rural schools; no associations between soil Mn and blood Mn, or dust Mn and blood Mn
Bowler (2017), USA[b]	Mn refinery or open-air Mn storage and packaging facility	Cross-sectional; 83 adults aged 30-64 yrs living near Mn refinery (Marietta, OH) and 63 adults aged 30-64 yrs living near storage/packaging facility (East Liverpool, OH)	Age, gender, education, household income, depression, anxiety	Modeled air: mean (SD) 0.55 (0.90) $\mu g/m^3$	Blood: mean (SD) 10.1 (3.5) µg/L	Self-report of concentration and memory problems.	No associations between air or blood Mn and self-reported concentration and memory problems
Fulk (2017), USA[d]	Mn refinery	Cross-sectional; 88 children aged 7-9 yrs	Heating, ventilation, and air conditioning score, parent education, time spent outdoors	Modeled air: median 19.3, range 5.8-159.9 ng/m^3; Soil: median 552, range 94-2229 µg/g, n=71;	Hair: median 0.44, range 0.10-7.38 µg/g, n=77	na	Pearson correlations with log hair Mn: air (0.01), soil (0.22), dust (0.39, P<0.05). Structural equation model of exposure pathway from

First author (year), country	Source of exposure	Study type and population	Covariates	Environmental Mn measures	Mn biomarkers	Health outcomes	Study results
				Indoor dust: median 59, range 8-746 µg/m^2, n=71			environmental Mn to hair Mn. Significant pathways included direct exposure from indoor dust, and indirect exposures from ambient air and soil through indoor dust
Kornblith (2018), USA[b]	Mn refinery or open-air Mn storage and packaging facility	Cross-sectional; 182 adults aged 30-75 yrs living near Mn refinery (Marietta, OH) or storage/packaging facility (East Liverpool, OH)	Age, gender, race, education, yrs of residence, income, employment status	Modeled air: mean (SD) 0.53 (0.92) µg/m^3	na	Unified Parkinson's Disease Rating Scale (UPDRS) Motor Examination subscale, Coordination Ability Test System (CATSYS) tremor test, 5 executive function measures (Animal naming, Stroop Color Word Task, Trail making Test B, Rey Osterrith Complex Figure Test Copy Trial, Auditory Consonant Trigrams	Cluster analysis identified 4 clusters based on neurological testing: non-impaired (n=111), tremor (n=21), executive dysfunction (n=37), and no tremor (n=13); clusters did not differ significantly on air Mn exposure (P=0.14)
Wahlberg (2018), Italy[a]	FeMn alloy plants	Cross-sectional; 686 children aged 11-14 yrs from 1 of 3 areas: area with active FeMn plant, area with 3 historically active plants, and area with no history of plant activity	Age, gender, plasma ferritin, blood lead, BMI, drinking habits, SES, maternal education, parity, *SLC30A10* rs1776029, *SLC30A10* rs12064812, *SLC39A8*	Soil: median 706 ppm, 5th, 95th percentile 267, 1898 ppm, n=666	Blood: median 10.9 µg/L, 5th, 95th percentile 6.5, 17.0 µg/L, n=681	Wechsler Intelligence Scale, Luria Nebraska Motor Battery, Finger Tapping Test, Visual Simple Reaction Time, Pursuit Aiming Test, Tremor 7.0 Test, Conners-Wells' Adolescent Self-Report Scale, Conners' Parent Rating Scale, Conners' Teacher Rating Scale	No association between soil Mn and blood Mn (r_s=-0.015, P=0.690); authors report "significant contribution of Mn in soil on some models with behavioral outcomes" in multiple regression analyses, but specific results not reported

First author (year), country	Source of exposure	Study type and population	Covariates	Environmental Mn measures	Mn biomarkers	Health outcomes	Study results
			rs13107325 genotypes				
Butler (2019), Italy[a]	FeMn alloy plants	Cross-sectional; 717 children aged 11-14 yrs and households from 1 of 3 areas: area with active FeMn plant (n=212), area with 3 historically active plants (n=259), and area with no history of plant activity (n=246)	Age, gender	24-hour personal air: median (IQR) 26.0 (12.9-50.4) µg/m^3, n=526; Soil: median 700, range 473-988 µg/g, n=697; Outdoor dust: median 1432, range 661-4970 µg/g, n=324; Indoor dust: median 380, range 251-722 µg/g, n=334	Blood: median (IQR) 10.9 (8.8-13.3) µg/L, n=687; Hair: median (IQR) 0.08 (0.05-0.15) µg/g, n=638; Fingernails: median (IQR) 0.19 (0.10-0.38) µg/g, n=521; Saliva: median (IQR) 4.9 (2.0-13.1) µg/L, n=389; Urine: median (IQR) 0.12 (0.09-0.28) µg/L, n=642	na	Multiple linear regression: no associations between air, dust, or soil Mn with blood or hair Mn; significant positive association between soil and fingernail Mn, significant positive associations for soil and air Mn with saliva Mn. Weighted quantile sum regression: weighted environmental exposure index comprised of air, dust, and soil Mn significantly positively associated with hair, fingernail, and saliva Mn
Broberg (2019), Italy[a]	FeMn alloy plants	Cross-sectional; children aged 11-14 yrs from 1 of 3 areas: 1) area with an active ferromanganese plant (n=183), 2) area with 3 historically active plants (n=243), and 3) area with no history of plant activity (n=219)	Age, gender, parent education and occupation (SES), maternal education, blood lead, *SLC30A10:1, SLC39A8 (ZIP8):4* genotypes combined into genotype scores on scales of 0-5, 1-2, and 1-3	Soil: median 712, range 272-1830 ppm	Blood: median 10.9, range 6.6-17.0 µg/L, n= 642	Conners-Wells' Adolescent Self-Report Scale-Long Form (CASS-L) cognitive problems/inattention, hyperactivity, attention deficit hyperactivity disorder (ADHD) index subscales, Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) total, Conners' Parent	For girls, statistically significant U-shaped associations between soil Mn and CASS DSM-IV total (P=0.007) and hyperactivity (P=0.003); positive linear associations between soil Mn and CPRS-R cognitive problems/inattention (P=0.040) and ADHD Index (P=0.017). For boys, positive linear

First author (year), country	Source of exposure	Study type and population	Covariates	Environmental Mn measures	Mn biomarkers	Health outcomes	Study results
						Rating Scale (CPRS-R) oppositional problems, cognitive problems/inattention, hyperactivity, ADHD index	association between soil Mn and CPRS hyperactivity (P=0.025). Interactions between soil Mn and genotypes were significant for associations with some CASS and CPRS-R subscales

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval; FeMn, ferromanganese; GM, geometric mean; GSD, geometric standard deviation; IQR, interquartile range; LOD, limit of detection; na, not applicable, *r*, Pearson correlation coefficient; r_s, Spearman rank correlation coefficient; SD, standard deviation.

[a]Lucchini (2012a), Lucchini (2012b), Rentschler (2012), Lucchini (2014), Lucas (2015), Rosa (2016), Wahlberg (2018), Butler (2019), and Broberg (2019): these studies are part of a larger study conducted in the Province of Brescia, Italy and have overlapping subjects.

[b]Kim (2011), Bowler (2012), Bowler (2015), Bowler (2016a), Bowler (2016b), Bowler (2017), and Kornblith (2018): these studies are part of a larger study conducted in Marietta, East Liverpool, and Mount Vernon, OH, and have overlapping subjects.

[c]Gulson (2006) and Gulson (2014): these studies are conducted on the same cohort of subjects.

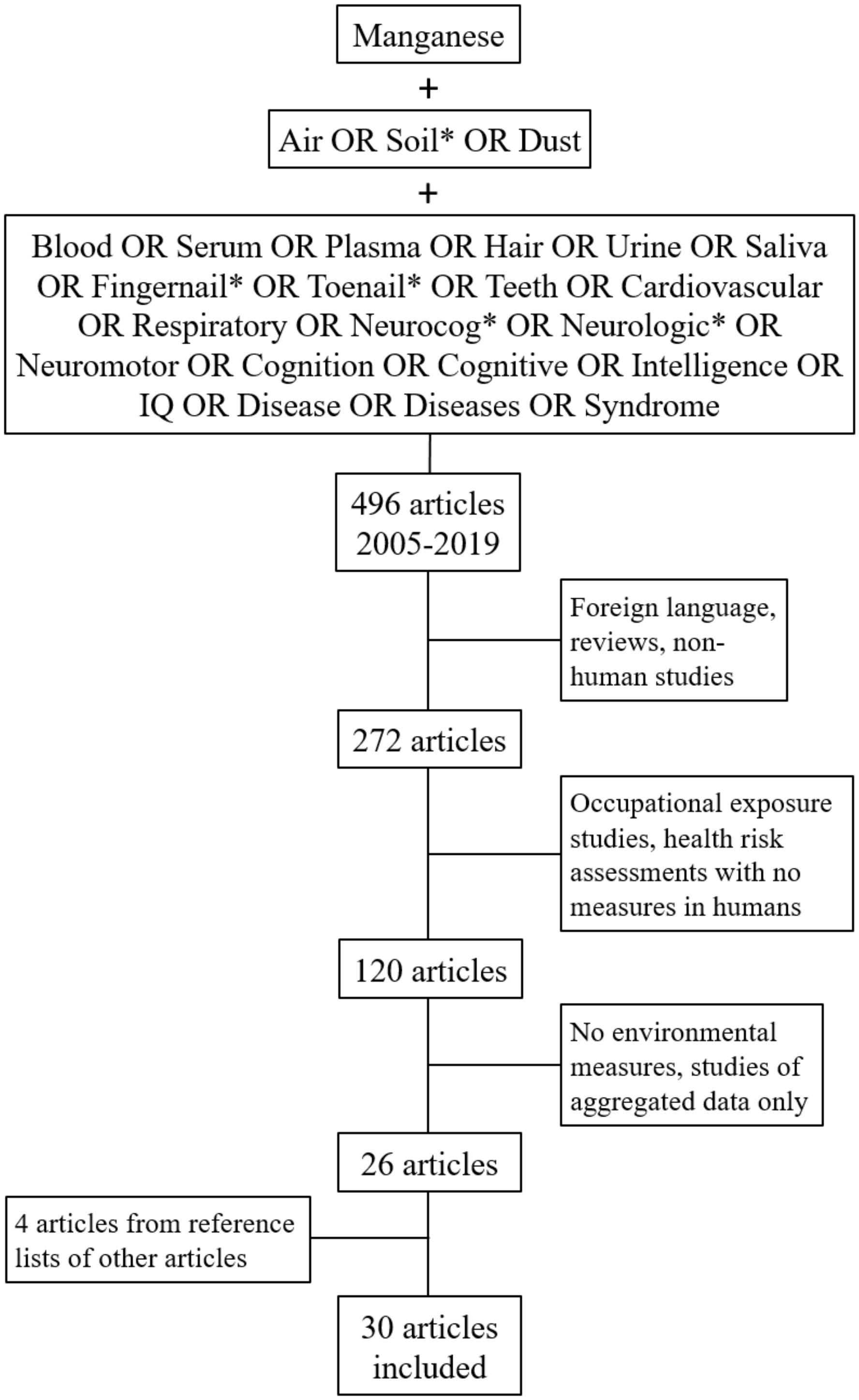
[d]Haynes (2012) and Fulk (2017): these studies have overlapping subjects.

Table 2. Summary of Correlations between Environmental Manganese and Biomarkers Reported in the Studies in Table 1

Environmental medium	Blood	Hair	Nails	Saliva	Urine
Air					
Solis-Vivanco (2009)	0.22*	-	-	-	-
Haynes (2010)	0.05	0.17	-	-	-
Haynes (2012)	NS	NS	-	-	-
Lucas (2015)	-0.16*	0.13*	0.14	0.20*	-
Fulk (2017)	-	0.01	-	-	-
Butler (2019)	-0.05	0.12*	0.17*	0.23*	0.01
Soil					
Callan (2012)	-	NS	-	-	NS
Rentschler (2012), Adults	-0.14*	-	-	-	-0.03
Rentschler (2012), Children	0.01	-	-	-	0.09
Callan (2013)	NS	-	-	-	NS
Gulson (2014)	0.14	-	-	-	-
Pena-Fernandez (2014)	-	-0.08	-	-	-
Lucas (2015)	-0.02	0.04	0.20*	0.14*	-
Massaquoi (2015), Males	-	-0.15	-	-	-
Massaquoi (2015), Females	-	0.57*	-	-	-
Zota (2016)	NS	NS	-	-	-
Akinwunmi (2017)	NS	-	-	-	-
Fulk (2017)	-	0.22	-	-	-
Wahlberg (2018)	-0.02	-	-	-	-
Butler (2019)	-0.02	-0.01	0.22*	0.08	0.14*
Outdoor dust					
Gulson (2014)	0.01	-	-	-	-
Lucas (2015)	-0.16*	0.26*	0.36*	0.15*	-
Butler (2019)	-0.10	0.11	0.27*	0.00	0.08
Indoor dust					
Gulson (2006)	NS	-	-	-	-
Callan (2012)	-	NS	-	-	NS
Callan (2013)	NS	-	-	-	NS
Gulson (2014)	0.07	-	-	-	-
Lucas (2015)	-0.08	0.28*	0.24*	0.08	-
Zota (2016)	NS	**	-	-	-
Akinwunmi (2017)	NS	-	-	-	-
Fulk (2017)	-	0.39*	-	-	-
Butler (2019)	-0.07	0.12*	0.23*	-0.03	0.04

Values in the table are Pearson or Spearman rank correlation coefficients.
*P<0.05; NS, not significant (values not reported); **Reported as P<0.05 but correlation not reported.

Figure 1. Literature Search Terms and Results



* = wildcard for all word endings

Chapter 2: AERMOD Modeling of Environmental Manganese Exposure and Associations with Soil Concentrations and Indoor Dust Loadings

Abstract

Background: Environmental exposure to manganese (Mn) is associated with adverse health outcomes. In Marietta, Ohio and surrounding communities, residents are exposed to Mn emissions from Eramet Marietta, Inc. (EMI), the largest Mn refinery in the U.S. Atmospheric dispersion modeling of ambient air Mn may be useful in quantifying ambient air exposures and estimating deposition in soil and dust in the area.

Objective: To perform AERMOD modeling of ambient air Mn during 2008-2013, and measure associations with residential soil and indoor dust Mn in the Marietta area.

Methods: Ambient air Mn concentrations were modeled with AERMOD using reported emissions for EMI obtained from the U.S. EPA. Soil concentrations and indoor dust loadings for 248 sites were obtained from the Marietta Communities Actively Researching Exposure Study (CARES). Air Mn concentrations measured at a stationary site in 2009-2010 were also obtained from CARES. U.S. Census block population data were used to estimate the population size over the time period. Associations between modeled ambient air, soil, and indoor dust were determined with Pearson correlation coefficients.

Results: Median modeled air Mn concentrations ranged from 6.33 to 43.09 ng/m^3 across the years. In five of the years, a population of over 10,000 residents was exposed to >50 ng/m^3, the U.S. EPA guideline for chronic exposure. For 2009-2010, the median modeled air Mn concentration at the stationary site was 20.27 ng/m^3, compared to 18.41 ng/m^3 measured with the stationary air sampler. All model performance measures for monthly modeled concentrations compared to measured concentrations were within acceptable limits. Soil and indoor dust Mn

levels were significantly correlated, but were not consistently correlated with modeled ambient air Mn across the years modeled or the air Mn averaged over different time periods.

Conclusion: AERMOD modeling of ambient air Mn in Marietta is a viable method for estimating exposures, and shows that the area population is at times exposed to Mn levels that exceed U.S. EPA guidelines.

Introduction

Manganese (Mn) is an essential nutrient required for normal brain development and functioning, but can be toxic in excess, Mn occurs naturally in the environment, in air, surface water and groundwater, rocks, soil, crops, and other vegetation. In the U.S. the average ambient air concentration is 0.02 $\mu g/m^3$, ranging from 0.01$\mu g/m^3$ in rural or remote areas to 0.04 $\mu g/m^3$ in urban environments (ATSDR 2012). Ambient air Mn concentrations can range much higher than background levels in areas with anthropogenic sources. In the U.S., the Environmental Protection Agency (EPA) has set a reference concentration (RfC) of 50 ng/m^3 for chronic exposure to Mn in the respirable fraction, while the Agency for Toxic Substances and Disease Registry (ATSDR) established 300 ng/m^3 as the chronic duration inhalation minimal risk level (U.S. EPA, 2002; ATSDR, 2012). The World Health Organization (WHO) recommended a guideline of average annual ambient air exposure of 150 ng/m^3 (WHO, 2000). Primary sources of excess Mn in the environment include industrial emissions, mining activities, pesticides, fungicides, and the gasoline additive methylcyclopentadienyl manganese tricarbonyl. Globally, ferromanganese alloy plants have been associated with some of the highest average annual air Mn concentrations in communities near the plants (Otero-Pregigueiro and Fernández-Olmo, 2018). Ledoux et al. (2006) found a 12-h average air Mn concentration of 7560 ng/m^3 near a ferromanganese plant in France, and Boudissa et al. (2006) reported a 2-h concentration of 3500 ng/m^3 near a ferromanganese plant in Canada. Across five stationary sampling sites near a ferromanganese refinery in Marietta OH, the site of the present study, Colledge et al. (2015) reported monthly average Mn concentrations of 110-390 ng/m^3 from 2003 through October 2013.

A number of methods have been used to monitor airborne exposure to environmental pollutants from specific industrial sources in or near communities. Personal exposures can be quantified with personal air samplers worn by individuals that measure continuous exposures over specified periods of time. This is considered the most accurate method but is expensive and not suitable for large populations (Han et al., 2017). A more feasible method is to employ stationary air samplers placed at different locations in a community, but these lack spatial and temporal resolution and may not adequately capture individual variability (Ozkaynak et al., 2013). Distances from homes to the exposure site are often used as surrogate measures of exposure. The limitations to this method are that wind speeds and directions, terrain, and land use are not taken into account.

Air dispersion modeling is a method frequently used in air quality assessments for regulatory purposes but less so in epidemiologic studies. Air dispersion models predict concentrations of pollutants in the environment using information about emission sources, topography, meteorological data, distances and other factors. Compared to direct exposure assessment methods, air dispersion models have several advantages, including the ability to separate contributions of different chemicals, reconstruct historical exposures, and predict future exposures (Zou et al., 2009). For epidemiologic studies where direct measurement of Mn exposure levels from industrial sources is prohibitive, air dispersion modeling can be a viable option.

In addition to Mn in the air, surface soil and indoor dust contain settled Mn particles and represent additional sources of exposure. Children are at greater risk than adults due to spending greater amounts of time close to the floor as well as having increased hand-to-mouth contact (Moya et al., 2004). In uncontaminated environments soil Mn levels range from 40-900 μg/g, but much higher levels have been measured in areas near industrial Mn sources (Boudissa et al., 2006; Aelion et al., 2009; ATSDR, 2012; Pavilonis et al., 2015). Elevated levels of Mn have also been found in indoor dust near industrial Mn sources. Pavilonis et al. (2015) found that in homes within 0.5 km of a ferromanganese plant in Italy house dust Mn levels were 2.4 times higher than in homes 1.0 km from the plant. In Brazil, classroom dust loadings were negatively associated with distance from a ferromanganese alloy plant and positively associated with Mn levels in outdoor dust (Menezes-Filho et al., 2016). Further, a number of studies have found significant associations between Mn in soil or indoor dust and blood, hair, or other biomarkers in children (Zota et al., 2016; Fulk et al., 2017; Lucchini et al., 2017; Butler et al., 2019).

A significant gap in the literature on environmental Mn exposures near industrial sources concerns the associations between measured air, modeled air, soil, and dust Mn levels in exposed communities, and how these vary with proximity to the exposure site. Modeled air Mn has been compared to measured air Mn in three studies in Marietta, Ohio, a community near a ferromanganese refinery (Haynes et al., 2010; Colledge et al., 2015; Fulk et al., 2016). One study (Fulk et al., 2017) determined associations among air, soil, and indoor dust Mn levels for a one-year period. Modeled air Mn was positively associated with indoor dust Mn but not soil Mn, while soil and indoor dust Mn were positively correlated (Table 1). Other studies have been varied in findings of associations between environmental Mn measures, with some studies finding no correlations and others finding significant positive correlations (Table 1).

The purpose of this study was to model air Mn concentrations and determine associations with measured air, soil, and indoor dust Mn in an exposed community. The study site is Marietta, Ohio and neighboring towns, which are exposed to airborne Mn from Eramet Marietta, Inc. (EMI), a ferromanganese refinery in operation for over 60 years. EMI is the largest emitter of Mn in the U.S. (U.S. EPA, 2015). Air Mn concentrations over the six-year period of 2008-2013 were modeled using the American Meteorological Society/Environmental Protection Agency

Regulatory Model (AERMOD), a steady-state Gaussian plume air dispersion model recommended by the U.S. EPA for modeling emissions from industrial sources (U.S. EPA, 2004). Data for stationary air, soil, and indoor dust measurements were obtained from the Marietta Communities Actively Researching Exposure Study (CARES), a cross-sectional, community-based participatory research partnership that investigates the impact of increased environmental exposure to Mn on neurological outcomes in children.

The specific aims of this study were to 1) Determine ambient air Mn concentrations in Marietta, Ohio and the surrounding area during 2008-2013, using the regulatory air dispersion model AERMOD; 2) Measure the accuracy of AERMOD results by comparing modeled ambient air Mn to ambient air Mn measured at a stationary monitoring site in Marietta from January 2009 through October 2010; and 3) Determine whether modeled annual air Mn concentrations averaged over each year are associated with soil and indoor dust Mn concentrations measured during the same years at sites in Marietta and the surrounding area. It was hypothesized that modeled ambient air Mn concentrations would be associated with stationary ambient air Mn and predictive of soil and indoor dust Mn. It was further hypothesized that soil and indoor dust would be correlated, and would both be correlated with distance from the ferromanganese refinery.

Methods

Modeled Study Area and Population Estimates

The modeled study area is from the Marietta Communities Actively Researching Exposure Study (CARES) conducted from October 2008 through February 2013 in Washington County, Ohio and Wood County, West Virginia. The CARES study is a cross-sectional, community-based participatory research partnership between investigators from the University of Cincinnati Department of Environmental Health and residents of Marietta, Ohio and surrounding communities. The purpose of the CARES study is to address the impact of increased environmental exposure to Mn on neurological outcomes in 7-9 year old children. Data collected from child participants included neurological testing, biomarkers (blood, hair, toenails) of exposure to Mn and other metals, and residential and indoor dust samples.

From October 2008 through February 2013, 323 children aged 7-9 years and their primary caregivers were recruited to participate in the CARES study. The children resided in 258 different homes; the homes farthest from EMI in all directions were used to establish the geographic boundary for modeling exposure. Of the 258 homes, 241 had residential soil and indoor dust samples collected and were included in the present study. Since no participant data from the CARES study were used, the homes where soil and dust samples were collected are referred to as “sites” rather than homes or residences.

For estimating the population size exposed to Mn in the study area, census block data including census block code, 2010 total population size, population size for children aged 0-14 years, and block centroid latitude and longitude from the 2010 U.S. Census were downloaded from the U.S. Census Bureau website (U.S. Census Bureau, n.d.-a). All census blocks in Washington Co., Ohio and Wood Co., West Virginia were extracted from the data file and merged with a census block boundaries shapefile obtained from the Esri Data & Maps website (Environmental Systems Research Institute, n.d.). ArcGIS Pro Desktop software from the Environmental Systems Research Institute, Inc. was used to create a map of the counties with census blocks, population sizes, the modeled study area, and location of EMI (Figure 1). For 105 of the 116 census blocks in the counties, the census block centroid was within the modeled study area; these 105 blocks were included in the study.

Modeling of Ambient Air Mn Concentrations in Marietta and Surrounding Areas

Ambient air concentrations of Mn were modeled using the American Meteorological Society/Environmental Protection Agency Regulatory Model (AERMOD). AERMOD is a steady-state Gaussian plume dispersion model designed for modeling pollutant concentrations for up to 50 km from a source. AERMOD is the U.S. EPA's preferred dispersion model, incorporating planetary boundary layer turbulence structure and scaling concepts, meteorological conditions, elevated sources and emissions, and simple or complex terrains (U.S. EPA, 2004). The AERMOD model has three components: a meteorological preprocessor (AERMET), a terrain preprocessor (AERMAP), and the dispersion model. Within AERMET are two additional preprocessors, AERMINUTE and AERSURFACE, that prepare data for input into AERMET. Model inputs include wind data, hourly surface weather data, upper air data, land cover data, elevation data, emissions sources and quantities, and receptor locations. All modeling was conducted using AERMOD View version 9.7.0 from Lakes Environmental Software, Waterloo, Ontario.

For AERMET preprocessing of meteorological data, Automated Surface Observing System (ASOS) 1-and 5-minute wind data files for the Parkersburg/Wilson station at Mid-Ohio Valley Regional Airport, the closest weather station, were downloaded from the National Climatic Data Center, Automated Surface Observing System (ASOS) website (National Centers for Environmental Information, n.d.-a). The ASOS 1- and 5-minute data files are monthly files that contain information on wind speeds and directions by day and time. The 1-minute data files were the primary files processed, with 5-minute data used to fill in missing 1-minute data wherever possible. The files were processed through the AERMINUTE component of AERMET to calculate average hourly wind speeds and directions. Integrated Surface Hourly (ISH) weather observations data files were downloaded for the Parkersburg/Wilson station from the National Climatic Data Center, Quick Links website (National Centers for Environmental Information, n.d.-b). The ISH files contain additional information on hourly winds, as well as visibility and air temperatures measured between ground level and 10 meters. Upper air data files for the Wilmington, OH, U.S. Upper Air Station, which is the closest station to the study area, were downloaded from the NOAA/ESRL Radiosonde Database website (National Oceanic and Atmospheric Administration, n.d.).

National Land Cover Data (NLCD) files were obtained from the Multi-Resolution Land Characteristics Consortium (MLRC). The MLRC is a consortium of federal agencies that provides land cover data for land management and modeling applications for the continental United States (CONUS). NLCD 2006 and 2011 Land Cover CONUS data files were downloaded from the MLRC website (MLRC, n.d.). The NLCD 2006 data file was used for the 2008-2010 AERMOD modeling, and the NLCD 2011 data file was used for 2011-2013. The files were preprocessed with AERSURFACE within AERMET to obtain the average surface characteristics albedo, surface roughness length, and Bowen ratio for input into AERMET. Albedo is the proportion of solar radiation reaching the earth that is reflected back into space from the surface. The lighter the surface, the higher the albedo. For different land cover types, seasonal albedo values range from 0.10 for open water to 0.70 for perennial ice and snow (U.S. EPA, 2008). Surface roughness is the height in meters above the ground where horizontal wind velocity is zero. Seasonal surface roughness ranges from 0.001 meters for open water to 1.3 meters for deciduous, evergreen, and mixed forests (U.S. EPA, 2008). The Bowen ratio, a measure of surface moisture, is the ratio of sensible heat flux (changes in temperature of a gas with no change in phase) to latent heat flux (changes in temperature with changes between gas, liquid, and solid phases). The higher the Bowen ratio, the greater the dryness of an area. Seasonal Bowen ratio values for the different land cover types range from 0.10 for open water to 10.0 for bare rock arid regions (U.S. EPA, 2008). For 2008-2010, the surface characteristics were albedo = 0.16, surface roughness = 0.219 meters, and Bowen ratio = 0.64. For 2011-2013, the values were albedo = 0.16, surface roughness = 0.222 meters, and Bowen ratio = 0.65.

The digital terrain elevation data file for the AERMAP preprocessor was directly accessed from within the AERMOD View terrain processor from webGIS.com, a geographical information systems resource website (http://www.webgis.com/). The data file, created by the U.S. Geological Survey, is a National Elevation Dataset (NED) consisting of ground surface elevation data at a resolution of 1/3 arc second (~10 meters). The terrain elevations were used for all emissions sources and receptors in the AERMOD models.

Annual Mn emissions data reported by EMI for the years 2008-2013 were obtained from the U.S. EPA through a Freedom of Information Act (FOIA) request (EPA-HQ-2019-004104, FOIA online, n.d.). The FOIA data received included point source and fugitive annual Mn emissions in lb, stack locations, heights, diameters, and exit temperatures, fugitive heights, lengths, widths, and rotation angles, emission rates, and days operating per year. Manganese emissions were reported as elemental Mn (Chemical Abstracts Service Registry Number 7439-96-5). The primary point sources of emissions were stack emissions from three submerged electric arc furnaces, the metal oxygen refining process, and the crushing, sizing, and packing system. Fugitive sources were roadways, storage piles, and furnace casting operations. The percent of total emissions comprised of fugitive emissions varied over the 6-year period from 18% to 47%. Complete operating parameters for emissions sources by year are shown in Tables 2-7. Global Positioning System (GPS) coordinates for the emissions sources were determined using Google Earth Pro and were converted to the Universal Transverse Mercator Zone 17 coordinate system (UTM) with ArcGIS Pro Desktop.

Receptors for AERMOD modeling included all soil/indoor dust sampling sites, census block centroids, and a single stationary air sampler site located in Marietta. All addresses were geocoded and distances from EMI in kilometers were determined with ArcGIS Pro Desktop. For AERMOD processing, GPS coordinates were converted to the UTM coordinate system. Ambient air Mn concentrations for census block centroids were modeled for all years of the study, to determine whether changes in concentrations were correlated with changes in reported annual emissions.

For each year, AERMOD modeling was conducted with a modeling domain of 32 km from the emissions source. The default regulatory options were used, with a rural setting and output concentrations set to ng/m^3. Annual and monthly averaging time options were selected for concentration outputs. Building downwash, which is aerodynamic turbulence caused by buildings near emissions sources, was modeled using the Building Profile Input Program (BPIP) within AERMOD. EMI building lengths, widths, and heights were measured with Google Earth Pro and the data were entered into the BPIP algorithm. Four buildings were modeled that were in close proximity to the vertical stacks, and housed the furnaces that were the primary source of emissions. For building downwash calculations, the EMI site was rotated 18 degrees so that the site North coincided with True North.

The U.S. EPA FOIA data included information on total hours in operation for each source operating in a given year. Sources are assumed to be operating 24 hours per day, 365 days per year, for a total of 8760 hours. For modeling, emissions in grams/second were evenly distributed across all hours and days per year. For sources that were in operation for fewer than

8760 hours, no information was available as to the specific days and times the sources were operating. In these cases, AERMOD variable emissions options were used to distribute the reduced operating hours evenly over the 365 day period. For example, if a source was listed as operating for 8304 hours for the year, the emissions were modeled as 22.75 hours per day over the 365 days. The only exception was for emission sources from a furnace that only operated for the first 64 days of 2010. The total emissions amount for that furnace's stacks was modeled as occurring over the first 64 days of the year, with zero emissions occurring after 64 days.

Output from the AERMOD modeling included a text file with average annual Mn concentration for each receptor, a text file with average monthly concentrations for each receptor, and contour plots of Mn concentrations across the study area. The average annual concentrations contour plots and receptor locations were exported to ArcGIS Pro Desktop for final formatting and labeling of contour map figures.

Stationary Mn Air Sampling

For all of 2009 and the first 10 months of 2010, the CARES study team measured air Mn with a stationary air sampler positioned on the roof of the Rickey Science Center at Marietta College, 7.8 km northeast of EMI (Haynes et al., 2012). A detailed description of the sampling equipment and methodology is available from Haynes et al. (2012). Briefly, stationary samples were collected with Harvard-type $PM_{2.5}$ impactors with a high volume sampling pump calibrated to 10 ± 0.5 liters per minute. Samples were collected on 37 mm pre-weighed Teflon membrane filters with 2 μm pore size to collect airborne particles with diameters of 2.5 μm or less. Samples were collected three times per week over 48-hour time periods for the duration of the monitoring period. The stationary samples were analyzed for Mn (ng/m^3) with an inductively coupled plasma mass spectrometer at a commercial laboratory at Research Triangle Institute in NC. The analysis method had a detection limit of 2.5 ng/sample. The data from the stationary air sampler were available for this study and were used to compare AERMOD modeled vs. measured ambient air Mn for a subset of the 2008-2013 study data. Average monthly values of measured Mn were determined from the 48-hour samples for comparisons to modeled Mn for 2009-October 2010.

Collection and Analysis of Residential Soil and Indoor Dust Samples

Over the 6-year study period, CARES team members collected soil and indoor dust samples from 241 participant homes. Samples were collected following U.S. Department of Housing and Urban Development (HUD) protocols and guidelines (HUD, 1995). Details of the sampling methodology for soil and dust have been described in detail in Fulk et al. (2017). At each site, surface soil samples were collected from six separate locations in the yard free of rocks and other materials. Half-inch soil samples were collected with a stainless steel spatula and transferred to a sealable plastic bag. To avoid contamination, collectors wore protective gloves and decontaminated the spatula between samples by cleaning with wet wipes until no visible soil remained. The six samples from a site were all transferred to the same plastic bag, double-bagged and labeled for analysis as a composite sample.

On the same day as the soil sample collection, indoor dust samples were collected from the floors of three areas of the residence: the front entrance of the home, the kitchen, and the child's bedroom or other room where the child spent the most awake time. Dust samples were collected using a wet wipe method in 1-square-foot sample areas marked off with tape boundaries or a plexiglass template. Sample areas were cleared of foreign objects and dusted using a two-pass approach. The first step was to pass a wet wipe from right to left in an S-shaped pattern across the marked off surface; the wet wipe was then folded in half and a second pass was made in an S-shaped pattern from top to bottom, using the side of the wipe opposite of the side used in the first pass. The wet wipe was then folded, placed in a centrifuge tube, and labeled with sample identification number, room location, surface type (vinyl, bare wood, carpet, painted, concrete, or other), and surface condition (good, fair, poor). A total of 696 dust wipe samples were collected from the 241 homes. The majority were from vinyl or bare wood surfaces (80%), 11% were from carpeted surfaces, and 9% were from other surface types. Where surface conditions were specified, 79% were good, 20% fair, and 1% poor.

Soil and indoor dust samples were analyzed for Mn at Research Triangle Institute (Research Triangle Park, NC) using a method modified from USEPA Method 3050B Acid Digestion of Sediments, Sludge's, and Soils. (U.S. EPA, 1996). A description of the analysis process is provided in Fulk et al. (2017), and briefly summarized here. For each composite soil sample, one gram was removed and placed in an extraction tube. For indoor dust samples, each wipe collected from a residence was placed in a separate extraction tube. Five ml of equal parts water and nitric acid (HNO_3), 0.05 ml of 1000 ppm of gold (Au), and 2 ml of hydrochloric acid (HCl) were added to each extraction tube. Samples were placed in a 48-well SCP Science DigiPREP digestion block for 1 h at 95 °C to allow a 15-20 minute reflux of the sample. Samples were then removed and cooled to room temperature. After cooling, 2.5 ml of concentrated HNO_3 was added and samples were returned to the digestion block for 2 h at 95 °C. Once again, samples were removed and cooled to room temperature, after which 1 ml of deionized water and 1.5 ml of hydrogen peroxide (H_2O_2) were added. The samples were returned to the digestion block for a final 2 h at 95 °C. Samples were diluted to a final volume of 50 ml with deionized water after removal and cooling to room temperature, then capped, shaken and centrifuged at 1700 rpm for 20 min. For dust wipe samples, all samples from a single residence were combined prior to final dilution to create a single sample from a residence. All samples were analyzed with a Thermo X-Series II Inductively Coupled Plasma Mass Spectrometer (ICP-MS) (Thermo Fisher Scientific, Inc., Waltham, MA). The limit of detection (LOD) for Mn in dust was 5.0 µg, and for soil Mn the LOD was 25 µg/g. For statistical analysis of dust Mn levels, the number of grams of Mn was divided by the number of sample wipes, each 1 square foot in size, to obtain dust loadings of Mn in $\mu g/ft^2$. Values were then converted to $\mu g/m^2$ for all analyses.

Data Analysis

Descriptive and Inferential Statistics for Modeled Average Annual Air Mn Concentrations

Average annual ambient air Mn concentrations in ng/m^3 for the 105 census block centroids were summarized with mean (SD), median (interquartile range, IQR), minimum and maximum values. The data were right-skewed, so a Friedman test was used to compare concentrations over the study period, followed by Wilcoxon signed ranks tests to determine whether the concentrations decreased in a sequential manner from 2008-2013. A Bonferroni correction to the Wilcoxon tests P values was applied to account for multiple comparisons. Nine comparisons were made: each year versus 2008, and each year versus the previous year. The P value for significance was 0.05/9 = 0.005 (VanderWeele and Mathur, 2019). For each centroid, the association between the natural log-transformed Mn concentration and distance from EMI was determined within each year with Pearson correlation coefficients and 95% confidence intervals (CI). Within each year, the proportion of census blocks and the estimated total population sizes with Mn concentrations that exceeded 50 ng/m^3 were determined. The 2010 U.S. Census populations were used for exposure estimates, although the populations varied slightly over the 6-year period. Over the 2008-2013 time period, the estimated populations ranged from 61,333 to 61,705 in Washington Co. and from 86,502-87,147 in Wood Co (U.S. Census Bureau, n.d.-b).

Comparisons between Modeled and Measured Air Mn

The 48-hour ambient air Mn concentrations measured at the Rickey Science Center for 2009 through October 2010 were used to determine average monthly concentrations, and compared to average monthly concentrations determined with AERMOD. Three statistical measures of model performance were calculated: Fractional Bias, Normalized Mean Square Error, and the fraction of modeled concentrations within a factor of 2 of the observed concentrations (FAC2) (Hanna and Chang, 2012; Herring and Huq, 2018). A Pearson correlation coefficient for the log-transformed values was also determined.

Fractional bias (FB) is a measure of the difference between modeled (C_M) and measured (observed, C_O) concentrations calculated as:

$$FB = \frac{(\overline{C_O} - \overline{C_M})}{0.5(\overline{C_O} + \overline{C_M})}$$

While FB is a measure of systematic error only, the NMSE reflects both systematic and random error. The NMSE is calculated as:

$$NMSE = \frac{\overline{(C_O - C_M)^2}}{(\overline{C_O})(\overline{C_M})}$$

The FB ranges from -2.0 to +2.0; the closer to 0, the less the model is biased. Absolute values of 0.30 or less are considered within the bounds of acceptable performance for air dispersion models using a rural setting. Acceptable values for NMSE and FAC2 are <3.0 and >0.5 respectively (Herring and Huq, 2018).

A quantile-quantile (Q-Q) plot was used to qualitatively assess whether the distributions of modeled and measured concentrations were comparable across the 22-month period. A Q-Q plot is created by independently rank-ordering the measured and modeled concentrations and plotting them against each other. Q-Q plots are useful for determining whether the modeled concentrations under or overestimate values at lower, upper, or middle measured concentrations (Chang and Hanna, 2004).

<u>Analyses for Soil and Indoor Dust Mn Concentrations</u>

To determine whether soil concentrations and dust loadings were associated with modeled air Mn concentrations, and whether different averaged time periods for ambient air Mn affected the associations, the following protocol was performed: for each site with soil and dust measures, modeled air Mn concentrations were averaged for the year the soil and dust samples were collected, then for 1, 3, 6, and 12 months prior to the soil and dust sample collections. Air, soil, and dust Mn levels were summarized with descriptive statistics and then natural log transformed for correlation analyses. Pearson correlation coefficients were determined for soil and dust Mn with the air Mn concentrations, and with distance from EMI for the different years. Correlations between soil and dust Mn were determined for all years combined, and for the years 2009-2012 separately. The correlations for the separate years were determined in order to explore whether correlations were higher for years with higher Mn emissions. Correlations were not determined for 2008 and 2013 due to the small sample sizes (n=4 for both years).

All descriptive and inferential statistics were conducted with SAS version 9.4 statistical software (SAS Institute, Cary, NC). Continuous variables were tested for normality with Shapiro-Wilk tests, and natural log transformed if the data were not normally distributed. For all

Pearson correlation coefficients, 95% confidence intervals were calculated using the Fisher z transformation method. P values less than 0.05 were considered statistically significant.

Results

EMI Mn Emissions Across 2008-2013

The Mn emissions at EMI varied widely over the study period, primarily due to changes in the number and hours of operation of the furnaces as well as upgrades to emissions-limiting systems. Emissions were highest in 2008, with 237,012 lb, and lowest in 2010, with 41,531 lb. Beginning in March 2009, EMI curtailed operation of two of its three furnaces due to a significant reduction in demand for steel products, which in turn reduced demand for Mn alloys (Corathers, 2011). Production was resumed at full capacity in 2010, but in March one furnace was shut down due to damage caused by a buildup of pressure that blew material off its top (Corathers, 2012). To date the furnace has remained idle. In early 2011, EMI completed construction of a new baghouse emissions abatement system on one of its furnaces, reducing emissions plantwide (U.S. EPA, 2015). The proportion of stack emissions, which would tend to travel farther than fugitive emissions, also varied across the years. The lowest percent was in 2013, with 53% of total emissions comprised of stack emissions, and the highest percent was in 2010, with 82% of total emissions comprised of stack emissions (Tables 2-7).

Ambient Air Mn Concentrations Modeled with AERMOD

Contour maps of the concentration gradients for modeled average air Mn in ng/m^3, and locations of the census block centroids and EMI are shown in Figure 2A-F. For 2009 and 2010, the location of the stationary air sampler site is also shown. Air Mn concentrations decreased with distance from EMI but not uniformly because of the effects of wind speed and direction on dispersion. In general the direction of the winds from EMI were toward the northeast, with speeds of 0.50-11.10 m/s. The percent of calm periods (wind speeds <0.50 m/s), which AERMOD cannot use in dispersion calculations, ranged from 3.82% to 7.13% across the years (Figure 3A-F).

For all census blocks combined, the median (IQR) air Mn concentrations (ng/m^3) varied from 6.33 (8.07) in 2010 to 43.09 (38.17) in 2008 ($P<0.001$ across all years). The changes in air Mn concentrations over 2008-2013 followed the pattern of changes in Mn emissions over the same years (Figure 4). From 2009-2013, all median (IQR) air Mn concentrations were significantly lower ($P<0.005$) than the concentrations in 2008. However, the decrease was not sequential; while the concentration significantly decreased from 2009 to 2010 ($P<0.005$), it significantly increased from 2010 to 2011 ($P<0.005$) and remained higher in 2012-2013 than the average concentration in 2010 (Figure 4). The median (IQR) distance from EMI for census block centroids was 11.22 (5.47) km, range 2.89-29.20 km. For all years, log-transformed modeled air Mn concentrations were negatively correlated with distance from EMI, with correlation coefficients ranging from -0.654 (95% CI -0.751, -0.529) to -0.840 (-0.888, -0.773). The R^2 values for the log-transformed air Mn concentrations indicated that 43% to 71% of the variability in modeled air Mn could be explained by the distance from the centroids to EMI (Figure 5A-F).

Table 8 shows the descriptive statistics for modeled air Mn concentrations by year separately for census block centroids, and Table 9 shows the percent of centroids with concentrations exceeding U.S. EPA (50 ng/m^3) and WHO (150 ng/m^3) guidelines. In 2008, 41% of the census blocks, representing an estimated total population of 56,201, including 9370 children aged 0-14 years, had average annual ambient air Mn concentrations >50 ng/m^3. The percent was lower in 2009 and 2010 but was then again relatively high in 2011 (26.7%, estimated population 36,911) before decreasing in 2012 and 2013 from 2011. Only a few census blocks had average concentrations above 150 ng/m^3, with the highest of 5.7% (estimated population of 8,715) in 2008.

Modeled Air Mn Compared to Measured Air Mn at a Stationary Monitoring Site

Measurements of ambient air Mn taken from January 2009 through October 2010 at the stationary sampling site were used to evaluate the accuracy of air Mn concentrations modeled with AERMOD. The median ambient air Mn measured across 2009-2010 was 18.41 ng/m^3, compared to 20.27 ng/m^3 for modeled air Mn over the same time period (Table 10). For individual monthly averages, the modeled values were higher than measured values for 13 of 22 months, with no discernable pattern to the under or overestimation across the time period (Figure 6). For the entire time period as well as 2009 and 2010 analyzed separately, the measures of model performance were all within acceptable limits (Table 10). The modeled ambient air Mn averages across 2009-2010 slightly overestimated the measured air Mn values, with an FB of -0.099. For 2009 the FB was also negative, but for 2010 the value was positive, indicating the modeled values slightly underestimated the measured values. Overall deviation in modeled and measured values (NMSE) was 0.202, suggesting that air Mn concentrations modeled with AERMOD can reasonably represent measured air Mn concentrations.

A scatter plot of measured versus modeled air Mn is shown in Figure 7. All but one of the differences between modeled and measured air Mn were within a factor of 2, resulting in a very high FAC2 of 0.955. The outlier occurred at the lowest measured monthly concentration of air Mn of 7.50 ng/m^3, with a modeled concentration of 17.51 ng/m^3. Of the 9 times that the modeled concentrations underestimated the measured concentrations, 3 occurred at the highest measured values of air Mn, which may suggest that the model is more accurate at lower concentrations, but more data would need to be evaluated to determine if this is true. To determine whether the measured and modeled air Mn values followed a similar distribution, a quantile-quantile plot of the individually ranked data was constructed (Figure 8). For this plot, the closer the values are to the diagonal line, the more similar the distributions, although the assessment is qualitative only. The plot shows that when the concentrations are ranked the distributions are similar.

Residential Soil and Indoor Dust Mn Samples

During 2008-2013, soil and indoor dust samples were collected at 212 sites in the study area. For 29 of the 212 sites, samples were collected at two different times because sibling participants were enrolled in different years, resulting in 241 soil and indoor dust samples for analyses. The distribution of soil and indoor dust samples by year is shown in Figure 9.

The median soil concentration was 537 μg/g, and ranged from 94-2604 μg/g. Forty of the soil samples (17%) exceeded the range of 40-900 μg/g, considered the normal background range (ATSDR, 2012). The median indoor dust loading was 70.5 $\mu g/m^2$ (Table 11). For 2008-2013 combined, the correlation (95% CI) between log transformed soil and dust Mn was 0.243 (0.121, 0.358) (Figure 10). For individual years, the correlations were r=0.293 (0.066, 0.491) for 2009 (n=72), r=0.019 (-0.269, 0.304) for 2010 (n=47), r=0.217 (-0.015, 0.427) for 2011 (n=72), and r=0.287 (-0.018, 0.543) for 2012 (n=42). For the individual years, only the correlation for 2009 was statistically significant. Among the four years, the Mn emissions were highest for 2011 (126, 821 lb), followed by 2012 (83,924 lb), 2009 (68,845 lb), and 2010 (41,531 lb), suggesting that higher correlations were not related to higher Mn emissions. For 2008 (n=4) and 2013 (n=4) correlations were not assessed due to the small sample sizes.

Table 12 shows the correlations for soil and indoor dust Mn levels with distance from EMI and modeled ambient air Mn levels. Soil Mn concentration was not associated with distance from EMI for any of the years. Indoor dust Mn was negatively associated with distance from EMI in 2011, but was not associated for any other years. For soil Mn, the only statistically significant association with modeled ambient air Mn was the correlation with air Mn averaged over the 12 months prior to the soil sample collection in 2009. Indoor dust was significantly associated with air Mn averaged over the year the sample was collected in 2009 and 2011, and averaged over 3, 6, and 12 months prior to the sample collection in 2011. No other correlations between soil or indoor dust with modeled average ambient air Mn were observed (Table 12).

Discussion

The results of this study show that air dispersion modeling of Mn concentrations in the vicinity of industrial sources can be a viable option in epidemiologic studies of environmental Mn exposures. For the time period of January 2009-October 2010, the association between modeled ambient air Mn and stationary air sampler ambient air Mn was well within acceptable limits based on the three criteria measures used. Modeled air Mn levels were negatively correlated with distance from EMI for all modeled years. Soil and indoor dust Mn were not associated with distance from EMI with the exception of indoor dust for 2011. None of the time periods assessed for associations between ambient air Mn and soil or indoor dust (12, 6, 3, and 1 month prior) appeared to be a more accurate measure than any other.

A concerning result of the study is the estimated size of the population exposed to ambient air Mn exceeding the U.S. EPA guideline of 50 ng/m^3, posing a potential health risk to those living in the area. Based on the models, from 12,000-56,000 individuals were exposed to ambient air Mn levels exceeding 50 ng/m^3 in five of the six years modeled. The exception was

2010, the year with unusually low reported emissions. In four of the modeled years, more than 2000 individuals were exposed to >150 ng/m^3 (Table 9). Further, an estimated 10,000 individuals in the six census blocks immediately surrounding EMI would have been exposed to >50 ng/m^3 for the entire time period with the exception of 2010, if they lived in the area from 2008-2013.

Studies in adults and children have found significant negative associations between air Mn levels similar to those in this study and adverse health outcomes. Lucchini et al. (2014) measured 24-hour personal air Mn in 254 adults aged 65-75 years living near ferromanganese plants. The median (range) air Mn was 21.2 (30.1-103.0) ng/m^3. Air Mn was negatively associated with a test of odor discrimination and identification, Luria Nebraska Psychological battery tests of motor coordination, and tests of clear-thinking ability and spatial planning. For other neurological tests air Mn was not associated with the outcomes. Kim et al. (2011) and Bowler et al. (2012) compared neurological outcomes in adult residents of Marietta with adults in Mount Vernon, Ohio, a town with no industrial Mn exposure. Median (range) modeled air Mn levels for the Marietta group were 160 (40-960) ng/m^3. Marietta residents scored significantly poorer on the Unified Parkinson's Disease Rating Scale (UPDRS) motor and bradykinesia scales, tests of postural sway, Fingertapping Test, and Symptoms Checklist 90-Revised Generalized Anxiety T score. There were no differences between exposure groups on the UPDRS Activities of Daily Living subscale or the Wechsler Adult Intelligence Scale Similarities score. In a study of children aged 7-11 years living in the Molango mining district in Mexico, Torres-Augustin et al. (2013) found that the children scored significantly lower on the Children's Auditory Verbal Learning Test for almost all subscales compared to children of the same age living outside of the exposure area. The median (range) outdoor air Mn was 80 (20-240) ng/m^3 in the exposed group compared to 20 (3-90) ng/m^3 in the unexposed group.

Elevated soil Mn has been associated with adverse health outcomes, and in this study 17% of the homes had soil Mn levels greater than 900 μg/g, the upper limit of what is considered normal. The median (range) level of soil Mn was consistent with levels measured in other studies conducted near ferromanganese plants that were associated with poorer performance on neurological measures. Rentschler et al. (2012) studied 311 children aged 11-14 years and 255 adults aged 63-80 years near ferromanganese plants in Italy, where home soil levels ranged from 160-1730 ppm. In both groups, soil Mn was associated with poorer motor coordination (r_s=-0.130, P<0.05 adults, r_s=-0.200, P<0.001 children), and in children was associated with poorer odor identification (r_s=-0.170, P<0.05). Broberg et al. (2019) studied a larger sample of 642 11-14 year olds near the same ferromanganese plants in Italy, with soil levels of 272-1830 ppm. For girls, there were statistically significant U-shaped associations between soil Mn and Conners-Wells' Adolescent Self-Report Scale (CASS) DSM-IV total (P=0.007) and hyperactivity (P=0.003), and positive linear associations between soil Mn and Conners' Parent Report Scale (CPRS) cognitive problems/inattention (P=0.040) and ADHD Index (P=0.017). For boys, there was a positive linear association between soil Mn and CPRS hyperactivity (P=0.025).

Indoor dust Mn loadings in this study were highly variable, with a median of 70.5 (μg/m^2) and range of 7.8-2206. These values are lower than the median (range) of 314 (1.3-29,600) μg/m^2 measured in 147 homes near an active ferromanganese plant by Lucas et al. (2015), but this may be due to in part to homes being in closer proximity to the Mn source than in the present study. Most of the homes in the Lucas et al. (2015) study were within 5 km of the plant, whereas in the present study only eight homes were within 5 km of EMI. The Lucas et al.

investigators did not study health outcomes but did measure a number of Mn biomarkers in children aged 11-14 years, and determined correlations with indoor dust Mn concentrations (μg/g) as well as loadings. Indoor dust Mn concentrations were significantly associated with hair and fingernail Mn, but not saliva or blood Mn. Indoor dust Mn loadings were not associated with any of the biomarkers. A study by Rodrigues et al. (2018) measured indoor dust deposition rates (μg/m^2/30 days) from four elementary schools with varying distances from a ferromanganese plant. Associations with hair and toenail Mn, and scores on the Child Behavior Checklist (CBCL) were determined in 165 children aged 7-12 years. The dust deposition rates were correlated with hair Mn (r=0.412, P<0.001) and toenail Mn (r=0.503, P<0.001), but were not correlated with CBCL total scores (r=-0.079, P=0.270). Several other studies have found significant associations between indoor dust Mn and biomarkers in adults or children, but whether this would translate into negative effects on health outcomes was not studied (Reis et al., 2015; Zota et al., 2016; Fulk et al., 2017).

The correlations among modeled air, soil, and indoor dust in this study, although small, were consistent with numerous other studies of environmental Mn exposures (Table 1). Correlations in the studies in Table 1 were 0.06-0.22 for air and soil Mn, 0.09-0.34 for air and indoor dust Mn, and 0.08-0.37 for soil and indoor dust Mn. In two studies that measured both indoor dust concentrations and indoor dust loadings, the correlations with air and soil Mn were higher for the dust concentrations than the dust loadings (Lucas et al., 2015; Zota et al., 2016). There are several possible reasons that correlations among the different environmental measures in the present study were not higher. Modeled air Mn concentrations have inherent uncertainties associated with various model inputs that can affect the resulting estimates. In addition, the parent material of soils in the Marietta area is sedimentary rock, which varies in natural Mn concentrations (Carter et al., 2015). Soil Mn concentrations are cumulative and most likely reflect many years of deposition rather than the single year prior to sample collection for which air Mn concentrations were modeled. A number of factors can affect indoor dust Mn levels, including location of the samples, heating, ventilation, and air conditioning systems, overall housekeeping, number of occupants, and secondhand smoke. Finally, soil and dust Mn samples were collected at different times of the year, so seasonal variations in indoor dust composition as well as soil Mn deposition may also be a factor (Lioy et al., 2002; Carter et al., 2015).

There are a number of limitations to the study that require consideration. First, the accuracy of AERMOD modeling is dependent on the quality of emissions data reported by the facility and used as model inputs. At EMI, reported annual emissions of Mn in pounds are estimated based on mass balance equations that incorporate data subject to measurement error. Concentrations of different Mn compounds, as well as particle sizes are not reported. AERMOD models Mn concentrations without regard to particle size, so an assumption made for the study was that the Mn concentration was in the $PM_{2.5}$ fraction (Fulk et al., 2016). The assumption was based on the distances traveled by different particle sizes, with finer particles traveling greater distances from the source (WHO, 2000). The closest receptor to EMI was 2.5 km, and all but eight were greater than 5.0 km from the site. Another limitation of the model is that the operating days and hours for the refinery are provided as total hours per year, so can only be equally distributed across the year in the model. This can have major effects on daily or monthly modeled Mn concentrations, but average annual Mn estimates are less likely to be influenced.

For this study Mn emissions were only modeled for EMI, so modeled air Mn concentrations may be underestimated because other sources in the study area were not taken into account. However, the ATSDR studied health effects of Mn in Marietta in 2009 and concluded that EMI was the largest emitter, and was responsible for the majority of the Mn emissions in the area (ATSDR, 2009). National Emissions Inventory data available for download for the years 2008 and 2011 showed that in 2008, of eight facilities with Mn emissions in Washington Co., Ohio, 99.0% of total emissions were from EMI; in 2011, of ten facilities with Mn emissions, 97% were from EMI (U.S. EPA, n.d.)

A limitation of using modeled ambient air Mn concentrations to estimate individual exposures is that the values may not fully reflect actual personal exposures. Individuals spend varying amounts of time at home, work, school, and other locations, as well as varying amounts of time outdoors, and these variations are not captured with modeling. However, one study (Fulk et al., 2016) compared 48-hour air Mn concentrations modeled with AERMOD to personal air Mn in 19 children aged 7-9 years in Marietta. After removal of one outlier, approximately 42% of the variability in personal air Mn was explained by modeled air Mn concentrations (R^2=0.4196, P=0.004).

In conclusion, this study shows that air dispersion modeling with AERMOD in communities near industrial sources may be a useful method for quantifying environmental air Mn exposures in epidemiological studies. It also shows that during the six-year study period, residents in Marietta and the surrounding communities were exposed to air Mn levels that often times exceeded U.S. EPA guidelines. The total amount of Mn emitted by EMI in 2013, the last year of the study, was 87,471 lb; in 2017, the most recent year available for data on Mn emissions from NEIS, the total amount for EMI was 127,260 lb, suggesting that the excess exposure is continuing to present a health risk to the community.

Table 1. Correlations between Environmental Measures of Mn in the Literature

First author (year), country	Air (μg/m^3)	Soil (μg/g)	Outdoor dust (μg/g)	Outdoor dust load (μg/m^2)	Indoor dust (μg/g)
Callan et al. (2012), Australia					
Indoor dust (μg/g)	-	0.36*	-	-	-
Callan et al. (2013), Australia					
Indoor dust (μg/g)	-	0.34*	-	-	-
Gulson et al. (2014), Australia					
Outdoor dust load (μg/m^2)	-	0.36*	-	-	-
Indoor dust load (μg/m^2)	-	0.04	-	0.08	-
Lucas et al. (2015), Italy					
Soil (μg/g)	0.10*	-	-	-	-
Outdoor dust (μg/g)	0.43*	0.18*	-	-	-
Outdoor dust load (μg/m^2)	0.23*	0.22*	0.68*	-	-
Indoor dust (μg/g)	0.29*	0.15*	0.68*	0.43*	-
Indoor dust load (μg/m^2)	0.09	0.08	0.33*	0.29*	0.60*
Menezes-Filho et al. (2016), Brazil					
Indoor dust load (μg/m^2)	-	-	-	0.43*	-
Zota et al. (2016), USA					
Soil (μg/g)	0.22	-	-	-	-
Indoor dust (μg/g)	0.34*	0.37*	-	-	-
Indoor dust load (μg/m^2)	0.22	0.12	-	-	0.44*
Fulk et al. (2017), USA					
Soil (μg/g)	0.06	-	-	-	-
Indoor dust load (μg/m^2)	0.29	0.27*	-	-	-
Rodrigues et al. (2018), Brazil					
Indoor dust load (μg/m^2)	-	-	-	0.62*	-
Butler et al. (2019), Italy					
Soil (μg/g)	0.13*	-	-	-	-
Outdoor dust (μg/g)	0.34*	0.17*	-	-	-
Indoor dust (μg/g)	0.27*	0.16*	0.65*	-	-

*P<0.05 or lower; values in table are Pearson or Spearman rank correlations.
For Gulson et al. (2014), Menezes-Filho et al. (2016), and Rodrigues et al. (2018), indoor and outdoor dust are measured in (μg/m^2/30 days); for Lucas et al. (2015) and Butler et al. (2019), air is from 24-hour personal air samplers; for Zota et al. (2011) air is indoor $PM_{2.5}$ Mn; for Fulk et al. (2017) air Mn is modeled using AERMOD.

Table 2. Reported Emissions for Eramet Marietta, Inc., 2008

A. Point Source Emissions

Point source ID	Source type	Base elevation (m)	Stack height (m)	Stack diameter (m)	Exit velocity (m/s)	Exit temp (°F)	Emission rate (g/s)	Days operating per year	Annual emissions (lb)
68500812	Vertical stack	194.93	33.53	1.22	13.73	90	0.0492	338	3165
68501412	Horizontal stack	195.21	30.18	3.66	10.56	95	0.7599	365	52833
68501512	Vertical stack	195.11	33.53	3.05	20.47	200	1.4815	302	85108
68501612	Vertical stack	195.04	37.80	2.44	17.11	140	0.4001	346	26365
68501712	Vertical stack	194.93	27.43	0.49	20.72	105	0.0984	338	6330
68502012	Vertical stack	194.93	27.43	1.52	2.86	90	0.0523	338	3363
68502412	Vertical stack	194.93	27.43	1.52	7.54	90	0.0523	338	3363
68503212	Vertical stack	194.93	33.53	1.22	12.11	90	0.0523	338	3363
Total									183890

B. Fugitive Emissions

Fugitive source ID	Source type	Base elevation (m)	Fugitive height (m)	Fugitive length (m)	Fugitive width (m)	Rotation angle (degrees)	Emission rate (g/s)	Days operating per year	Annual emissions (lb)
68502712	Roadways	194.95	0.30	3048.0	3.0	18	1.65×10^{-5}	365	10670
68503112	Storage piles	194.95	4.27	1012.9	659.3	18	1.53×10^{-7}	365	7093
68502612	Furnace casting	195.11	33.53	201.2	83.8	18	1.55×10^{-5}	302	15004
68502512	Furnace casting	195.04	33.53	201.2	53.3	18	1.53×10^{-5}	346	13403
85855212	Furnace casting	194.93	33.53	109.7	53.3	18	1.53×10^{-5}	338	6953
Total									53122

Table 3. Reported Emissions for Eramet Marietta, Inc., 2009

A. Point Source Emissions

Point source ID	Source type	Base elevation (m)	Stack height (m)	Stack diameter (m)	Exit velocity (m/s)	Exit temp (°F)	Emission rate (g/s)	Days operating per year	Annual emissions (lb)
68500812	Vertical stack	194.93	33.53	1.22	13.73	90	0.1274	341	8275
68501712	Vertical stack	194.93	27.43	0.49	20.72	105	0.2549	341	16550
68502012	Vertical stack	194.93	27.43	1.52	2.86	90	0.1354	341	8792
68502412	Vertical stack	194.93	27.43	1.52	7.54	90	0.1354	341	8792
68503212	Vertical stack	194.93	33.53	1.22	12.11	90	0.1354	341	8792
Total									51201

B. Fugitive Emissions

Fugitive source ID	Source type	Base elevation (m)	Fugitive height (m)	Fugitive length (m)	Fugitive width (m)	Rotation angle (degrees)	Emission rate (g/s)	Days operating per year	Annual emissions (lb)
68502712	Roadways	194.95	0.30	3048.0	3.0	18	1.64×10^{-5}	365	10620
68503112	Storage piles	194.95	4.27	1012.9	659.3	18	na	365	na
85855212	Furnace casting	194.93	33.53	109.7	53.3	18	1.85×10^{-5}	341	7024
Total									17644

na, not available

Table 4. Reported Emissions for Eramet Marietta, Inc., 2010

A. Point Source Emissions

Point source ID	Source type	Base elevation (m)	Stack height (m)	Stack diameter (m)	Exit velocity (m/s)	Exit temp (°F)	Emission rate (g/s)	Days operating per year	Annual emissions (lb)
68500812	Vertical stack	194.93	33.53	1.22	13.73	90	0.1302	64	1587
68501512	Vertical stack	195.11	33.53	3.05	20.47	200	0.1682	340	10890
68501612	Vertical stack	195.04	37.80	2.44	17.11	140	0.3431	205	13385
68501712	Vertical stack	194.93	27.43	0.49	20.72	105	0.2604	64	3174
68502012	Vertical stack	194.93	27.43	1.52	2.86	90	0.1383	64	1686
68502412	Vertical stack	194.93	27.43	1.52	7.54	90	0.1383	64	1686
68503212	Vertical stack	194.93	33.53	1.22	12.11	90	0.1383	64	1686
Total									34094

B. Fugitive Emissions

Fugitive source ID	Source type	Base elevation (m)	Fugitive height (m)	Fugitive length (m)	Fugitive width (m)	Rotation angle (degrees)	Emission rate (g/s)	Days operating per year	Annual emissions (lb)
68502712	Roadways	194.95	0.30	3048.0	3.0	18	na	365	na
68503112	Storage piles	194.95	4.27	1012.9	659.3	18	1.53×10^{-7}	365	7093
68502612	Furnace casting	195.11	33.53	201.2	83.8	18	1.01×10^{-7}	340	110
68502512	Furnace casting	195.04	33.53	201.2	53.3	18	3.23×10^{-7}	205	135
85855212	Furnace casting	194.93	33.53	109.7	53.3	18	1.39×10^{-6}	64	99
Total									7437

na, not available

Table 5. Reported Emissions for Eramet Marietta, Inc., 2011

A. Point Source Emissions

Point source ID	Source type	Base elevation (m)	Stack height (m)	Stack diameter (m)	Exit velocity (m/s)	Exit temp (°F)	Emission rate (g/s)	Days operating per year	Annual emissions (lb)
68500912	Vertical stack	195.11	9.14	1.46	20.47	50	0.4666	365	3142
68501312	Vertical stack	195.04	9.14	1.22	17.11	50	0.3841	365	143
68501412	Horizontal stack	195.21	30.18	3.66	10.56	95	0.3712	360	25423
68501512	Vertical stack	195.09	33.53	3.05	16.22	200	0.0452	337	29977
68501612	Vertical stack	194.98	37.80	2.44	17.85	140	0.0021	351	25700
68501912	Vertical stack	195.05	9.14	1.22	18.43	50	0.0021	365	143
Total									84528

B. Fugitive Emissions

Fugitive source ID	Source type	Base elevation (m)	Fugitive height (m)	Fugitive length (m)	Fugitive width (m)	Rotation angle (degrees)	Emission rate (g/s)	Days operating per year	Annual emissions (lb)
68502712	Roadways	194.95	0.30	3048.0	3.0	18	1.64×10^{-5}	365	10620
68503112	Storage piles	194.95	4.27	1012.9	659.3	18	7.54×10^{-8}	365	7093
68502612	Furnace casting	195.11	33.53	201.2	83.8	18	1.12×10^{-5}	337	12180
68502512	Furnace casting	195.04	33.53	201.2	53.3	18	1.71×10^{-5}	354	12400
Total									42293

Table 6. Reported Emissions for Eramet Marietta, Inc., 2012

A. Point Source Emissions

Point source ID	Source type	Base elevation (m)	Stack height (m)	Stack diameter (m)	Exit velocity (m/s)	Exit temp (°F)	Emission rate (g/s)	Days operating per year	Annual emissions (lb)
68500912	Vertical stack	195.11	9.14	1.46	20.47	50	0.0541	237	1109
68501312	Vertical stack	195.04	9.14	1.22	17.11	50	0.2294	237	50
68501412	Horizontal stack	195.21	30.18	3.66	10.56	95	0.3741	357	25423
68501512	Vertical stack	195.09	33.53	3.05	16.22	200	0.0246	355	3663
68501612	Vertical stack	194.98	37.80	2.44	17.85	140	0.0011	342	14929
68501912	Vertical stack	195.05	9.14	1.22	18.43	50	0.0011	237	50
Total									45224

B. Fugitive Emissions

Fugitive source ID	Source type	Base elevation (m)	Fugitive height (m)	Fugitive length (m)	Fugitive width (m)	Rotation angle (degrees)	Emission rate (g/s)	Days operating per year	Annual emissions (lb)
68502712	Roadways	194.95	0.30	3048.0	3.0	18	1.64×10^{-5}	365	10620
68503112	Storage piles	194.95	4.27	1012.9	659.3	18	7.54×10^{-8}	365	3500
68502612	Furnace casting	195.11	33.53	201.2	83.8	18	1.07×10^{-5}	355	12180
68502512	Furnace casting	195.04	33.53	201.2	53.3	18	1.78×10^{-5}	342	12400
Total									38700

Table 7. Reported Emissions for Eramet Marietta, Inc., 2013

A. Point Source Emissions

Point source ID	Source type	Base elevation (m)	Stack height (m)	Stack diameter (m)	Exit velocity (m/s)	Exit temp (°F)	Emission rate (g/s)	Days operating per year	Annual emissions (lb)
68501412	Horizontal stack	195.21	30.18	3.66	10.56	95	0.2663	365	18513
68501512	Vertical stack	195.11	33.53	3.05	20.47	200	0.0871	365	6059
68501612	Vertical stack	195.04	37.80	2.44	17.11	140	0.3192	365	22196
Total									46768

B. Fugitive Emissions

Fugitive source ID	Source type	Base elevation (m)	Fugitive height (m)	Fugitive length (m)	Fugitive width (m)	Rotation angle (degrees)	Emission rate (g/s)	Days operating per year	Annual emissions (lb)
68502712	Roadways	194.95	0.30	3048.0	3.0	18	1.80×10^{-5}	365	11620
68503112	Storage piles	194.95	4.27	1012.9	659.3	18	1.16×10^{-7}	365	3500
68502612	Furnace casting	195.11	33.53	201.2	83.8	18	1.04×10^{-5}	365	12180
68502512	Furnace casting	195.04	33.53	201.2	53.3	18	1.80×10^{-5}	365	13403
Total									40703

Table 8. Descriptive Statistics for Modeled Average Ambient Air Mn (ng/m^3) for 105 Census Blocks within the Modeled Area

Year	Mean (SD)	Median (IQR)	Range
2008	61.35 (58.46)	43.09 (38.17)	16.88-431.06
2009	28.43 (22.83)	23.20 (16.07)	4.58-162.65
2010	9.98 (10.71)	6.33 (8.07)	2.60-88.00
2011	44.35 (50.93)	27.06 (34.98)	9.97-377.43
2012	29.85 (31.48)	20.53 (22.36)	5.89-248.03
2013	26.77 (31.44)	17.10 (20.75)	6.85-241.32

Table 9. Number of Census Blocks and Estimated Population Sizes with Modeled Average Annual Air Mn Greater than 50 ng/m^3 and Greater than 150 ng/m^3 by Year

	Annual air Mn >50 ng/m^3			Annual air Mn >150 ng/m^3		
Year	Number of census blocks n (%)	Estimated total population	Estimated population aged 0-14 yrs	Number of census blocks n (%)	Estimated total population	Estimated population aged 0-14 yrs
2008	43 (41.0)	56,210	9,370	6 (5.7)	8,715	1,535
2009	9 (8.6)	13,209	2,311	1 (1.0)	984	167
2010	1 (1.0)	959	179	0 (0.0)	0	0
2011	28 (26.7)	36,911	6,219	3 (2.9)	4,655	835
2012	12 (11.4)	15,868	2,743	2 (1.9)	2,374	391
2013	10 (9.5)	12,711	2,193	2 (1.9)	2,374	391

The number of census blocks is based on the location of the census block centroids. The percent is the percent of all 105 census blocks in the modeled area. The estimated population is the sum of the populations of the census blocks listed for each year, based on 2010 U.S. Census data.

Table 10. Modeled and Measured Ambient Air Mn (ng/m^3) at the Stationary Air Sampler Site for January 2009-October 2010

Time Period	n	Mean (SD)	Median (IQR)	Range	FB	NMSE	FAC2
Jan 2009-Oct 2010							
Measured	22	18.61 (8.37)	18.41 (7.61)	7.50-38.00	-0.099	0.202	0.955
Modeled	22	20.56 (7.80)	20.27 (12.14)	7.61-37.53			
Jan 2009-Dec 2009							
Measured	12	15.81 (6.92)	18.41 (11.60)	7.50-28.31	-0.220	0.225	0.917
Modeled	12	19.73 (8.85)	18.86 (10.04)	7.61-37.53			
Jan 2010-Oct 2010							
Measured	10	21.98 (9.05)	17.58 (13.07)	14.46-38.0	0.020	0.182	1.000
Modeled	10	21.55 (6.67)	23.25 (11.21)	8.85-30.07			

FB, fractional bias; NMSE, normalized mean square error; FAC2, fraction of modeled concentrations within a factor of 2 of the observed concentrations.

Table 11. Descriptive Statistics for Soil, Indoor Dust, Modeled Ambient Air Mn, and Distance from EMI for 241 Modeled Sites

Variable	Mean (SD)	Median (IQR)	Range
Soil Mn (μg/g)	615.72 (341.15)	537.00 (378.00)	93.90-2604.00
Dust Mn (μg/m^2)	121.60 (198.18)	70.50 (86.47)	7.82-2206.60
Annual air Mn (ng/m^3)	35.06 (33.52)	26.49 (29.13)	2.64-251.42
Air Mn previous 1 m (ng/m^3)	32.54 (31.39)	23.84 (29.72)	0.48-226.15
Air Mn previous 3 m (ng/m^3)	32.75 (33.19)	25.00 (26.64)	0.84-325.82
Air Mn previous 6 m (ng/m^3)	32.26 (29.14)	25.59 (26.77)	1.22-261.14
Air Mn previous 12 m (ng/m^3)	31.59 (24.58)	24.61 (26.51)	4.44-228.51
Distance from EMI (km)	11.73 (5.03)	10.92 (6.37)	2.52-30.51

Annual air Mn (ng/m^3) is the modeled ambient air Mn averaged over the calendar year that the soil and indoor dust sample was collected.

Table 12. Pearson Correlations for Soil and Indoor Dust with Distance from EMI and Modeled Ambient Air Mn by Year

	Distance from EMI	Ln annual air Mn	Ln air Mn previous 1 m	Ln air Mn previous 3 m	Ln air Mn previous 6 m	Ln air Mn previous 12 m
Ln soil Mn						
2009 (n=72)	-0.228 (-0.436, 0.003)	0.207 (-0.025, 0.418)	0.046 (-0.187, 0.274)	0.012 (-0.220, 0.242)	0.090 (-0.144, 0.315)	0.296 (0.070, 0.493)
2010 (n=47)	-0.111 (-0.385, 0.181)	0.180 (-0.113, 0.444)	-0.091 (-0.368, 0.201)	-0.047 (-0.329, 0.243)	0.098 (-0.194, 0.374)	0.169 (-0.124, 0.435)
2011 (n=72)	0.099 (-0.135, 0.323)	0.008 (-0.224, 0.239)	0.060 (-0.174, 0.287)	0.008 (-0.224, 0.239)	0.023 (-0.209, 0.253)	0.069 (-0.165, 0.295)
2012 (n=42)	-0.150 (-0.434, 0.161)	0.035 (-0.271, 0.335)	0.109 (-0.201, 0.399)	0.128 (-0.183, 0.415)	0.128 (-0.183, 0.415)	0.018 (-0.287, 0.320)
Ln dust Mn						
2009 (n=72)	-0.121 (-0.343, 0.113)	0.246 (0.016, 0.451)	0.057 (-0.177, 0.284)	0.105 (-0.129, 0.328)	0.050 (-0.183, 0.278)	0.147 (-0.087, 0.366)
2010 (n=47)	-0.088 (-0.365, 0.204)	0.087 (-0.205, 0.365)	0.192 (-0.100, 0.454)	0.135 (-0.158, 0.406)	-0.102 (-0.378, 0.190)	-0.112 (-0.386, 0.180)
2011 (n=72)	-0.243 (-0.449, -0.013)	0.283 (0.055, 0.483)	0.215 (-0.017, 0.425)	0.234 (0.003, 0.441)	0.266 (0.037, 0.468)	0.288 (0.061, 0.487)
2012 (n=42)	-0.096 (-0.388, 0.214)	0.104 (-0.206, 0.395)	0.051 (-0.256, 0.349)	0.130 (-0.181, 0.417)	0.149 (-0.162, 0.433)	0.076 (-0.233, 0.453)

Values in parentheses are 95% confidence intervals. m, month. Ln annual air Mn is the ambient air Mn modeled over the calendar year that the soil and dust sample was collected. Correlations were not determined for 2008 (n=4) and 2013 (n=4) due to the small sample sizes.

Figure 1. Modeled Exposure Area and 2010 Census Block Populations

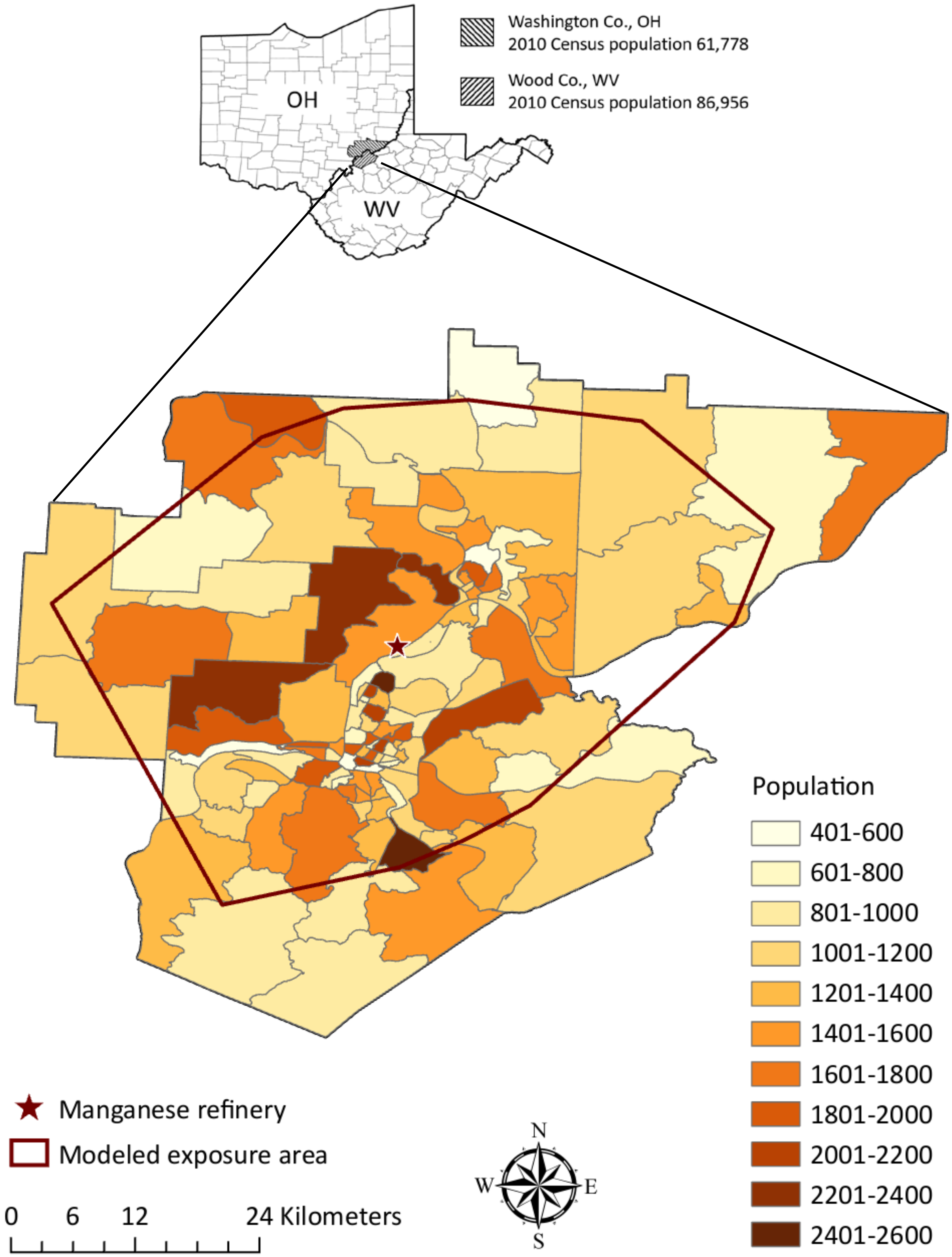


Figure 2. Modeled Average Ambient Air Mn by Year and 2010 Census Block Populations

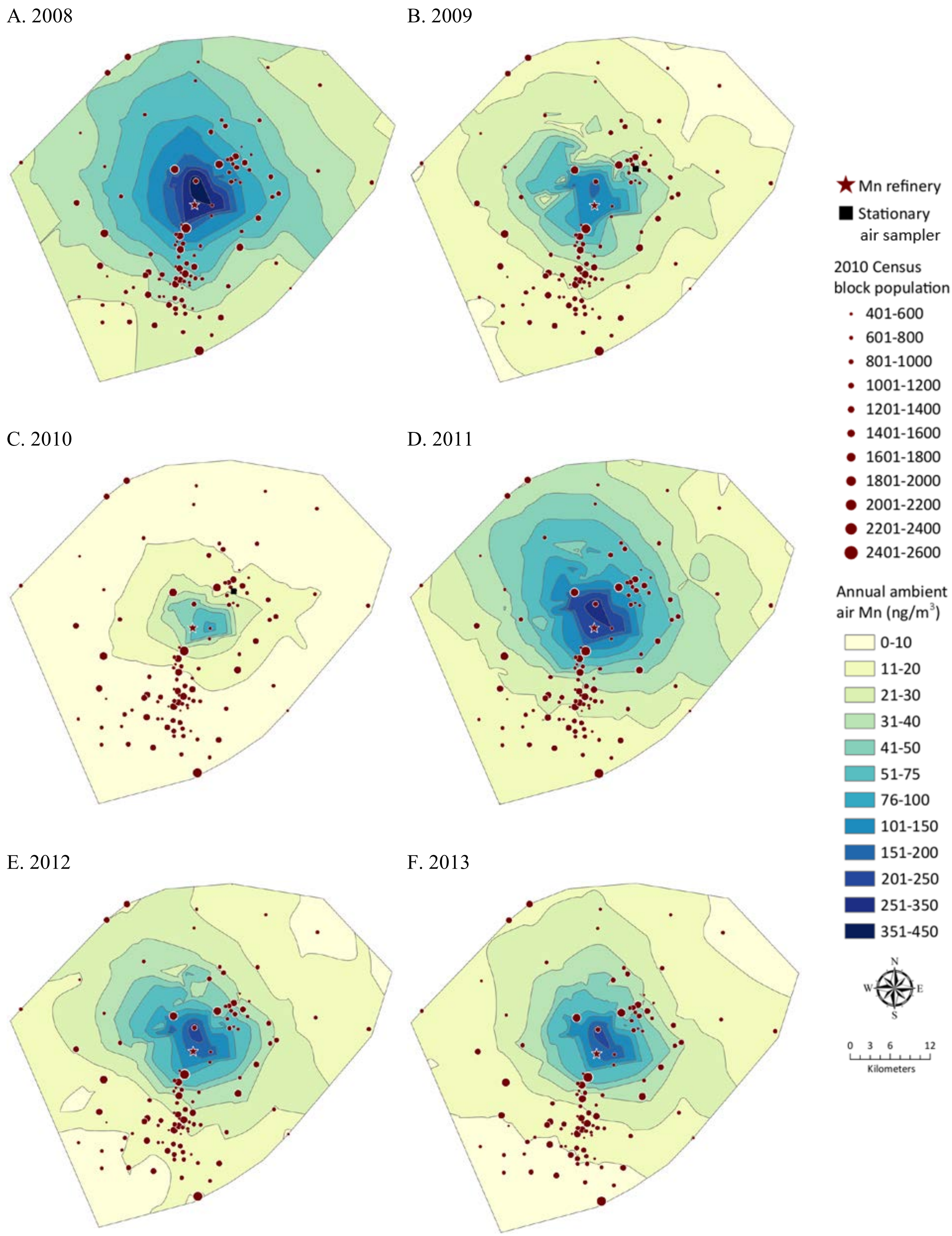


Figure 3. Wind Roses for AERMET Meteorological Preprocessing Surface Files

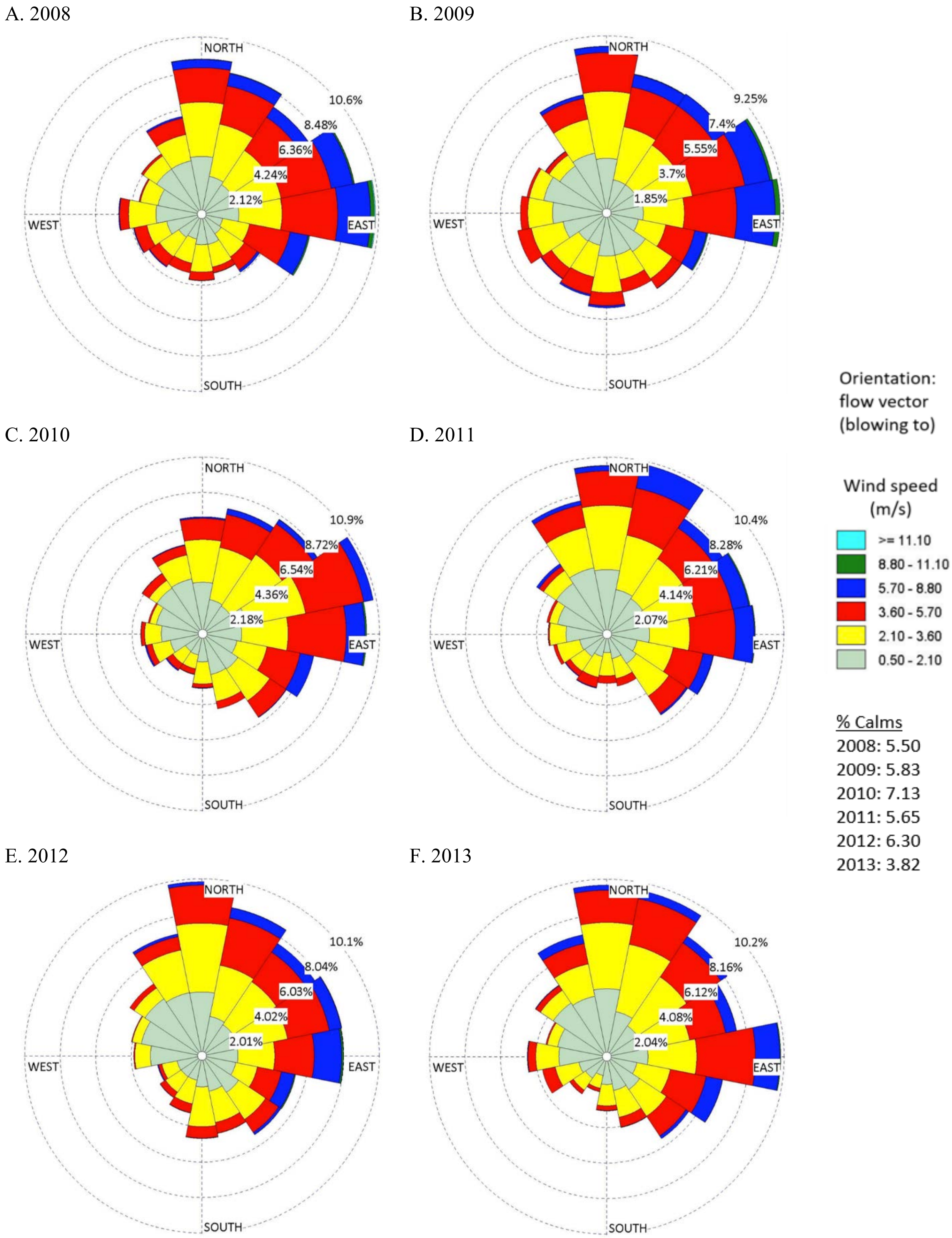
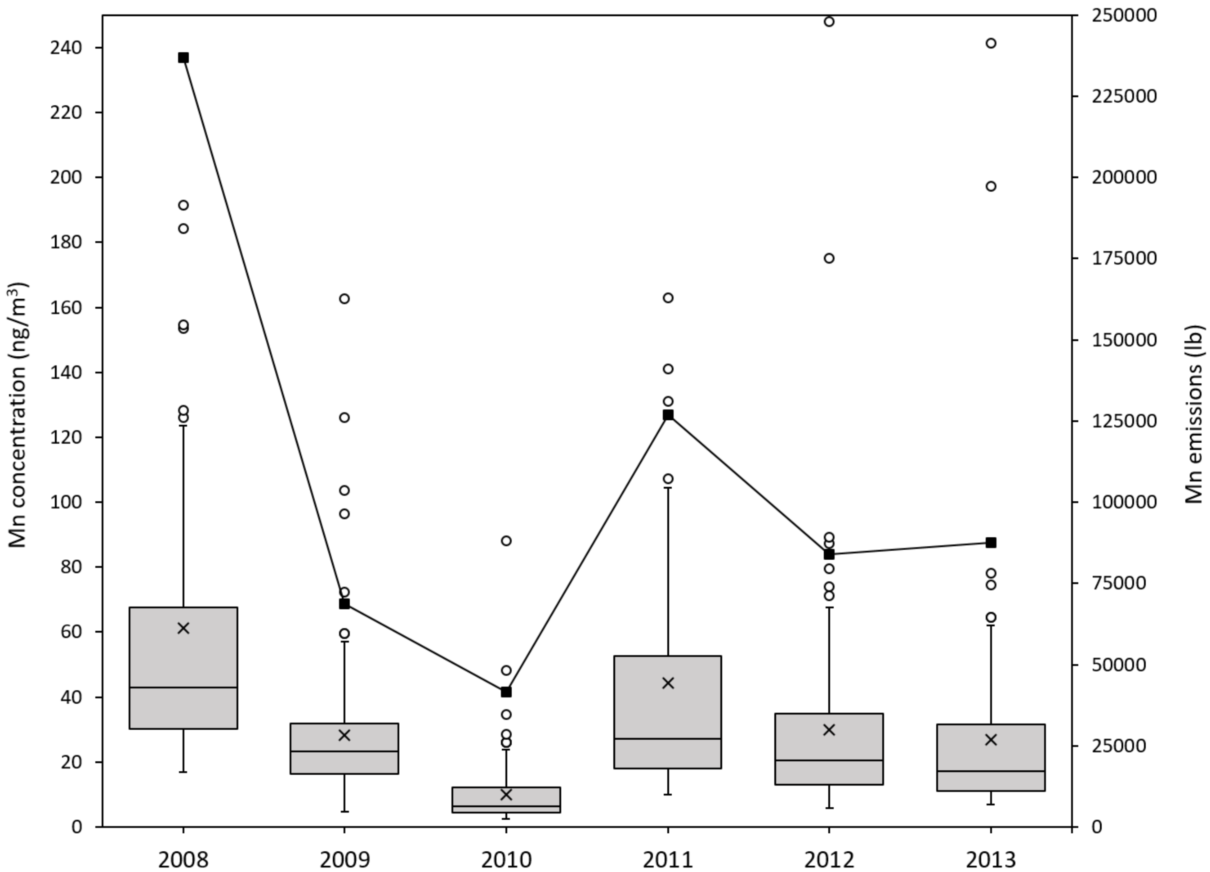


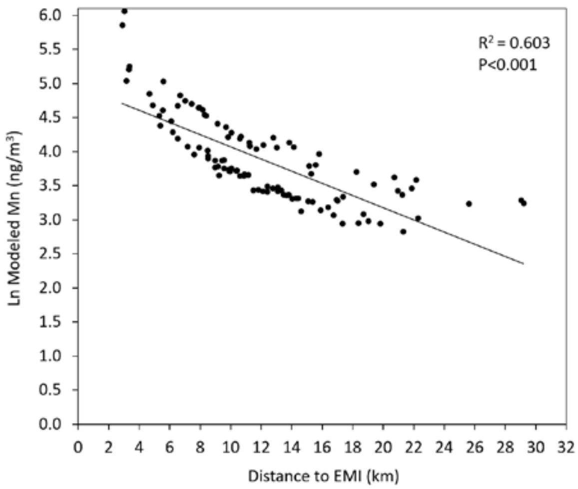
Figure 4. Annual EMI Mn Emissions and Annual Ambient Air Mn Concentrations Averaged Across All 105 Census Blocks in Modeled Area by Year



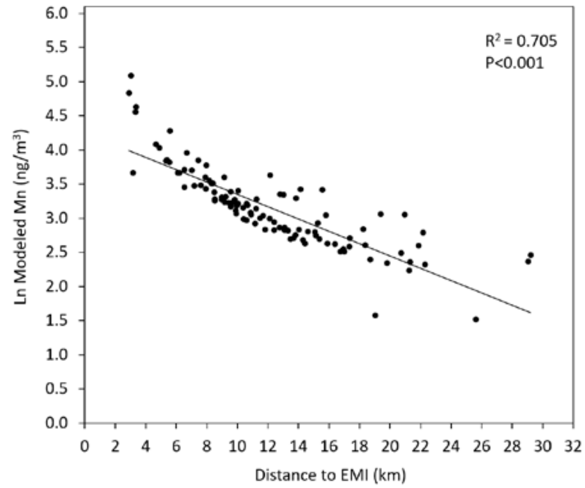
Mn emissions by year are represented by the closed black squares; horizontal line = median; x = mean; upper error bars represent quartile 3 + 1.5*interquartile range, lower error bars represent the minimum values, and open circles represent outliers. Four outliers are not shown on the graph: for 2008, values of 350.66 and 431.06 ng/m^3 are not shown; for 2011, values of 300.28 and 377.43 ng/m^3 are not shown.

Figure 5. Associations between Modeled Ambient Air Mn at Census Block Centroids and Distance from EMI by Year

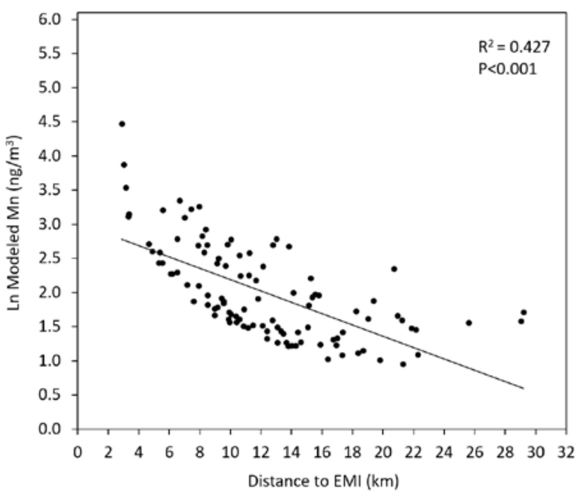
A. 2008



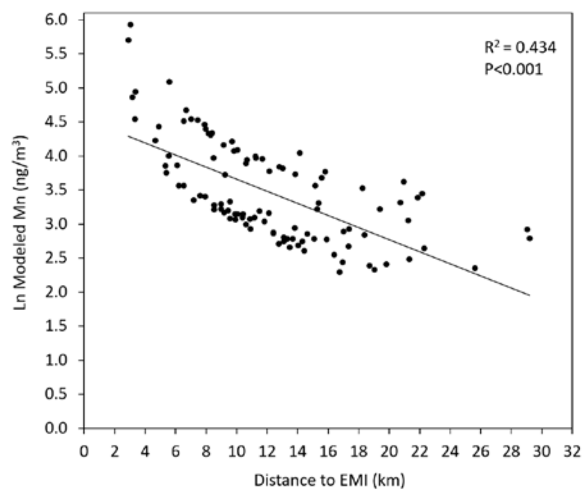
B. 2009



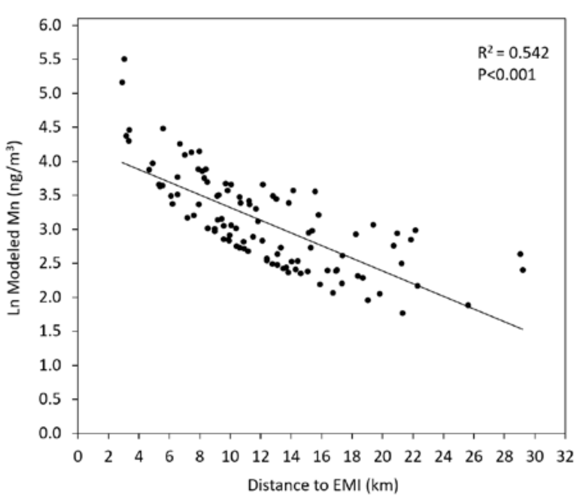
C. 2010



D. 2011



E. 2012



F. 2013

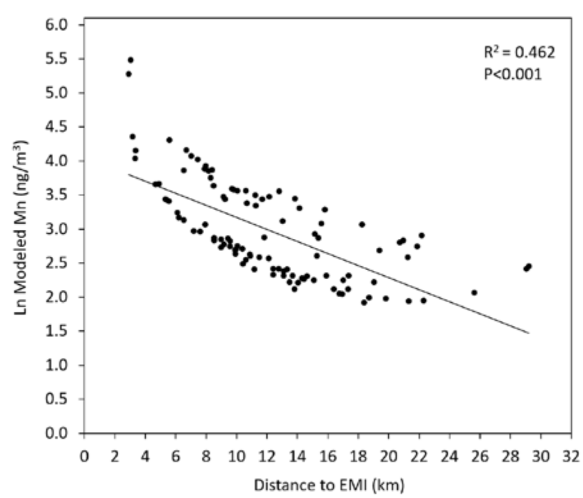


Figure 6. Modeled and Measured Ambient Air Mn at the Stationary Air Sampler Site for January 2009-Oct 2010

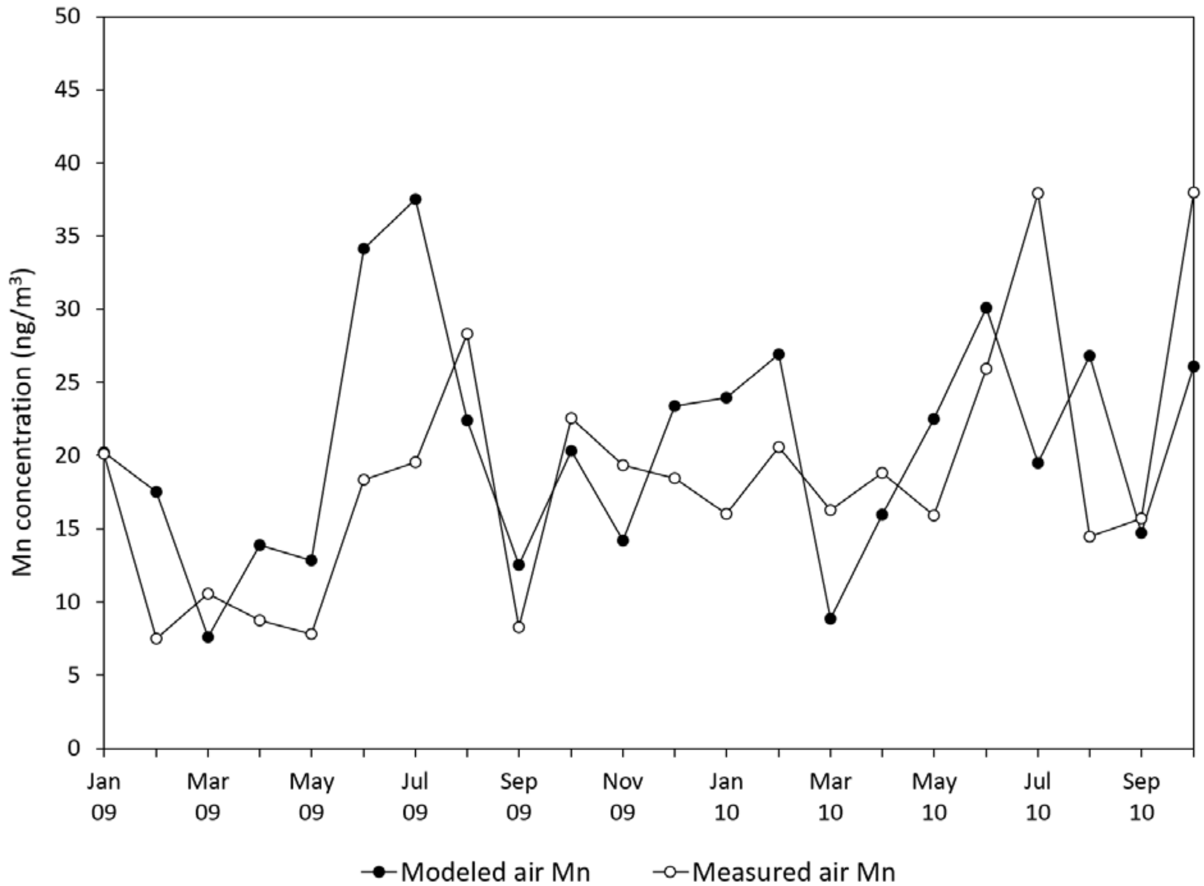
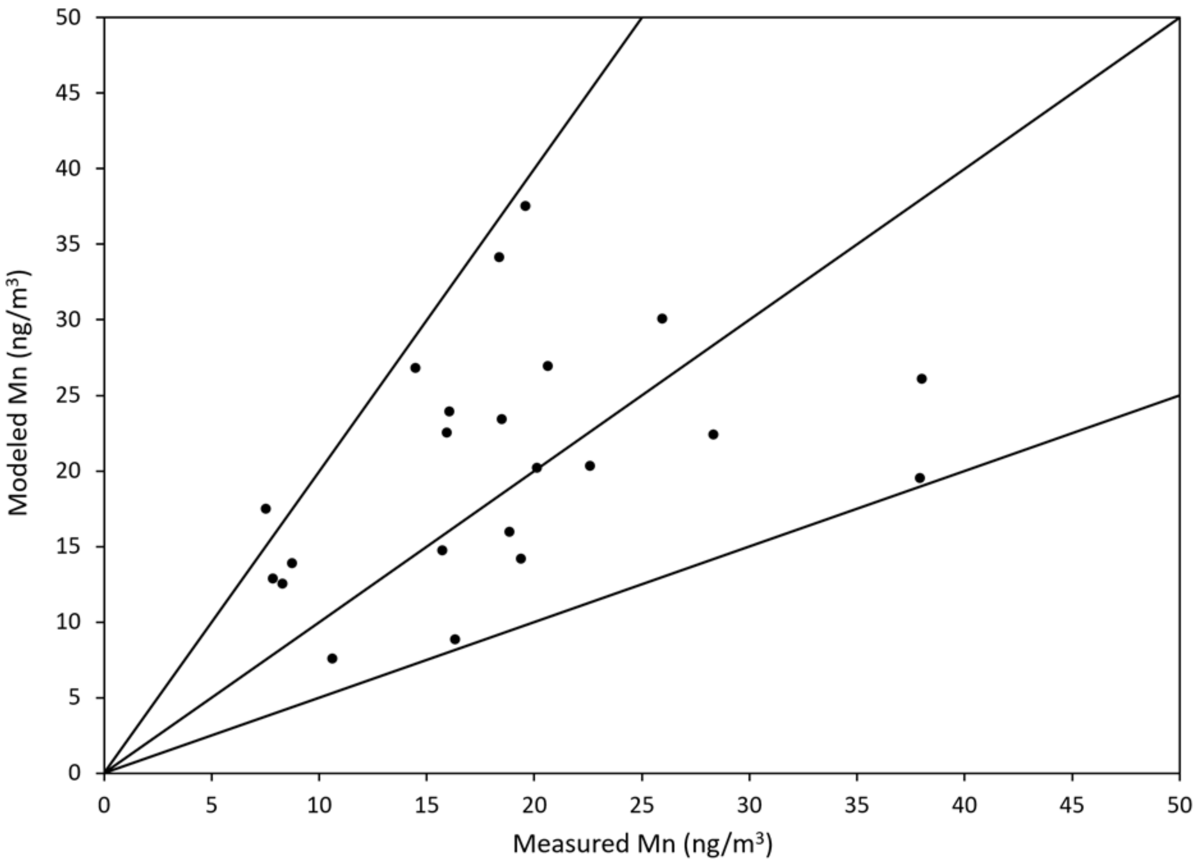


Figure 7. Scatter Plot of Modeled Versus Measured Ambient Air Mn at the Stationary Air Sampler Site



The center diagonal line represents a 1:1 relationship between modeled and measured Mn; the upper line represents 2:1 modeled to measured; the lower line represents 1:2 modeled to measured Mn concentrations.

Figure 8. Quantile-Quantile Plot of Modeled Versus Measured Mn Concentrations at the Stationary Air Sampler Site

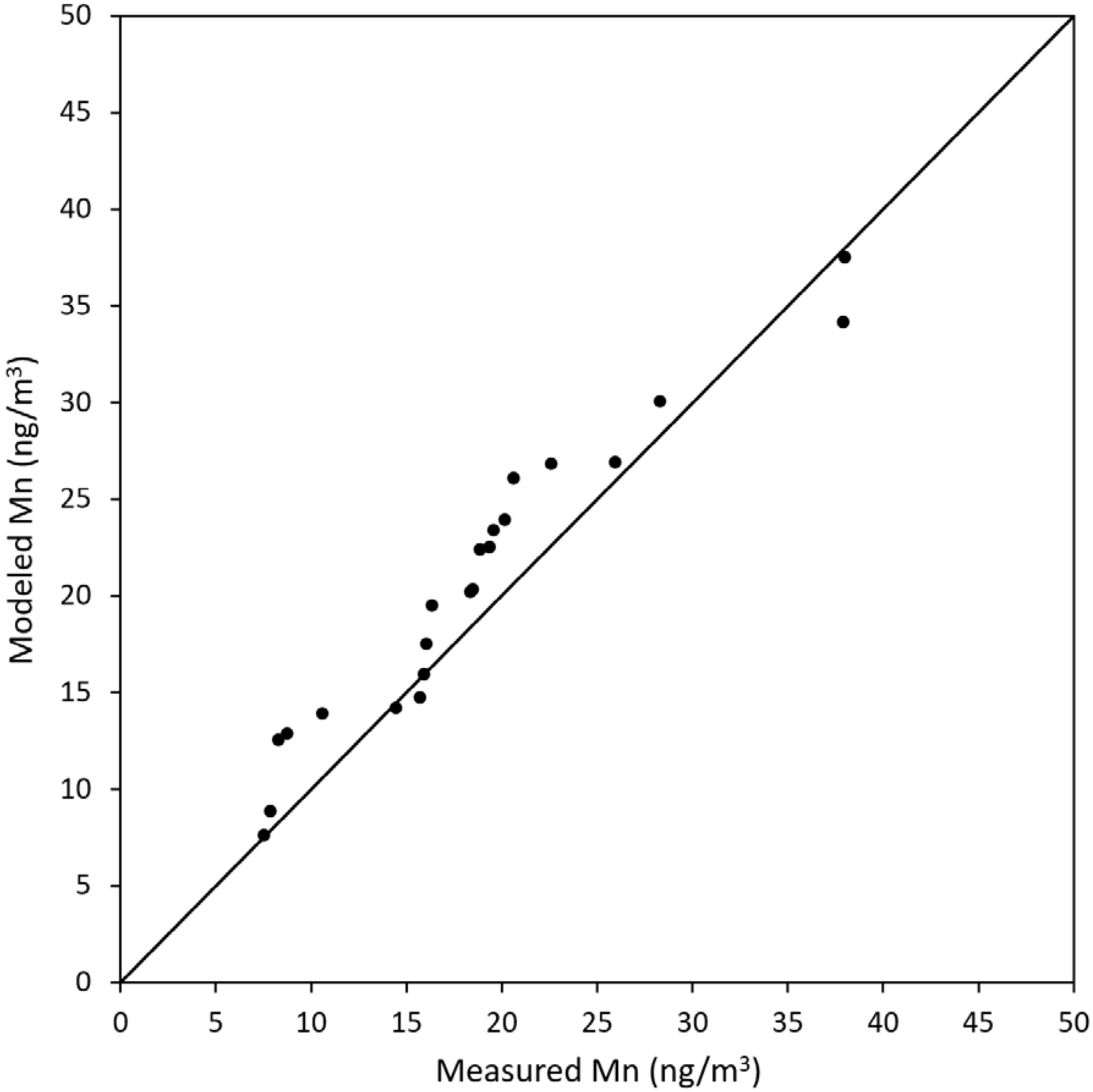


Figure 9. Modeled Average Ambient Air Mn and Soil/Indoor Dust Sample Sites by Year

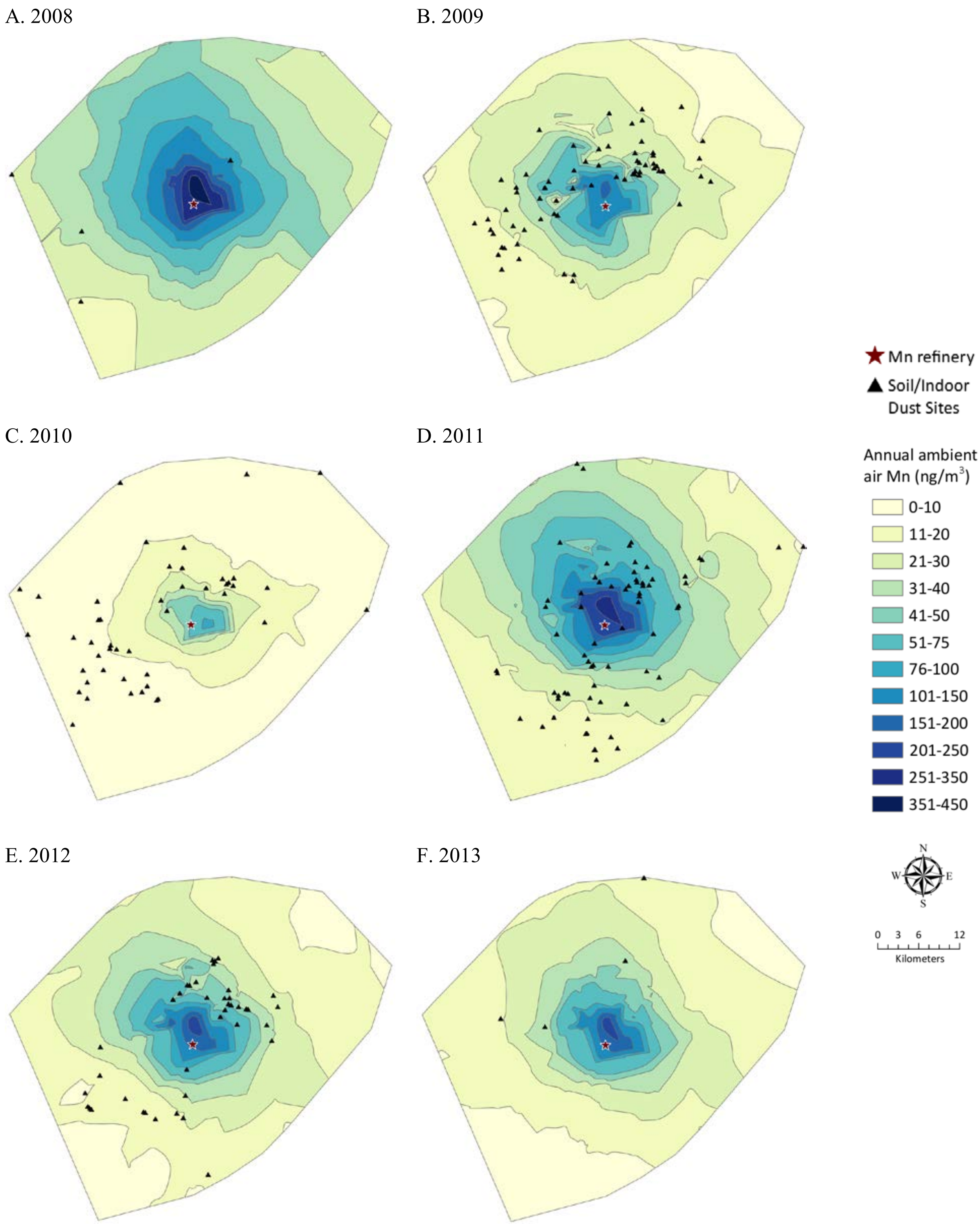
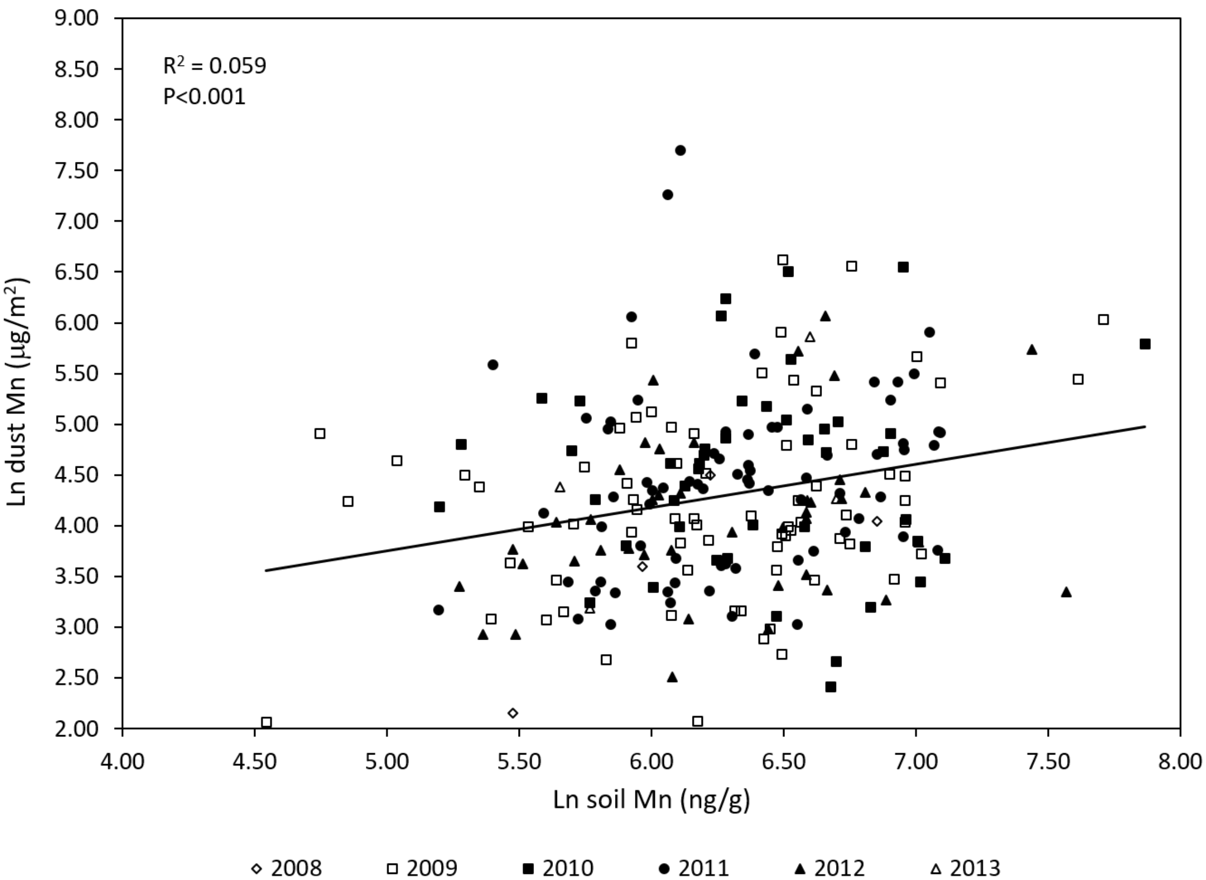


Figure 10. Scatter Plot of Modeled Ln Soil Mn and Ln Dust Mn by Year



Chapter 3: Structural Equation Modeling of Pathways of Environmental Manganese Exposures to Biomarkers of Manganese in 7-9 Year Old Children

Abstract

Introduction: Manganese (Mn) is an essential trace element necessary for normal growth and development that can be toxic in excess amounts. High environmental levels of Mn can occur due to emissions released from industrial sources. Airborne particles can settle in soil and dust and may lead to increased biomarker Mn levels, but exposure pathways have not been delineated.

Objectives: To determine pathways of exposure from environmental Mn sources to biomarker levels in children exposed to excess Mn in the environment.

Methods: Data from the Communities Actively Researching Exposure Study (CARES), conducted from 2008-2013 in Marietta, Ohio area were used for the study. CARES was designed to investigate neurological effects of Mn exposure in 7-9 year old children. Residential soil, indoor dust, blood, hair, and toenail Mn samples were obtained from CARES. Emissions from the Mn refinery in Marietta were used to model average annual ambient air Mn exposures with the air dispersion model AERMOD. Structural equation modeling (SEM) was used to model pathways of exposure from modeled ambient air, soil, and indoor dust Mn to biomarkers, accounting for time spent at home and school, time spent outside, heating, ventilation, and air conditioning in the home (HVAC score), and parent education.

Results: Significant pathways from soil Mn to indoor dust Mn, and from indoor dust Mn to hair Mn and toenail Mn were identified. A significant indirect path was observed from soil Mn to both hair and toenail Mn through indoor dust Mn. In models that excluded data from 2010, a

year with atypically low Mn emissions, ambient air Mn was a significant contributor to indoor dust Mn. Significant indirect pathways from ambient air Mn to hair and toenail Mn through indoor dust Mn were also observed.

Conclusions: Ambient air Mn, soil Mn, and indoor dust Mn are important exposure pathways leading to increased levels of hair and toenail Mn in children. Efforts to reduce indoor dust levels may help in reducing biomarker levels of Mn.

Introduction

Manganese (Mn) is an essential trace element that occurs naturally in the environment, but can be toxic to humans at high levels. Occupational exposure to Mn is known to have adverse neurologic effects, and even chronic, low-level exposures can be detrimental (Racette, 2014; O'Neal and Zheng, 2015). Environmental exposure to Mn through air, soil, dust, or water has been associated with tremor, impaired motor and cognitive functions, postural instability, and lower intelligence in both adults and children (Zoni and Lucchini, 2013; Rodriguez-Barranco et al., 2013; Rugless et al., 2014; Vollet et al., 2016; Haynes et al., 2018). Children are thought to be more susceptible than adults to environmental Mn exposure through ingestion or inhalation due to higher intestinal absorption rates, lower excretion rates, a higher ratio of inhaled air volume per body weight, and higher inhalation rates per body mass unit (Zota et al., 2011; Lucchini et al., 2017).

Excess environmental Mn levels in communities can result from emissions from nearby ferromanganese alloy plants, mining activities, and other industrial activities. Airborne particles then settle in soils, water, outdoor dust, and indoor dust, resulting in multiple sources of exposure for community residents. Numerous studies have examined associations between environmental Mn exposures and biomarkers, with varying results. For blood Mn, Solis-Vivanco et al. (2009) found a correlation of 0.22 between air Mn and blood Mn in a study of 288 adults living in a mining district in Mexico. Air Mn was measured with stationary monitors placed in the communities, and exposure levels were assigned to participants based on the closest monitor to their home. The positive correlation between air and blood Mn was statistically significant. Lucas et al. (2015) collected 24-hour personal PM_{10} air samples in the homes of residents living near ferromanganese alloy plants in Italy. In 376 children aged 11-14 years, air Mn was significantly negatively correlated with blood Mn (*r*=-0.16). Three additional studies using overlapping subjects with Lucas et al. (2015) determined correlations between soil Mn and blood Mn, and found no significant correlations in the children (Rentschler et al., 2012; Wahlberg et al., 2018; Butler et al., 2019). Correlations between environmental Mn and hair Mn were stronger than for blood, but still varied widely among the studies. Three studies of 7-9 year old children in Marietta, Ohio exposed to Mn from a Mn refinery (Haynes et al., 2010; Haynes et al., 2012; Fulk et al.; 2017) found no association between hair Mn and air Mn measured with personal monitors. Fulk et al., 2017 also determined associations with soil and indoor dust loadings. The correlation between hair Mn and soil Mn was 0.22 ($P>0.05$), and was 0.39 ($P<0.05$) for hair Mn and indoor dust Mn. Lucas et al. (2015) found that soil Mn was not associated with hair Mn, but both outdoor and indoor dust were associated with hair Mn. Lucas et al. (2015) and Butler et al. (2019) also determined associations between fingernail and saliva Mn and environmental exposures. The correlations for fingernail Mn with air, soil, outdoor dust and indoor dust were similar between the studies, and ranged from 0.14-0.17 for air Mn, 0.20-0.22 for soil Mn, 0.27-0.36 for outdoor dust Mn, and 0.23-0.24 for indoor dust Mn.

Although many studies have determined associations between sources of environmental Mn and biomarkers, only one has modeled pathways of exposure incorporating ambient air, soil, dust, and hair Mn using structural equation modeling (SEM). Fulk et al. (2017) determined pathways of exposure in 88 children aged 7-9 years, and found that the pathways from ambient air Mn and soil Mn to indoor dust Mn were statistically significant. Indoor dust Mn, in turn, was a significant predictor of hair Mn.

The purpose of this study is to determine pathways of exposure from ambient air, soil, and indoor dust Mn to blood, hair and toenail Mn in children exposed to excess environmental

Mn from a nearby Mn refinery, using a structural equation modeling approach. The setting is Marietta, Ohio and the surrounding communities, where residents are exposed to emissions from Eramet Marietta, Inc. (EMI), the largest Mn refinery in the U.S. Average annual ambient air concentrations of Mn will be modeled using EMI emissions data and the regulatory air dispersion model AERMOD.

Methods

Study Design and Participants

This study uses data collected from participants enrolled from October 2008 through February 2013 in the Marietta Communities Actively Researching Exposure Study (CARES). CARES is a cross-sectional, community-based participatory research study. The study was designed to answer the community's primary research question, "Does Mn effect the neurocognitive development of our children?" Families were eligible to participate if they had a child 7-9 years of age that had lived in the Marietta or Cambridge, Ohio area since birth, and their mother lived in the area since the 16^{th} week of pregnancy with the child. Cambridge, Ohio was selected as a comparison community. Recruitment was through letters sent home with children through their schools, newspaper ads, radio ads, and flyers. CARES was approved by the Institutional Review Board of the University of Cincinnati.

All enrolled parents/legal guardians signed informed consents, and children signed assents to participate in the study (Haynes et al., 2012, Rugless et al., 2014). Data from the CARES study visit that were used in this dissertation included home address, school attended, child's age, gender, and race, parent education, information about heating, ventilation, and air conditioning in the home, and the amount of time the child spent outside, all obtained by parent/legal guardian report. Residential soil and indoor dust samples, and children's blood, hair, and toenail samples for Mn levels were collected by trained CARES personnel. All 323 children enrolled in CARES from the Marietta area were included in the study. Cambridge area participants were excluded since the community did not have a point source for Mn. The addresses for participants' homes and schools were geocoded using ArcGIS Pro Desktop (Environmental Systems Research Institute, Inc.) for determination of distances from EMI and for conversion to receptor sites for modeling average ambient air Mn exposure at each home and school.

Modeling of Ambient Air Mn Exposures

The American Meteorological Society/Environmental Protection Agency Regulatory Model (AERMOD) was used to model average annual ambient air concentrations of Mn at the homes and schools of the study participants. AERMOD is the U.S. EPA's preferred model for steady-state Gaussian plume dispersion modeling of pollutant concentrations up to 50 km from a source (U.S. EPA, 2004). AERMOD uses data on wind, hourly surface weather, upper air, land cover, elevation, and emissions from the source to model average pollutant concentrations at specified receptor locations. The model has three components: a meteorological preprocessor (AERMET), a terrain preprocessor (AERMAP), and the dispersion model. Annual Mn emissions data reported by EMI for the years 2008-2013 were obtained from the U.S. EPA through a Freedom of Information Act request. The emissions data included point source and fugitive annual Mn emissions in lb, stack locations, heights, diameters, and exit temperatures, fugitive heights, lengths, widths, and rotation angles, emission rates, and days operating per year (EPA-HQ-2019-004104, FOIA online, n.d.). Automated Surface Observing System (ASOS) 1- and 5-minute wind data files for the closest weather station, Parkersburg/Wilson station at Mid-Ohio

Valley Regional Airport, were downloaded from the National Climatic Data Center, Automated Surface Observing System (ASOS) website (National Centers for Environmental Information, n.d.-a). Integrated Surface Hourly (ISH) weather observations data files for the Parkersburg/Wilson station were downloaded from the National Climatic Data Center, Quick Links website (National Centers for Environmental Information, n.d.-b). Upper air data files for the closest upper air station, the Wilmington, OH, U.S. Upper Air Station were downloaded from the NOAA/ESRL Radiosonde Database website (National Oceanic and Atmospheric Administration, n.d.). National Land Cover Data (NLCD) files were obtained from the Multi-Resolution Land Characteristics Consortium (MLRC). NLCD 2006 and 2011 Land Cover CONUS data files were downloaded from the MLRC website (MLRC, n.d.) for use in the 2008-2010 models (NLCD 2006) and 2011-2013 models (NLCD 2011). A digital terrain elevation data file for the AERMAP preprocessor was directly accessed from within the AERMOD software from webGIS.com, a geographical information systems resource website.

AERMOD modeling was performed using AERMOD View version 9.7.0 from Lakes Environmental Software, Waterloo, Ontario. For each year, AERMOD modeling was conducted with a modeling domain of 32 km from the emissions source, default regulatory options, and output concentrations set to ng/m^3. Average annual ambient air concentrations of Mn were modeled for all participants' homes and schools. For each participant, a weighted air Mn concentration was determined using 70% of the concentration at home combined with 30% of the concentration at the school attended by the participant, to account for the estimated time spent at each location. The weights were based on daily activity logs for 38 children participating in a previous CARES study of personal Mn exposure (Haynes et al., 2012; Rugless et al., 2014). For home-schooled participants, the concentration at the home was weighted 100%.

Collection and Analysis of Residential Soil and Indoor Dust Samples

Soil and indoor dust samples were collected from 241 homes representing 258 study participants. Samples were collected by trained CARES study personnel following U.S. Department of Housing and Urban Development (HUD) protocols and guidelines (HUD, 1995). Details of the sampling methodology for soil and dust have been described in detail in Fulk et al. (2017) and are briefly described here. Half-inch soil samples were collected from six separate locations at each residence with a stainless steel spatula and transferred to a sealable plastic bag. The CARES personnel wore plastic gloves and decontaminated the spatula with wet wipes between sample collection to avoid contamination. The samples collected at the six sites were combined into a single sample for analysis. Indoor dust samples were collected from three areas of the residence on the same day as soil sample collection. The dust samples were collected using a wet wipe method in 1-square-foot sample areas that were cleared of foreign objects and marked off with tape or a plexiglass template. A two-pass approach was used to collect the dust samples. First, a wet wipe was passed from right to left in an S-shaped pattern across the marked off surface; next, the wet wipe was folded in half and a second pass was made in an S-shaped pattern from top to bottom, using the side of the wipe opposite of the side used in the first pass. The wet wipe was folded and placed in a centrifuge tube labeled with sample identification number, room location, surface type (vinyl, bare wood, carpet, painted, concrete, or other), and surface condition (good, fair, poor). The majority of dust samples were collected from vinyl or bare wood surfaces (80%), 11% were from carpeted surfaces, and 9% were from other surface types. Where surface conditions were specified, 79% were considered good, 20% fair, and 1% poor.

Soil and indoor dust samples were analyzed for Mn at Research Triangle Institute (Research Triangle Park, NC) using a method modified from USEPA Method 3050B Acid Digestion of Sediments, Sludge's, and Soils. (U.S. EPA, 1996). A description of the analysis process is provided in Fulk et al. (2017), and briefly summarized here. One gram of soil or one dust wipe collected from a residence was placed in an extraction tube with five ml of equal parts water and nitric acid (HNO_3), 0.05 ml of 1000 ppm of gold (Au), and 2 ml of hydrochloric acid (HCl). Samples were placed in a 48-well SCP Science DigiPREP digestion block for 1 h at 95° C to allow a 15-20 minute reflux of the sample, and then removed and cooled to room temperature. After cooling, 2.5 ml of concentrated HNO_3 was added, samples were returned to the digestion block for 2 h at 95 °C, and once again removed and cooled to room temperature. One ml of deionized water and 1.5 ml of hydrogen peroxide (H_2O_2) were then added and the samples were returned to the digestion block for a final 2 h at 95 °C. Samples were diluted to 50 ml with deionized water, capped, shaken and centrifuged at 1700 rpm for 20 min. For dust wipe samples, all samples from a single residence were combined prior to final dilution to create a single sample from a residence. Soil and dust samples were analyzed with Inductively Coupled Plasma Mass Spectrometry (ICP-MS) using a Thermo X-Series II ICP-MS instrument (Thermo Fisher Scientific, Inc., Waltham, MA). The limit of detection (LOD) for Mn in dust was 5.0 μg, and for soil Mn the LOD was 25 μg/g. Indoor dust Mn loadings in $\mu g/m^2$ were obtained by dividing the number of grams of Mn by the number of 1-square-foot sample wipes to obtain $\mu g/ft^2$, and then converting to $\mu g/m^2$.

Collection and Analysis of Blood, Hair, and Toenail Samples for Mn

Details of the methods for collection and analysis of blood samples have been previously published (Haynes et al., 2012; Rugless et al., 2014). Briefly, blood samples were collected from the antecubital vein by trained phlebotomists using 3-mL purple top (K2EDTA) vacutainer tubes certified by the analyzing laboratory for trace element analysis. Immediately after collection the tubes were gently inverted 5-10 times and placed covered on an orbital mixer for 15 min. The whole blood specimens were refrigerated at 5 °C until shipped monthly to the Laboratory of Inorganic and Nuclear Chemistry at the New York State Department of Health's Wadsworth Center in Albany, New York for analysis. Whole blood samples were analyzed with Graphite Furnace Atomic Absorption Spectroscopy (GFAAS) using a Perkin Elmer Model 5100ZL Atomic Absorption Spectrometer with Zeeman background correction and equipped with an AS-70 auto-sampler (PerkinElmer Life & Analytical Sciences, Shelton, CT). Blood samples were first diluted 1 to 9 in a solution of 0.015% $Mg(NO_3)_2$, $6H_2O$, 0.1% Triton® X-100, and 0.2% HNO_3. Twenty µL of the solution was placed in a graphite tube by an auto-sampler for analysis. The method detection limit (MDL) for blood Mn was 1.5 µg/L.

Hair samples were collected from CARES participants and analyzed for Mn as described by Haynes et al. (2012), Rugless et al. (2014), and Fulk et al. (2017). Approximately, twenty strands of hair were collected from the occipital region of the scalp with ceramic scissors, placed in clean white envelopes, and stored at room temperature. The samples were then shipped to the Channing Trace Metals Laboratory, Harvard School of Public Health (Boston, MA) for analysis. Hair samples were cleaned in 10 mL of 1% Triton X-100 solution for 15 min, followed by repeated rinsing with distilled deionized water. Samples were dried at 70 °C for 24 h, then acid digested with 1 mL concentrated nitric acid for 24 h and diluted to 5 mL with deionized water. Acid-digested samples were analyzed by ICP-MS using an Elan DRC II instrument (PerkinElmer, Inc., Waltham, MA). Each sample was analyzed five times and averaged for the final hair Mn level. The MDL for hair Mn was <2 ng/g.

Participants' toenail clippings were collected by the parent/guardian using regular nail clippers and placed in labeled envelopes for analysis. CARES personnel obtained the samples and shipped them to the Microbiology and Environmental Toxicology Department at the University of California Santa Cruz for analysis of toenail Mn. Nail samples were placed in a 2 mL microfuge tube and cleaned for 10 min by sonication in 0.5% triton with 5 Milli-Q water rinses. Next, samples were sonicated in 1 N trace metal grade nitric acid for 10 min, with 1 N nitric acid rinse and 5 Milli-Q water rinses. Nails were dried at 65 °C for 48 h, and then transferred to a 7 mL polypropylene tube and weighed. Concentrated quartz distilled nitric acid was added (0.5 mL), and samples were heated at 80 °C for 6 h. When the nails were completely digested, 3 mL Milli-Q water was added. A 600 μL sample was transferred to a 1 mL microfuge tube for analysis, with 50 μL of internal standard containing 250 ppb Rh and Ti added. Samples were analyzed on an Element XR ICP-MS for Mn-55 at medium resolution (Thermo Fisher Scientific, Inc., Waltham, MA). Methane was added to the carrier gas to minimize ArCl formation. The MDL for toenail Mn was <0.03 ng/mL.

Demographic Variables

<u>CARES Parent/Guardian Questionnaire</u>

A questionnaire was administered to the parent/guardian of each CARES participant to obtain demographic and other information about the participant including date of birth, school attended name and location, and the amount of time the child played outside during the school year and summer. Other variables from the questionnaire that are used in this study are parent/guardian education level, and information about heating, ventilation, and air conditioning in the home. The participant's age was calculated from the date of enrollment and date of birth.

Time-weighted Distance from EMI

Time-weighted distance (TWD) was calculated based on the distances from EMI of the child's home and school, and an estimate of time spent at home and school of 70% and 30% respectively. The time spent at each location was estimated from daily activity logs for 38 children participating in a previous CARES study of personal Mn exposure (Haynes et al., 2012; Rugless et al., 2014). Distances from homes and schools to EMI were determined using ArcGIS Pro Desktop. Home and school addresses were first geocoded to obtain global positioning system coordinates in decimal degrees, which were then used to calculate distances in meters. Meters were converted to kilometers (km) for all further analyses. TWD was then calculated as:

*TWD = (0.70*distance of home)+(0.30*distance of school)*

For home-schooled participants, the TWD was determined using only the distance from the home to EMI.

Hours/week Spent Outside

Time spent outside was estimated from 4 questions asked at the initial study visit: "On a typical day during the school year, how many hours does your child spend outdoors, a) on a week day, and b) on a weekend?", and "On a typical day during the summer, how many hours does your child spend outdoors, a) on a week day, and b) on a weekend?" The school year and summer were assigned weights of 0.75 and 0.25 respectively to reflect calendar dates of September 1 - May 31 and June 1 - August 31. Average time spent outside in hours per week (hrs/wk) over a one-year period was then calculated using:

*Hrs/wk during school year =(5*hrs/day school week day)+(2*hrs/day school weekend);*
*Hrs/wk during summer = (5*hrs/day summer week day)+(2*hrs/day summer weekend);*

Average hrs/wk spent outside during a one-year period =
*[(0.75*hrs/wk during school year) + (0.25* hrs/wk during summer)]*

Heating, Ventilation, and Air Conditioning (HVAC) Score

Information collected from CARES participants on heating and air conditioning sources in the home was combined into a heating, ventilation, and air conditioning (HVAC) score following the method developed by Fulk et al. (2017). The HVAC score ranged from 0-8 points based on the primary and secondary heating sources, air conditioning sources, air filtration and frequency of filter changes, and air purification systems. Two points were assigned if the primary heating source was an electric, gas, or heating oil furnace, and one point was assigned if any of these were a secondary heating source. For cooling the home, central air conditioning or individual air conditioning units were assigned two points. For both the primary heating and primary cooling systems, points were assigned based on the presence and frequency of changing of air filters. One point was assigned if a filter was changed once per month, 0.75 points if changed once every three months, 0.50 points for once every six months, and 0.25 points for once per year. Finally, one point was assigned if an air purifier was present in the home. The higher the HVAC score on the 0-8 scale, the greater the air filtration in the home.

Barratt Total Education Score

The total education score from the Barratt Simplified Measure of Social Status (BSMSS) (Barratt, 2012) was used as a surrogate measure of socioeconomic status. The education score was based on the highest education levels of the primary caregiver, their parents, and spouse. For each member the points assigned were: less than 7th grade = 3, 9th grade = 6, 10th-11th grade = 9, high school graduate = 12, partial college = 15, college education = 18, and graduate degree = 21. The parent's scores were averaged and combined with the average score of the primary caregiver and spouse to create a final composite score ranging from 3-21, with higher scores indicating higher education. For primary caregivers with only one parent, or who were unmarried, the scores for the single parent and/or the primary caregiver alone were averaged for the final score.

Data Analyses

Descriptive statistics included frequency (percent) for categorical variables and mean (SD), median (IQR), and range for continuous variables. The modeled average ambient air Mn concentrations, soil Mn concentrations, and indoor dust Mn loadings for participants enrolled in each year were compared with Kruskal-Wallis tests, followed by paired comparisons with Mann-Whitney U tests if the Kruskal-Wallis test was statistically significant. The P values for the paired tests were adjusted for multiple comparisons with Bonferroni corrections. Continuous variables were assessed for normality with Shapiro-Wilk tests. For non-normal data, variables were natural log transformed and the transformed data were used in correlation analysis and SEM. Some participants were missing data for one or more of the following variables: soil Mn, dust Mn, blood Mn, hair Mn, and toenail Mn. Since these variables were included in the SEM, participants were divided into those with vs. without data and were compared on all variables used in the study. Chi-square or Fisher's exact tests were used to compare categorical variables, and Mann-Whitney U tests were used for continuous variables. Pearson correlations were used to determine associations between the log transformed study variables.

The initial hypothesized SEM model included five exogenous variables and three endogenous variables. The exogenous variables were modeled average annual ambient air Mn, HVAC score, hours/week spent outside, parent education, and child gender. The endogenous variables were soil Mn, indoor dust Mn, and either blood Mn, hair Mn, or toenail Mn. The pathways included a direct path from ambient air Mn to the biomarker as well as indirect paths through soil and dust Mn, direct and indirect paths from soil Mn to the biomarker, and a direct path from indoor dust Mn to the biomarker. Hours/week spent outside was hypothesized to have a direct positive path to the biomarker. HVAC score were hypothesized to have a negative direct path to the biomarker and a negative indirect path through indoor dust Mn. Parent education was included in the model as a proxy for socioeconomic status, with a negative direct path to the biomarker, and an indirect path through indoor dust Mn. The indirect pathway was considered plausible because socioeconomic status has been shown to be a factor in accumulation of trace metals, including Mn, in house dust (Chattopadhyay et al., 2003; Salem Ali Albar et al., 2020). Child gender was included to control for a difference between male and female participants in the proportion missing data for hair Mn. The complete hypothesized model is shown in Figure 3.

All SEM models were analyzed with Mplus version 8.2 (Muthen & Muthen). Full information maximum likelihood estimation was used because missing data were assumed to be missing at random or missing completely at random. A cluster variable was added to the models to account for the lack of independence between sibling participants. The output from the SEM analyses included unstandardized and standardized direct and indirect path coefficients with standard errors, t statistics and P values for standardized coefficients, R^2 values for the endogenous variables, standardized residuals for covariances, and model fit statistics. The standardized residuals for covariances (z scores) were considered significantly different from zero if they exceeded ±1.960. For all three biomarker models, the coefficients for pathways that did not include the biomarker, and the R^2 values for soil Mn and indoor dust Mn differed slightly, primarily due to differences in sample sizes between the models.

For each model, the model fit statistics reported were the chi-square test of model fit, the root mean square error of approximation (RMSEA), comparative fit index (CFI), Tucker-Lewis index (TLI, also called the non-normed fit index), and the standardized root mean square residual (SRMR). For the chi-square test, the null hypothesis is that the model fits the data, so P values greater than 0.05 indicate a good fitting model. The RMSEA is an estimate of the lack of fit of a model compared to a saturated model. It ranges from 0 to 1.0, with smaller values indicating better fit. Values less than 0.05 are considered indicative of a good fit (Kline, 2016). The CFI is an incremental measure of fit that ranges from 0 to 1.0, with higher values indicating better fit. The value of the CFI represents the model fit as the amount (in percent) of improvement in model fit for the final model compared to the null or baseline model. Values greater than 0.95 indicate good fit. The TLI is similar to the CFI but controls for the degrees of freedom. The TLI can exceed 1.0; values greater than 0.95 are considered an indication of good fit (Kline, 2016). The SRMR is the standardized difference between the sample variances and covariances and the estimated population variances and covariances. It ranges from 0 to 1.0, with values less than 0.08 indicating good fit (Tabachnick and Fidell, 2013). The modification indices in Mplus were evaluated for determining whether addition of other specific pathways among the variables would improve model fit.

For all correlation analyses and SEM, the analyses were conducted using all 323 participants enrolled in CARES for the years 2008-2013. In 2010, emissions from EMI were lower than all other years because of reduced operating hours for two of the three submerged electric arc furnaces at the refinery, and a complete shutdown of the third furnace due to a malfunction. Modeled ambient air Mn concentrations for participants enrolled in 2010 (n=58) were significantly lower than the concentrations for all other years. Therefore, the correlation analyses and SEM that were conducted using all participants were repeated excluding participants enrolled in 2010.

Results

Characteristics of Study Participants

Three hundred twenty-three CARES participants were included in the study. Of these, 159 (49.2%) were female, 313 (96.9%) were White, 6 (1.9%) were Black/African American, and 4 (1.2%) were other race. For 186 (57.6%) participants, they were the only child from a family enrolled in the study. There were 61 sibling pairs enrolled (122 participants, 37.8% of total sample), and five sets of three siblings (15 participants, 4.6% of total sample). Six participants (1.9%) were enrolled in 2008, 88 (27.2%) in 2009, 58 (17.9%) in 2010, 95 (29.4%) in 2011, 69 (21.4%) in 2012, and 7 (2.2%) in 2013. Descriptive statistics for study participants are shown in Table 1. The mean (SD) age was 8.37 (0.92) years, and the mean (SD) hours/week spent outside was 25.64 (9.87). Blood Mn ranged from 5.0-18.8 μg/L, hair Mn from 54-7379 ng/g, and toenail Mn from 45-9663 ng/g. Eleven (4.2%) of the 262 participants with blood Mn levels had values above the normal range of 4-15 μg/L defined by the Agency for Toxic Substances and Disease Registry (ATSDR, 2012). Parent education score ranged from 8.00-21.00, and HVAC scores ranged from 0.50-8.00.

All participants' homes and schools were within 32 km of EMI. About 40% of the 323 participants lived within 10 km of EMI, 52% from 10-20 km, and 8% >20 km from EMI. The median distance was 11.3 km, range 2.5-30.5 km. The median (IQR) time-weighted distance from EMI, which incorporates distance from home and school using a 70%-30% ratio, was 11.1 km, and ranged from 3.5-28.9 km. The participants resided in 18 cities/towns in Washington Co.

and 6 cities/towns in Wood Co. The largest number (39.3%) lived in Marietta, OH. Figure 1 shows a map of the study area and locations of the major cities relative to EMI.

Modeled Annual Ambient Air, Soil, and Indoor Dust Mn Levels

The modeled ambient air Mn exposure, determined from the exposure at home and at school using a 70%-30% ratio, ranged from 2.8-256.1 ng/m^3 (Table 1). Of the 323 participants, 78 (24.1%) had ambient air Mn levels greater than 50 ng/m^3, the reference concentration for chronic exposure to air Mn (U.S. EPA, 2002). Seven participants (2.2%) were exposed to ambient air Mn concentrations greater than 150 ng/m^3, the guideline value recommended by the World Health Organization (WHO, 2000). The modeled ambient air Mn concentrations and locations of all homes and schools by year are shown in the contour maps in Figure 2A-F. Ambient air Mn concentrations varied widely by year across the study area, reflecting the different Mn emissions totals for the years. At EMI, emissions were highest in 2008, then production was reduced in 2009 and 2010 due to a reduction in demand for Mn alloys (2009) and a permanent furnace shutdown in 2010 (Corathers, 2011; Corathers, 2012). Production was resumed at full capacity in 2011-2013 with two of three furnaces, resulting in increased emissions and modeled ambient air concentrations relative to 2009-2010.

Table 2 shows the EMI emissions and modeled average ambient air Mn concentrations for participants for each year of the study. The median (IQR) air Mn concentrations ranged from 6.8 (10.2) ng/m^3 in 2010 to 48.6 (57.9) ng/m^3 in 2011. The median air Mn concentration for participants in 2010 was significantly lower than the medians for all other years. No other years' median air Mn concentrations were significantly different from each other.

For the 258 participants with residential soil and indoor dust Mn levels, the median soil Mn level was 535.5 μg/g, and the levels ranged from 93.9-2604 (Table 1). For 44 participants (17.1%), soil Mn levels exceeded 900 μg/g, the upper limit of the normal background range set by the ATSDR (ATSDR, 2012). Indoor dust Mn loadings had a median of 70.9 $\mu g/m^2$, and ranged from 7.8-2206 $\mu g/m^2$ (Table 1). There were no differences in soil Mn concentrations or indoor dust Mn loadings between the study years.

Analyses of Missing Data for Variables Included in the SEM Models

A number of CARES participants were missing data on one or more of the endogenous variables included in the SEM models; 20.1% were missing soil and indoor dust Mn, 18.9% were missing blood Mn, 3.7% were missing hair Mn, and 15.5% were missing toenail Mn. Biomarkers were missing because sample collection was attempted but a sample was not obtainable from some participants, or samples were collected but were not of sufficient weight to analyze. Soil and indoor dust samples were missing because they were not collected from some of the participant homes. The median (IQR) distance from EMI for the residences with soil and dust samples was 11.02 (6.37) km, and for residences with no soil and dust samples the median (IQR) was 11.66 (8.44) km. These distances were not significantly different (Mann-Whitney U test, P=0.084). For SEM exogenous variables, three participants were missing parent education, two were missing hours/week spent outside, and one was missing both hours/week spent outside and HVAC score.

Tables 3-6 show the results of univariate analyses for demographic and other variables, comparing participants with non-missing data vs. missing data for soil and indoor dust Mn, blood Mn, hair Mn, and toenail Mn. There were no statistically significant differences between participants with soil and indoor dust measures compared to those missing soil and indoor dust measures on any of the variables, although four P values were between 0.05 and 0.10 (Table 3). Participants with blood Mn levels had significantly higher HVAC scores compared to participants missing blood Mn levels (P=0.038); no other comparisons were statistically significant (Table 4). Only 12 participants were missing data for hair Mn, but 11 of the 12 (91.7%) were boys, a significantly higher proportion than of the participants with non-missing data (49.2%, P=0.004). Participants missing hair Mn also spent more hours/week outside (P=0.021), and had higher toenail Mn levels (P=0.025) (Table 5). There were no differences between participants with vs. without toenail Mn levels on any variables analyzed (Table 6).

Correlations between Continuous Study Variables

Table 7 shows the Pearson correlation coefficients for the continuous study variables. All variables in the table were natural log transformed except for parent education and HVAC score. For the biomarkers, blood Mn was not correlated with any other variables. Hair Mn was correlated with parent education, toenail Mn, soil Mn, and indoor dust Mn. Toenail Mn was correlated with hours/week spent outside, soil Mn and indoor dust Mn. Soil Mn and indoor dust Mn were correlated, and indoor dust Mn was correlated with ambient air Mn, but soil Mn and ambient air Mn were not correlated. There was a strong negative correlation between ambient air Mn and time-weighted distance from EMI (r=-0.742, P<0.001).

The correlations for the subset of data that excluded 2010 participants are shown in Table 8. Most of the correlations were of similar magnitudes to those found for the entire sample, with a few exceptions. The correlation between ambient air Mn and toenail Mn was statistically significant, and the correlation between ambient air Mn and indoor dust Mn increased from 0.138 (P<0.05) to 0.276 (P<0.01).

SEM Results for Blood Mn

The standardized coefficients for the modeled pathways to blood Mn are shown in Table 9 and Figure 4A. The SEM included 305 of the 323 participants, and 241 clusters. Six participants were excluded because they were missing data for at least one exogenous variable. An additional 12 participants were excluded because they were missing data for all three endogenous variables (soil Mn, indoor dust Mn, and blood Mn). All model fit statistics were within acceptable limits (Table 15). No path coefficients to blood Mn were statistically significant in the model. The path coefficients from soil Mn to indoor dust Mn (0.268, $P<0.001$), and from HVAC score to indoor dust Mn (-0.135, $P=0.013$) were statistically significant. The path from parent education to indoor dust was also statistically significant (-0.144, $P=0.045$). Ambient air Mn was not a significant exogenous variable leading to blood Mn either directly or indirectly through soil Mn or indoor dust Mn. The R^2 values for the endogenous variables were 0.005 ($P=0.581$) for soil Mn, 0.127 ($P=0.001$) for indoor dust Mn, and 0.027 ($P=0.202$) for blood Mn. The standardized residuals for covariances were all within ±1.96, ranging from -0.827 to 1.672. The most extreme value of 1.672 was between hours/week spent outside and soil Mn. Although the theoretical pathways from soil Mn to indoor dust Mn, and HVAC score to indoor dust Mn were supported by the model results, none of the hypothesized pathways to blood Mn were supported.

For the model that excluded 2010 participants (Table 10, Figure 4B), the most significant difference between the model and the one with all participants was the pathway from ambient air Mn to indoor dust Mn, with a path coefficient of 0.254 ($P<0.001$). The path from ambient air Mn to soil Mn was also improved, from 0.069 to 0.126, although it was not statistically significant ($P=0.079$). In this model, HVAC score and parent education were not significant paths to indoor dust Mn. The R^2 values for the endogenous variables were 0.016 (P=0.380) for soil Mn, 0.184 (P<0.001) for indoor dust Mn, and 0.037 (P=0.161) for blood Mn. The standardized residuals for covariances were all within ±1.96, ranging from -1.197 to 1.766. The value of 1.766 was for the covariance between hours/week spent outside and indoor dust Mn. The total sample size for the model was 249, with 199 clusters. All model fit statistics were within acceptable limits.

SEM Results for Hair Mn

Table 11 and Figure 5A show the standardized path coefficients for the results of the SEM for hair Mn. Since no participants were missing data for all endogenous variables, only the six participants missing data on the exogenous variables were excluded, resulting in a sample size of 317. The number of clusters was 247. All model fit statistics indicated a good fitting model (Table 15). The standardized coefficients for the pathways from ambient air Mn to soil Mn, indoor dust Mn, and hair Mn were small and not statistically significant, similar to the results for the SEM for blood Mn. The pathway from soil Mn to hair Mn also was not significant. The pathways from soil Mn to indoor dust Mn, and indoor dust Mn to hair Mn were statistically significant, with the largest coefficients of all continuous variables in the model (0.267, P<0.001 for soil Mn to indoor dust Mn, and 0.290, P<0.001 for indoor dust Mn to hair Mn). The indirect path from soil Mn to hair Mn through indoor dust Mn was also statistically significant (0.077, P=0.002). The negative standardized coefficient for HVAC score to indoor dust Mn was significant, but the coefficient for HVAC score to hair Mn was not. Two exogenous variables had significant paths to hair Mn; these were hours/week spent outside, and gender (Table 11, Figure 5A). For gender, the coefficient is standardized on Y only, so is not directly comparable to the other coefficients in the model. For the endogenous variables, the R^2 values were 0.005 (P=0.573) for soil Mn, 0.124 (P=0.001) for indoor dust Mn, and 0.208 (P<0.001) for hair Mn.

All standardized residuals for covariances were within ±1.96; the largest was 1.742 for the covariance between hours/week spent outside and soil Mn.

Table 12 and Figure 5B show the results of the SEM model for hair Mn with participants enrolled in 2010 excluded. For this model, the sample size was 261, and the number of clusters was 207. Similar to the models for blood Mn and the model for hair Mn with all participants included, all model fit statistics were within acceptable limits (Table 15). The indirect path from ambient air Mn to hair Mn through indoor dust Mn was statistically significant (0.060, P=0.015), which was different from the model including all participants. The direct pathway from ambient air Mn to indoor dust Mn was statistically significant, which also differed from the model with all participants included. The pathways from HVAC score to indoor dust Mn, and from parent education to indoor dust Mn were not significant in the model with 2010 participants excluded. R^2 values were 0.017 (P=0.367) for soil Mn, 0.185 (P=0.001) for indoor dust Mn, and 0.245 (P<0.001) for hair Mn. As with the model for hair Mn using all participants, all standardized residuals for covariances were within ±1.96, with the largest being 1.879 for the covariance between hours/week spent outside and dust Mn.

SEM Results for Toenail Mn

The results of the SEM model for toenail Mn are shown in Table 13 and Figure 6A. The SEM included 303 of the 323 participants, and 238 clusters. In addition to the six participants missing data for an exogenous variable, 14 participants were missing soil Mn, indoor dust Mn, and toenail Mn and were excluded from the model. The model fit was acceptable based on all model fit statistics (Table 15). As in the models for blood Mn and hair Mn, the pathways from ambient air Mn to soil Mn, indoor dust Mn, and toenail Mn were not statistically significant. Direct pathways that were significant were soil Mn to indoor dust Mn (0.269, P<0.001), HVAC score to indoor dust Mn (-0.125, P=0.018), parent education to indoor dust (-0.153, P=0.027), indoor dust Mn to toenail Mn (0.369, P<0.001), and hours/week spent outside to toenail Mn (0.167, P=0.006). The pathway from gender to toenail Mn was not significant, which was different than the model for hair Mn, where the coefficient for gender was large and statistically significant. Consistent with the model for hair Mn, the standardized coefficient for the pathway from indoor dust Mn to toenail Mn was relatively large (0.360), suggesting that indoor dust is a significant source of exposure to environmental Mn. The indirect path from soil Mn to toenail Mn through indoor dust Mn was 0.099, P<0.001. The R^2 value for soil Mn was 0.005 (P=0.568), for indoor dust Mn it was 0.129 (P=0.001), and for toenail Mn it was 0.199 (P<0.001). All standardized residuals for covariances were within ±1.96; the largest was 1.665, for the covariance between hours/week spent outside and soil Mn.

Table 14 and Figure 6B show the results for the model for toenail Mn with participants enrolled in 2010 excluded. The sample size was 247, with 191 clusters. The path from ambient air Mn to indoor dust Mn was statistically significant (0.250, P=0.001), as was the indirect path from ambient air Mn to toenail Mn through indoor dust Mn (0.084, P=0.004). The R^2 values for the endogenous variables were 0.015 (P=0.386) for soil Mn, 0.183 (P<0.001) for indoor dust Mn, and 0.204 (P<0.001) for toenail Mn. All standardized residuals for covariances were within ±1.96; the largest was 1.756 for the covariance between hours/week spent outside and indoor dust Mn. All model fit statistics were within acceptable limits (Table 15).

Discussion

This study determines pathways of exposure from measures of environmental Mn and demographic variables to Mn biomarkers, using a structural equation modeling approach. Significant direct pathways of exposure from soil Mn to indoor dust Mn, and from indoor dust

Mn to hair Mn and toenail Mn were identified. A significant indirect path from soil Mn to hair and toenail Mn through indoor dust Mn was also identified. In models that excluded participants enrolled in 2010, a study year with atypically low Mn emissions and ambient air Mn concentrations, ambient air Mn was identified as a significant direct exposure pathway to indoor dust Mn, and indirect exposure pathway to hair and toenail Mn through indoor dust Mn. Pathways from HVAC score and parent education to indoor dust Mn were identified in the models that included all participants, but these pathways were not significant in the models that excluded participants enrolled in 2010. The average hours/week spent outside was a significant predictor of hair Mn and toenail Mn, and gender was a significant predictor of hair Mn.

Although the models that included all participants did not identify an exposure pathway from ambient air Mn to indoor dust Mn, the pathway was revealed when the participants enrolled in the year with atypically low Mn emissions were excluded from the models. This may reflect that when air Mn concentrations are lower, other factors such as soil Mn and demographics play a larger role in indoor Mn deposition. In the U.S. the average background ambient air Mn concentration is 20 ng/m^3, and ranges from 10 ng/m^3 in rural or remote areas to 40 ng/m^3 in urban areas (ATSDR 2012). In this study, none of the air Mn concentrations exceeded 40 ng/m^3 in 2010, whereas up to 56% of air Mn concentrations were above 40 ng/m^3 in the other study years. Although not directly comparable, Layton and Beamer (2009) studied lead concentrations in household dust when leaded gasoline was in use in Sacramento, CA, and found that airborne lead was the dominant source. However, after leaded gasoline was phased out and airborne levels of lead declined, soil lead became the primary source of lead in household dust. Indoor dust Mn levels also can be affected by variables not measured in this study, such as overall housekeeping, number of occupants in the home, and secondhand smoke. The non-significant pathway from ambient air Mn to soil Mn may be explained by the nature of the soil samples, which likely represent years of deposition rather than a single year, and can vary depending on the parent material (Carter et al., 2015). In a previous study, Fulk et al. (2017) used SEM to model pathways from modeled ambient air Mn to hair Mn in 88 CARES participants enrolled in 2009. The standardized path coefficient from ambient air Mn to soil Mn was 0.055, similar to the results found in the present study.

Other studies determining relationships between air, soil, and dust Mn have had varied results, but studies differ on the methods used to measure the environmental sources, making direct comparisons difficult. In a study of children's exposure to metals in the environment, Callan et al. (2012) measured residential soil Mn, indoor dust Mn, blood Mn, and hair Mn in 39 children in Western Australia. Soil Mn was significantly associated with indoor dust Mn concentrations in µg/g (r_s=0.36). A second study by Callan et al. (2013) determined exposures to metals in 173 pregnant women in Western Australia, and found a similar association between soil Mn and indoor dust Mn concentrations (r_s=0.34). Lucas et al. (2015) measured environmental Mn sources and Mn biomarkers in 444 children aged 11-14 years living in areas with active or historically active ferromanganese alloy plants. The Spearman correlation (r_s) between air Mn measured with 24-hr personal air samplers and residential soil Mn was small but statistically significant (r_s=0.100). Correlations between air Mn and dust Mn were strongest for outdoor dust concentrations in µg/g (r_s=0.43), and weakest for indoor dust loadings in µg/m^2 (r_s=0.09), the measure used in the present study. There was no association between soil Mn and indoor dust Mn loading observed in the Lucas et al. study (r_s=0.08). Zota et al. (2016) measured Mn in indoor $PM_{2.5}$, indoor dust, and yard soil at 53 homes near the Tar Creek Superfund Site in Oklahoma (USA), in a study of infant exposures to metals in the environment. Mn in indoor

$PM_{2.5}$ was not correlated with soil Mn or dust Mn loading (r_s=0.22 for both), but was associated with indoor dust concentration (r_s=0.34). Soil and indoor dust concentrations were correlated (r_s=0.37), but soil and indoor dust loadings were not (r_s=0.12).

In this study, HVAC score was a significant predictors of indoor dust Mn loadings in the models with all participants included. The pathway coefficient for HVAC score was negative, indicating that use of electric, gas, or heating oil furnaces, air conditioning, and frequent filter changes were associated with lower indoor dust Mn loadings. In a recent study, Salem Ali Albar et al. (2020) determined associations between trace metals in indoor dust and sociodemographic factors in 20 randomly selected households in two Saudi Arabian cities. The mean (SD) dust Mn concentration was 343 (99) µg/g in homes with <10 hrs/day of air conditioning use compared to 270 (136) µg/g in home with >16 hrs/day of air conditioning use (P=0.09). Frequency of air filter cleaning was not associated with decreased dust Mn levels in the study. Tong and Lam (2000) studied household dust concentrations of heavy metals in 151 homes in Hong Kong, and examined associations with 16 characteristics of the homes, including heating, air conditioning, open windows, sweeping, dusting, and vacuum cleaner use. They found that homes without air conditioning, and homes with frequent opened windows, had higher dust metal concentrations.

The pathway from parent education, used as a proxy for socioeconomic status (SES), to indoor dust Mn was statistically significant in the SEM models that included all participants. Other studies have found associations between measures of SES and indoor dust Mn levels. Gunier et al. (2014) determined house dust Mn levels in the homes of 378 pregnant women in Salinas, CA, and examined associations with demographic and residential characteristics. Mother's education ≤ 6^{th} grade was associated with significantly higher house dust Mn concentrations and loadings compared to mother's education > 6^{th} grade. Household income was also found to be associated with house dust metal levels in a study by Chattopadhyay et al. (2003) in Sydney, Australia. In 82 households, those with incomes from 0-30,000 AUD had geometric mean (SD) dust Mn concentrations of 62.7 (2.3) μg/g, compared to 49.7 (2.2) μg/g, in those with incomes of 30,000-560,000, and 54.4 (2.4) μg/g in those with incomes >50,000 (P=0.034). In the study by Salem Ali Albar et al. (2020) mentioned above, economic conditions classified as low were associated with significantly higher indoor dust Mn levels compared to those classified as middle or high. A number of plausible reasons could account for these findings. Lower SES is associated with higher rates of smoking which may result in higher secondhand smoke exposure. In addition, low income households may have poorer ventilation and air filtration, and may be less likely to be air conditioned, resulting in greater exposure to outdoor pollutants.

In the models that excluded 2010, the year with atypically low air Mn concentrations, HVAC scores and parent education were not significantly associated with indoor dust Mn. This likely reflects the greater influence of air Mn on indoor dust Mn, both directly and indirectly through soil Mn. In these models, the pathways from ambient air Mn to soil Mn increased from 0.069-0.071 to 0.122-0.129, and from soil Mn to indoor dust Mn the pathways increased from 0.267-0.269 to 0.287-0.290. It's possible that higher HVAC scores and parent education are less effective in reducing indoor dust Mn levels at higher ambient air Mn concentrations, but further studies would be needed to determine whether this is true.

In the SEM model for blood Mn, no significant pathways from environmental or other variables to blood Mn were observed. These results are consistent with a number of other studies examining variables for associations with blood Mn levels. Gulson et al. (2014) used a path modeling approach in a study of environmental Mn exposures and blood Mn levels in 108 children aged 0.5-2.0 years living at varying proximity to roadways. Environmental Mn measures included soil, outdoor dust sweepings, indoor dust, interior wipes, and diet. None of the pathways to blood Mn were statistically significant. In the Lucas et al. (2015) study of 444 children aged 11-14 years living in areas with active or historically active ferromanganese alloy plants, blood Mn was not associated with indoor dust concentrations, indoor dust loadings, or soil Mn. Small negative associations were found between blood Mn and outdoor dust Mn concentrations and loadings (r_s=-0.16 and -0.19 respectively). Butler et al. (2019) measured associations between air, soil, and dust Mn with blood, hair, fingernail and saliva Mn in 717 children aged 11-14 years that included the group of 444 previously studied by Lucas et al. No associations between blood Mn and any of the environmental Mn measures were observed. The reason for the lack of associations between blood Mn and environmental Mn measures is that blood Mn may reflect short term exposures such as days to weeks rather than longer-term exposures (Smith et al., 2007; Eastman et al., 2013). Further, while blood Mn may be useful as a biomarker for high exposures such as those in occupational settings, it may not be as useful for environmental exposures (Smith et al., 2007). In the present study, the majority of the blood Mn levels in the study participants were within the normal range of 4-15 μg/L.

In contrast to blood Mn, significant pathways from environmental Mn and other variables to hair Mn were observed in this study. Direct pathways from indoor dust Mn, hours/week spent outside, and gender to hair Mn were positive and statistically significant. The indirect pathway from soil Mn to hair Mn through indoor dust Mn was also significant, and in the model excluding data from 2010, the indirect pathway from ambient air Mn to hair Mn through indoor dust Mn was significant. For gender, the median (IQR) hair Mn level was 463 (530) ng/g, and for females it was 295 (400) ng/g, a statistically significant difference (P<0.001). Only one other study was located that found significant gender differences in hair Mn levels in children, with boys having higher levels than girls. Rink et al. (2014) determined hair Mn levels in 60 children aged 14-45 months; mean (SD) log transformed hair Mn levels were 1.2 (1.0) ng/g for boys and 0.8 (0.5) ng/g for girls ($P=0.03$). A number of studies have found significant associations between indoor dust Mn and hair Mn, including the Fulk et al. (2017) SEM study of CARES participants enrolled in 2009. In the Lucas et al. (2015) and Butler et al. (2019) studies mentioned previously, the Spearman correlations between indoor dust Mn and hair Mn were 0.28 ($P<0.05$) and 0.12 ($P<0.05$) respectively. Hair Mn is considered to be a better biomarker of exposure than blood Mn, because it can provide exposure information for a period of 1-6 months (Eastman et al., 2013; Haynes et al., 2015).

Pathways from indoor dust Mn and hours/week spent outside to toenail Mn were statistically significant, while gender was not. Similar to the models for hair Mn, the indirect pathway from soil Mn to toenail Mn through indoor dust Mn was significant, and in the model excluding data from 2010, the indirect pathway from ambient air Mn to toenail Mn through indoor dust Mn was also significant. The significant pathway from indoor dust Mn to toenail Mn is consistent with the results in the Lucas et al. (2015) and Butler et al. (2019) studies, where correlations between indoor dust Mn and fingernail Mn were 0.24 ($P<0.05$) and 0.23 ($P<0.05$) respectively. In a recent review of toenails as a biomarker of trace metals exposures, Gutierrez-Gonzalez et al. (2019) determined that toenail Mn levels probably correspond to exposures from 3-12 months prior to sampling. The time frames of exposure were determined from three studies of occupationally exposed welders included in the review. The review authors concluded that toenail Mn concentrations can reflect long-term exposures for studies of both occupational and environmental sources of Mn.

There are several limitations to the present study. Ambient air Mn exposures were modeled rather than measured, which introduces measurement error due to inaccuracies in emissions reporting and model inputs. Modeled ambient air Mn concentrations may not reflect actual personal exposures, because individuals spend varying amounts of time at home, work, school, and other locations, as well as varying amounts of time outdoors, and these variations are not captured with modeling. To account for some of these differences, ambient air Mn exposures were weighted based on the amount of time spent at home and school and the concentrations modeled at each location. Data were collected on time spent outside, which was included in the SEM models to control for differences in biomarker levels that may be due to differences in exposures to outdoor versus indoor sources. A second limitation is that while modeled ambient air Mn levels were weighted to reflect time spent at home and school, soil and indoor dust samples were not available for the schools. Since indoor dust was a significant source of Mn for hair Mn and toenail Mn levels, the associations may have been strengthened by incorporating soil and dust exposures at school into the SEM models. In addition, indoor dust Mn levels depend to a degree on sociodemographic and residential factors such as house cleaning schedules and secondhand smoke, which could not be controlled for in the study. Finally, the soil and indoor dust Mn samples were collected at a single point in time and likely reflect different exposure times, with soil Mn reflecting cumulative exposures rather than short term exposures.

In conclusion, this study identifies pathways of exposure from environmental sources of Mn to biomarkers in children living near a Mn refinery. Ambient air Mn contributes significantly to indoor dust Mn when average ambient air concentrations exceed normal background levels. Soil Mn is a significant source of indoor dust Mn, likely through tracking in of particles by occupants of the home. Indoor dust is an important source of Mn exposure contributing to Mn levels in hair and toenails, and both ambient air Mn and soil Mn indirectly contribute to hair and toenail Mn levels through indoor dust Mn. Future studies could consider interventions or education on methods to decrease household dust levels and reduce Mn exposures to the occupants of the home.

Table 1. Summary Descriptive Statistics for Study Participants

Variable	n	Mean (SD)	Median (IQR)	Range
Age (years)	323	8.37 (0.92)	8.38 (1.58)	7.00-9.99
Hours/week spent outside	320	25.64 (9.87)	24.00 (13.44)	6.13-62.00
Blood Mn (μg/L)	262	10.09 (2.42)	9.80 (3.23)	5.00-18.80
Hair Mn (ng/g)	311	596.07 (792.32)	384.91 (482.56)	54.04-7379.09
Toenail Mn (ng/g)	273	975.19 (1177.15)	580.00 (825.50)	45.00-9663.00
Parent education	320	15.04 (2.40)	15.00 (4.00)	8.00-21.00
HVAC score	322	5.68 (1.19)	6.00 (1.50)	0.50-8.00
Time-weighted distance (km)	323	11.76 (4.90)	11.14 (6.59)	3.54-28.94
Ambient air Mn (ng/m^3)	323	39.33 (37.37)	27.06 (33.94)	2.77-256.11
Soil Mn (μg/g)	258	615.22 (336.67)	535.50 (371.50)	93.90-2604.00
Dust Mn (μg/m^2)	258	122.66 (196.16)	70.86 (88.53)	7.82-2206.60
Ln hours/week spent outside	320	3.17 (0.40)	3.18 (0.54)	1.81-4.13
Ln blood Mn (μg/L)	262	2.28 (0.24)	2.28 (0.33)	1.61-2.93
Ln hair Mn (ng/g)	311	5.96 (0.88)	5.95 (1.22)	3.99-8.91
Ln toenail Mn (ng/g)	273	6.40 (0.98)	6.36 (1.29)	3.81-9.18
Ln time-weighted distance (km)	323	2.38 (0.42)	2.41 (0.60)	1.26-3.27
Ln ambient air Mn (ng/m^3)	323	3.29 (0.90)	3.30 (1.15)	1.02-5.55
Ln soil Mn (μg/g)	258	6.29 (0.52)	6.28 (0.67)	4.54-7.86
Ln dust Mn (μg/m^2)	258	4.31 (0.92)	4.26 (1.17)	2.06-7.70

Table 2. Annual Mn Emissions and Modeled Ambient Air Mn Concentrations (ng/m^3) by Year for Study Participants

Year	n	Mn emissions (lb)	Participants with Air Mn >50 ng/m^3	Ambient air Mn Mean (SD)	Ambient air Mn Median (IQR)	Ambient air Mn Range
2008	6	237,012	2 (33.3%)	51.88 (31.13)	37.81 (56.65)	20.01-97.49
2009	88	68,845	15 (17.0%)	38.58 (26.05)	30.24 (20.34)	12.94-145.41
2010	58	41,531	0 (0.0%)	10.39 (8.05)	6.80 (10.18)[a]	2.77-38.49
2011	95	126,821	44 (46.3%)	58.95 (51.38)	48.60 (57.93)	9.89-256.11
2012	69	83,924	17 (24.6%)	37.62 (25.92)	32.64 (34.02)	7.57-96.02
2013	7	87,471	1 (14.3%)	28.45 (13.95)	21.58 (18.07)	17.63-55.11

[a]$P<0.05$ vs. all other years, Mann-Whitney U tests with Bonferroni corrections for multiple comparisons.

Table 3. Descriptive Statistics and Comparisons between Participants With vs. Without Soil and Indoor Dust Mn Levels

Variable	Participants with soil and dust Mn levels	Participants without soil and dust Mn levels	P value
Gender, n (%)			0.267
Female	131 (50.8)	28 (43.1)	
Male	127 (49.2)	37 (56.9)	
Race, n (%)			0.999
White	250 (96.9)	63 (96.9)	
Black/other	8 (3.1)	2 (3.1)	
Single or sibling participant, n (%)			0.071
Single	155 (60.1)	31 (47.7)	
Sibling	103 (39.9)	34 (52.3)	
Age (years)	8.37 (0.92) (n=258)	8.38 (0.90) (n=65)	0.920
Hours/week spent outside	24.00 (13.25) (n=256)	26.25 (14.63) (n=64)	0.776
Blood Mn (μg/L)	9.80 (3.33) (n=210)	9.85 (2.75) (n=52)	0.927
Hair Mn (ng/g)	368.18 (482.68) (n=247)	453.05 (525.79) (n=64)	0.061
Toenail Mn (ng/g)	551.00 (804.75) (n=222)	732.00 (1102.00) (n=51)	0.075
Parent education	15.05 (2.34) (n=255)	15.01 (2.59) (n=65)	0.911
HVAC score	5.69 (1.20) (n=258)	5.66 (1.19) (n=64)	0.836
Time-weighted distance (km)	10.94 (6.11) (n=258)	11.75 (9.01) (n=65)	0.085
Ambient air Mn (ng/m^3)	28.93 (32.94) (n=258)	19.34 (38.35) (n=65)	0.120

Values for age, parent education, and HVAC score are mean (SD); values for all other continuous variables are median (IQR). P values for gender, race, and single or sibling participant are from chi-square or Fisher's exact tests; P values for age, parent education, and HVAC score are from two-sample t tests; all others are from Mann-Whitney U tests.

Table 4. Descriptive Statistics and Comparisons between Participants With vs. Without Blood Mn Levels

Variable	Participants with blood Mn levels	Participants without blood Mn levels	P value
Gender, n (%)			0.770
Female	130 (49.6)	29 (47.5)	
Male	132 (50.4)	32 (52.5)	
Race, n (%)			0.218
White	252 (96.2)	61 (100.0)	
Black/other	10 (3.8)	0 (0.0)	
Single or sibling participant, n (%)			0.590
Single	149 (56.9)	37 (60.7)	
Sibling	113 (43.1)	24 (39.3)	
Age (years)	8.40 (0.91) (n=262)	8.23 (0.93) (n=61)	0.204
Hours/week spent outside	24.25 (13.81) (n=260)	23.75 (13.75) (n=60)	0.763
Hair Mn (ng/g)	376.38 (468.36) (n=252)	397.50 (652.38) (n=59)	0.577
Toenail Mn (ng/g)	589.50 (790.50) (n=226)	511.00 (1209.00) (n=47)	0.987
Parent education	15.12 (2.39) (n=259)	14.67 (2.38) (n=61)	0.185
HVAC score	5.75 (1.16) (n=262)	5.40 (1.29) (n=60)	0.038
Time-weighted distance (km)	11.54 (6.83) (n=262)	10.48 (4.91) (n=61)	0.336
Ambient air Mn (ng/m^3)	24.70 (34.35) (n=262)	30.53 (35.58) (n=61)	0.179
Soil Mn (μg/g)	529.75 (377.00) (n=210)	597.00 (376.75) (n=48)	0.582
Dust Mn (μg/m^2)	70.41 (80.95) (n=210)	75.17 (113.20) (n=48)	0.273

Values for age, parent education, and HVAC score are mean (SD); values for all other continuous variables are median (IQR). P values for gender, race, and single or sibling participant are from chi-square or Fisher's exact tests; P values for age, parent education, and HVAC score are from two-sample t tests; all others are from Mann-Whitney U tests.

Table 5. Descriptive Statistics and Comparisons between Participants With vs. Without Hair Mn levels

Variable	Participants with hair Mn levels	Participants without hair Mn levels	P value
Gender, n (%)			0.004
Female	158 (50.8)	1 (8.3)	
Male	153 (49.2)	11 (91.7)	
Race, n (%)			0.999
White	301 (96.8)	12 (100.0)	
Black/other	10 (3.2)	0 (0.0)	
Single or sibling participant, n (%)			0.588
Single	180 (57.9)	6 (50.0)	
Sibling	131 (42.1)	6 (50.0)	
Age (years)	8.38 (0.92) (n=311)	8.18 (0.87) (n=12)	0.473
Hours/week spent outside	24.00 (13.38) (n=309)	33.50 (17.00) (n=11)	0.021
Blood Mn (μg/L)	9.80 (3.28) (n=252)	9.55 (2.33) (n=10)	0.872
Toenail Mn (ng/g)	568.00 (823.50) (n=262)	1093.00 (985.00) (n=11)	0.025
Parent education	15.05 (2.42) (n=308)	14.83 (1.72) (n=12)	0.764
HVAC score	5.70 (1.19) (n=311)	5.32 (1.20) (n=11)	0.302
Time-weighted distance (km)	11.16 (6.63) (n=311)	10.97 (6.27) (n=12)	0.541
Ambient air Mn (ng/m^3)	26.45 (33.89) (n=311)	43.58 (43.25) (n=12)	0.112
Soil Mn (μg/g)	8.38 (0.92) (n=311)	8.18 (0.87) (n=12)	0.074
Dust Mn (μg/m^2)	24.00 (13.38) (n=309)	33.50 (17.00) (n=11)	0.191

Values for age, parent education, and HVAC score are mean (SD); values for all other continuous variables are median (IQR). P values for gender, race, and single or sibling participant are from chi-square or Fisher's exact tests; P values for age, parent education, and HVAC score are from two-sample t tests; all others are from Mann-Whitney U tests.

Table 6. Descriptive Statistics and Comparisons between Participants With vs. Without Toenail Mn Levels

Variable	Participants with toenail Mn levels	Participants without toenail Mn levels	P value
Gender, n (%)			0.620
Female	136 (49.8)	23 (46.0)	
Male	137 (50.2)	27 (54.0)	
Race, n (%)			0.657
White	265 (97.1)	48 (96.0)	
Black/other	8 (2.9)	2 (4.0)	
Single or sibling participant, n (%)			0.577
Single	159 (58.2)	27 (54.0)	
Sibling	114 (41.8)	23 (46.0)	
Age (years)	8.37 (0.90) (n=273)	8.36 (1.02) (n=50)	0.954
Hours/week spent outside	24.00 (12.97) (n=270)	26.57 (16.63) (n=50)	0.674
Blood Mn (μg/L)	9.80 (3.33) (n=226)	9.70 (2.63) (n=36)	0.901
Hair Mn (ng/g)	363.85 (467.94) (n=262)	478.17 (585.48) (n=49)	0.067
Parent education	15.13 (2.34) (n=272)	14.52 (2.64) (n=48)	0.105
HVAC score	5.73 (1.16) (n=272)	5.46 (1.35) (n=50)	0.140
Time-weighted distance (km)	11.11 (6.22) (n=273)	11.81 (9.10) (n=50)	0.197
Ambient air Mn (ng/m^3)	27.06 (33.27) (n=273)	26.89 (34.85) (n=50)	0.585
Soil Mn (μg/g)	8.37 (0.90) (n=273)	8.36 (1.02) (n=50)	0.590
Dust Mn (μg/m^2)	24.00 (12.97) (n=270)	26.57 (16.63) (n=50)	0.144

Values for age, parent education, and HVAC score are mean (SD); values for all other continuous variables are median (IQR). P values for gender, race, and single or sibling participant are from chi-square or Fisher's exact tests; P values for age, parent education, and HVAC score are from two-sample t tests; all others are from Mann-Whitney U tests.

Table 7. Pearson Correlation Coefficients for Continuous Study Variables, 2008-2013

Variable		Ln hrs/wk spent outside	Ln blood Mn (µg/L)	Ln hair Mn (ng/g)	Ln toenail Mn (ng/g)	Parent education	HVAC score	Ln time-weighted dist. (km)	Ln ambient air Mn (ng/m^3)	Ln soil Mn (mg/g)
Ln blood Mn (µg/L)	*r*	-0.088								
	n	260								
Ln hair Mn (ng/g)	*r*	0.186**	-0.023							
	n	309	252							
Ln toenail Mn (ng/g)	*r*	0.191**	-0.118	0.370**						
	n	270	226	262						
Parent education	*r*	0.039	-0.001	-0.133*	0.006					
	n	317	259	308	272					
HVAC score	*r*	0.007	-0.062	-0.084	-0.077	-0.026				
	n	320	262	311	272	319				
Ln time-weighted distance (km)	*r*	0.070	-0.047	0.017	-0.100	-0.007	-0.021			
	n	320	262	311	273	320	322			
Ln ambient air Mn (ng/m^3)	*r*	-0.091	0.021	0.073	0.089	0.017	-0.045	-0.742**		
	n	320	262	311	273	320	322	323		
Ln soil Mn (µg/g)	*r*	0.100	-0.064	0.172**	0.202**	0.014	-0.040	-0.097	0.052	
	n	256	210	247	222	255	258	258	258	
Ln dust Mn ($\mu g/m^2$)	*r*	0.077	-0.016	0.354**	0.404**	-0.144*	-0.160**	-0.196**	0.138*	0.260**
	n	256	210	247	222	255	258	258	258	258

Abbreviations: Hrs/wk, hours/week; dist, distance. *P<0.05; **P<0.01

Table 8. Pearson Correlation Coefficients for Continuous Study Variables, with 2010 Excluded

Variable		Ln hrs/wk spent outside	Ln blood Mn (µg/L)	Ln hair Mn (ng/g)	Ln toenail Mn (ng/g)	Parent education	HVAC score	Ln time-weighted dist. (km)	Ln ambient air Mn (ng/m^3)	Ln soil Mn (mg/g)
Ln blood Mn (µg/L)	*r*	-0.116								
	n	209								
Ln hair Mn (ng/g)	*r*	0.234**	-0.086							
	n	251	201							
Ln toenail Mn (ng/g)	*r*	0.215**	-0.132	0.352**						
	n	216	179	208						
Parent education	*r*	-0.031	-0.019	-0.132*	0.027					
	n	261	210	252	219					
HVAC score	*r*	-0.037	-0.066	-0.096	-0.112	-0.047				
	n	262	211	253	218	263				
Ln time-weighted distance (km)	*r*	0.051	-0.065	0.031	-0.086	-0.055	-0.029			
	n	262	211	253	219	264	264			
Ln ambient air Mn (ng/m^3)	*r*	-0.038	0.039	0.048	0.133*	0.093	-0.032	-0.844**		
	n	262	211	253	219	264	264	265		
Ln soil Mn (µg/g)	*r*	0.074	-0.080	0.195**	0.237**	0.002	-0.088	-0.083	0.105	
	n	206	167	197	176	207	208	208	208	
Ln dust Mn (µg/m^2)	*r*	0.128	-0.049	0.308**	0.396**	-0.107	-0.143*	-0.231**	0.276**	0.307**
	n	206	167	197	176	207	208	208	208	208

Abbreviations: Hrs/wk, hours/week; dist, distance. *P<0.05; **P<0.01

Table 9. Direct and Indirect Pathway Coefficients for Model for Blood Mn

Pathway	Unstandardized estimate (SE)	Standardized estimate (SE)	t statistic	P value
Air Mn → blood Mn	0.001 (0.018)	0.005 (0.069)	0.066	0.948
Air Mn → soil Mn → blood Mn	-0.001 (0.002)	-0.004 (0.006)	-0.665	0.506
Air Mn → dust Mn → blood Mn	<0.001 (0.002)	-0.001 (0.008)	-0.195	0.845
Air Mn → soil Mn → dust Mn → blood Mn	<0.001 (<0.001)	<0.001 (0.001)	-0.186	0.853
Soil Mn → blood Mn	-0.027 (0.031)	-0.057 (0.066)	-0.867	0.386
Soil Mn → dust Mn → blood Mn	-0.002 (0.009)	-0.004 (0.019)	-0.193	0.847
Dust Mn → blood Mn	-0.003 (0.018)	-0.013 (0.068)	-0.195	0.845
HVAC score → blood Mn	-0.012 (0.012)	-0.061 (0.062)	-0.995	0.320
HVAC score → dust Mn → blood Mn	<0.001 (0.002)	0.002 (0.009)	0.196	0.845
Hours/week spent outside → blood Mn	-0.043 (0.043)	-0.073 (0.073)	-1.005	0.315
Parent education → blood Mn	0.001 (0.006)	0.006 (0.063)	0.103	0.918
Parent education → dust Mn → blood Mn	<0.001 (0.001)	0.002 (0.010)	0.195	0.845
Gender → blood Mn	-0.052 (0.030)	-0.220 (0.125)	-1.759	0.079
Air Mn → dust Mn	0.112 (0.074)	0.111 (0.072)	1.553	0.120
Air Mn → soil Mn → dust Mn	0.019 (0.018)	0.018 (0.017)	1.058	0.290
Soil Mn → dust Mn	0.481 (0.111)	0.268 (0.062)	4.349	<0.001
HVAC score → dust Mn	-0.103 (0.041)	-0.135 (0.054)	-2.495	0.013
Parent education → dust Mn	-0.056 (0.027)	-0.144 (0.072)	-2.004	0.045
Air Mn → soil Mn	0.039 (0.035)	0.069 (0.062)	1.105	0.269

All variables except gender are standardized on Y and X; gender (binary variable) is standardized on Y. The t statistics and P values are for the standardized estimates. Air Mn is the weighted average annual ambient air Mn modeled at the participants' home and school.

Table 10. Direct and Indirect Pathway Coefficients for Model for Blood Mn with 2010 Data Excluded from Model

Pathway	Unstandardized estimate (SE)	Standardized estimate (SE)	t statistic	P value
Air Mn → blood Mn	0.014 (0.028)	0.041 (0.083)	0.490	0.624
Air Mn → soil Mn → blood Mn	-0.002 (0.003)	-0.007 (0.010)	-0.703	0.482
Air Mn → dust Mn → blood Mn	-0.006 (0.006)	-0.018 (0.019)	-0.933	0.351
Air Mn → soil Mn → dust Mn → blood Mn	-0.001 (0.001)	-0.002 (0.003)	-0.736	0.462
Soil Mn → blood Mn	-0.026 (0.034)	-0.055 (0.072)	-0.769	0.442
Soil Mn → dust Mn → blood Mn	-0.009 (0.011)	-0.020 (0.023)	-0.870	0.384
Dust Mn → blood Mn	-0.018 (0.020)	-0.069 (0.074)	-0.928	0.354
HVAC score → blood Mn	-0.014 (0.013)	-0.069 (0.067)	-1.037	0.300
HVAC score → dust Mn → blood Mn	0.001 (0.002)	0.007 (0.008)	0.821	0.411
Hours/week spent outside → blood Mn	-0.057 (0.046)	-0.097 (0.079)	-1.225	0.220
Parent education → blood Mn	-0.003 (0.007)	-0.029 (0.069)	-0.423	0.672
Parent education → dust Mn → blood Mn	0.001 (0.001)	0.009 (0.010)	0.819	0.413
Gender → blood Mn	-0.051 (0.034)	-0.210 (0.141)	-1.489	0.136
Air Mn → dust Mn	0.324 (0.103)	0.254 (0.073)	3.491	<0.001
Air Mn → soil Mn → dust Mn	0.046 (0.028)	0.036 (0.022)	1.650	0.099
Soil Mn → dust Mn	0.513 (0.119)	0.287 (0.067)	4.315	<0.001
HVAC score → dust Mn	-0.071 (0.043)	-0.095 (0.059)	-1.611	0.107
Parent education → dust Mn	-0.048 (0.028)	-0.124 (0.075)	-1.645	0.100
Air Mn → soil Mn	0.090 (0.053)	0.126 (0.072)	1.756	0.079

All variables except gender are standardized on Y and X; gender (binary variable) is standardized on Y. The t statistics and P values are for the standardized estimates. Air Mn is the weighted average annual ambient air Mn modeled at the participants' home and school.

Table 11. Direct and Indirect Pathway Coefficients for Model for Hair Mn

Pathway	Unstandardized estimate (SE)	Standardized estimate (SE)	t statistic	P value
Air Mn → hair Mn	0.065 (0.058)	0.067 (0.059)	1.133	0.257
Air Mn → soil Mn → hair Mn	0.005 (0.006)	0.005 (0.006)	0.763	0.446
Air Mn → dust Mn → hair Mn	0.033 (0.020)	0.034 (0.021)	1.637	0.102
Air Mn → soil Mn → dust Mn → hair Mn	0.005 (0.005)	0.005 (0.005)	1.053	0.292
Soil Mn → hair Mn	0.115 (0.104)	0.067 (0.061)	1.103	0.270
Soil Mn → dust Mn → hair Mn	0.133 (0.043)	0.077 (0.025)	3.039	0.002
Dust Mn → hair Mn	0.278 (0.060)	0.290 (0.061)	4.765	<0.001
HVAC score → hair Mn	-0.051 (0.039)	-0.069 (0.053)	-1.317	0.188
HVAC score → dust Mn → hair Mn	-0.026 (0.014)	-0.036 (0.019)	-1.885	0.059
Hours/week spent outside → hair Mn	0.330 (0.117)	0.151 (0.052)	2.891	0.004
Parent education → hair Mn	-0.036 (0.020)	-0.097 (0.054)	-1.789	0.074
Parent education → dust Mn → hair Mn	-0.015 (0.008)	-0.041 (0.021)	-1.950	0.051
Gender → hair Mn	0.400 (0.092)	0.455 (0.102)	4.469	<0.001
Air Mn → dust Mn	0.117 (0.073)	0.116 (0.070)	1.653	0.098
Air Mn → soil Mn → dust Mn	0.019 (0.017)	0.019 (0.017)	1.077	0.282
Soil Mn → dust Mn	0.479 (0.110)	0.267 (0.061)	4.354	<0.001
HVAC score → dust Mn	-0.094 (0.040)	-0.123 (0.053)	-2.343	0.019
Parent education → dust Mn	-0.055 (0.027)	-0.143 (0.071)	-2.005	0.045
Air Mn → soil Mn	0.039 (0.035)	0.070 (0.062)	1.128	0.259

All variables except gender are standardized on Y and X; gender (binary variable) is standardized on Y. The t statistics and P values are for the standardized estimates. Air Mn is the weighted average annual ambient air Mn modeled at the participants' home and school.

Table 12. Direct and Indirect Pathway Coefficients for Model for Hair Mn with 2010 Data Excluded from Model

Pathway	Unstandardized estimate (SE)	Standardized estimate (SE)	t statistic	P value
Air Mn → hair Mn	0.016 (0.073)	0.014 (0.061)	0.223	0.823
Air Mn → soil Mn → hair Mn	0.017 (0.015)	0.015 (0.012)	1.180	0.238
Air Mn → dust Mn → hair Mn	0.072 (0.031)	0.060 (0.025)	2.422	0.015
Air Mn → soil Mn → dust Mn → hair Mn	0.010 (0.007)	0.009 (0.006)	1.430	0.153
Soil Mn → hair Mn	0.189 (0.118)	0.113 (0.071)	1.597	0.110
Soil Mn → dust Mn → hair Mn	0.112 (0.046)	0.067 (0.027)	2.464	0.014
Dust Mn → hair Mn	0.218 (0.066)	0.233 (0.070)	3.320	0.001
HVAC score → hair Mn	-0.069 (0.042)	-0.098 (0.060)	-1.634	0.102
HVAC score → dust Mn → hair Mn	-0.014 (0.011)	-0.020 (0.016)	-1.244	0.213
Hours/week spent outside → hair Mn	0.379 (0.119)	0.180 (0.055)	3.272	0.001
Parent education → hair Mn	-0.031 (0.021)	-0.087 (0.060)	-1.448	0.148
Parent education → dust Mn → hair Mn	-0.010 (0.007)	-0.029 (0.019)	-1.565	0.117
Gender → hair Mn	0.536 (0.096)	0.623 (0.103)	6.047	<0.001
Air Mn → dust Mn	0.331 (0.103)	0.259 (0.073)	3.568	<0.001
Air Mn → soil Mn → dust Mn	0.047 (0.028)	0.037 (0.022)	1.688	0.091
Soil Mn → dust Mn	0.513 (0.119)	0.287 (0.066)	4.324	<0.001
HVAC score → dust Mn	-0.064 (0.042)	-0.085 (0.057)	-1.474	0.141
Parent education → dust Mn	-0.048 (0.028)	-0.125 (0.075)	-1.673	0.094
Air Mn → soil Mn	0.092 (0.053)	0.129 (0.072)	1.806	0.071

All variables except gender are standardized on Y and X; gender (binary variable) is standardized on Y. The t statistics and P values are for the standardized estimates. Air Mn is the weighted average annual ambient air Mn modeled at the participants' home and school.

Table 13. Direct and Indirect Pathway Coefficients for Model for Toenail Mn

Pathway	Unstandardized estimate (SE)	Standardized estimate (SE)	t statistic	P value
Air Mn → toenail Mn	0.064 (0.063)	0.059 (0.058)	1.018	0.309
Air Mn → soil Mn → toenail Mn	0.007 (0.008)	0.007 (0.008)	0.865	0.387
Air Mn → dust Mn → toenail Mn	0.046 (0.029)	0.043 (0.027)	1.614	0.107
Air Mn → soil Mn → dust Mn → toenail Mn	0.008 (0.007)	0.007 (0.007)	1.068	0.286
Soil Mn → toenail Mn	0.179 (0.119)	0.094 (0.063)	1.492	0.136
Soil Mn → dust Mn → toenail Mn	0.189 (0.056)	0.099 (0.029)	3.412	0.001
Dust Mn → toenail Mn	0.391 (0.067)	0.369 (0.056)	6.632	<0.001
HVAC score → toenail Mn	-0.021 (0.045)	-0.026 (0.056)	-0.474	0.635
HVAC score → dust Mn → toenail Mn	-0.037 (0.017)	-0.046 (0.021)	-2.178	0.029
Hours/week spent outside → toenail Mn	0.410 (0.148)	0.167 (0.061)	2.736	0.006
Parent education → toenail Mn	0.021 (0.025)	0.050 (0.058)	0.849	0.396
Parent education → dust Mn → toenail Mn	-0.024 (0.011)	-0.056 (0.027)	-2.085	0.037
Gender → toenail Mn	0.049 (0.110)	0.050 (0.113)	0.442	0.659
Air Mn → dust Mn	0.119 (0.073)	0.117 (0.071)	1.662	0.096
Air Mn → soil Mn → dust Mn	0.019 (0.018)	0.019 (0.018)	1.089	0.276
Soil Mn → dust Mn	0.484 (0.111)	0.269 (0.061)	4.377	<0.001
HVAC score → dust Mn	-0.096 (0.040)	-0.125 (0.053)	-2.375	0.018
Parent education → dust Mn	-0.060 (0.027)	-0.153 (0.069)	-2.207	0.027
Air Mn → soil Mn	0.040 (0.035)	0.071 (0.062)	1.141	0.254

All variables except gender are standardized on Y and X; gender (binary variable) is standardized on Y. The t statistics and P values are for the standardized estimates. Air Mn is the weighted average annual ambient air Mn modeled at the participants' home and school.

Table 14. Direct and Indirect Pathway Coefficients for Model for Toenail Mn with 2010 Data Excluded from Model

Pathway	Unstandardized estimate (SE)	Standardized estimate (SE)	t statistic	P value
Air Mn → toenail Mn	0.056 (0.092)	0.041 (0.066)	0.619	0.536
Air Mn → soil Mn → toenail Mn	0.021 (0.017)	0.015 (0.012)	1.226	0.220
Air Mn → dust Mn → toenail Mn	0.116 (0.041)	0.084 (0.029)	2.918	0.004
Air Mn → soil Mn → dust Mn → toenail Mn	0.016 (0.011)	0.012 (0.008)	1.527	0.127
Soil Mn → toenail Mn	0.234 (0.131)	0.123 (0.069)	1.780	0.075
Soil Mn → dust Mn → toenail Mn	0.185 (0.062)	0.098 (0.032)	3.051	0.002
Dust Mn → toenail Mn	0.358 (0.074)	0.337 (0.063)	5.317	<0.001
HVAC score → toenail Mn	-0.054 (0.051)	-0.068 (0.064)	-1.060	0.289
HVAC score → dust Mn → toenail Mn	-0.024 (0.016)	-0.030 (0.020)	-1.456	0.145
Hours/week spent outside → toenail Mn	0.430 (0.168)	0.177 (0.070)	2.523	0.012
Parent education → toenail Mn	0.027 (0.026)	0.064 (0.063)	1.022	0.307
Parent education → dust Mn → toenail Mn	-0.018 (0.011)	-0.043 (0.026)	-1.629	0.103
Gender → toenail Mn	0.088 (0.125)	0.091 (0.127)	0.712	0.477
Air Mn → dust Mn	0.324 (0.103)	0.250 (0.072)	3.478	0.001
Air Mn → soil Mn → dust Mn	0.046 (0.028)	0.035 (0.022)	1.635	0.102
Soil Mn → dust Mn	0.518 (0.120)	0.290 (0.067)	4.355	<0.001
HVAC score → dust Mn	-0.066 (0.043)	-0.088 (0.058)	-1.513	0.130
Parent education → dust Mn	-0.050 (0.028)	-0.128 (0.073)	-1.760	0.078
Air Mn → soil Mn	0.088 (0.052)	0.122 (0.070)	1.733	0.083

All variables except gender are standardized on Y and X; gender (binary variable) is standardized on Y. The t statistics and P values are for the standardized estimates. Air Mn is the weighted average annual ambient air Mn modeled at the participants' home and school.

Table 15. Model Fit Statistics for SEM Models for Blood Mn, Hair Mn, and Toenail Mn

		Blood Mn		Hair Mn		Toenail Mn	
Model fit index	Criteria for good model fit	Model including all years (n=305)	Model excluding 2010 (n=249)	Model including all years (n=317)	Model excluding 2010 (n=261)	Model including all years (n=303)	Model excluding 2010 (n=247)
χ^2 test							
χ^2		4.602	5.531	5.035	5.880	4.412	5.444
df		6	6	6	6	6	6
P	>0.05	0.596	0.478	0.539	0.437	0.6211	0.488
RMSEA	<0.06	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
CFI	>0.95	1.000	1.000	1.000	1.000	1.000	1.000
TLI (NNFI)	>0.95	1.164	1.040	1.036	1.004	1.068	1.023
SRMR	<0.08	0.033	0.039	0.036	0.043	0.034	0.041

Abbreviations: CFI, comparative fit index; NNFI, non-normed fit index; RMSEA, root mean square error of approximation; SRMR, standardized root mean square residual; TLI, Tucker-Lewis index.

Figure 1. Modeled Exposure Area

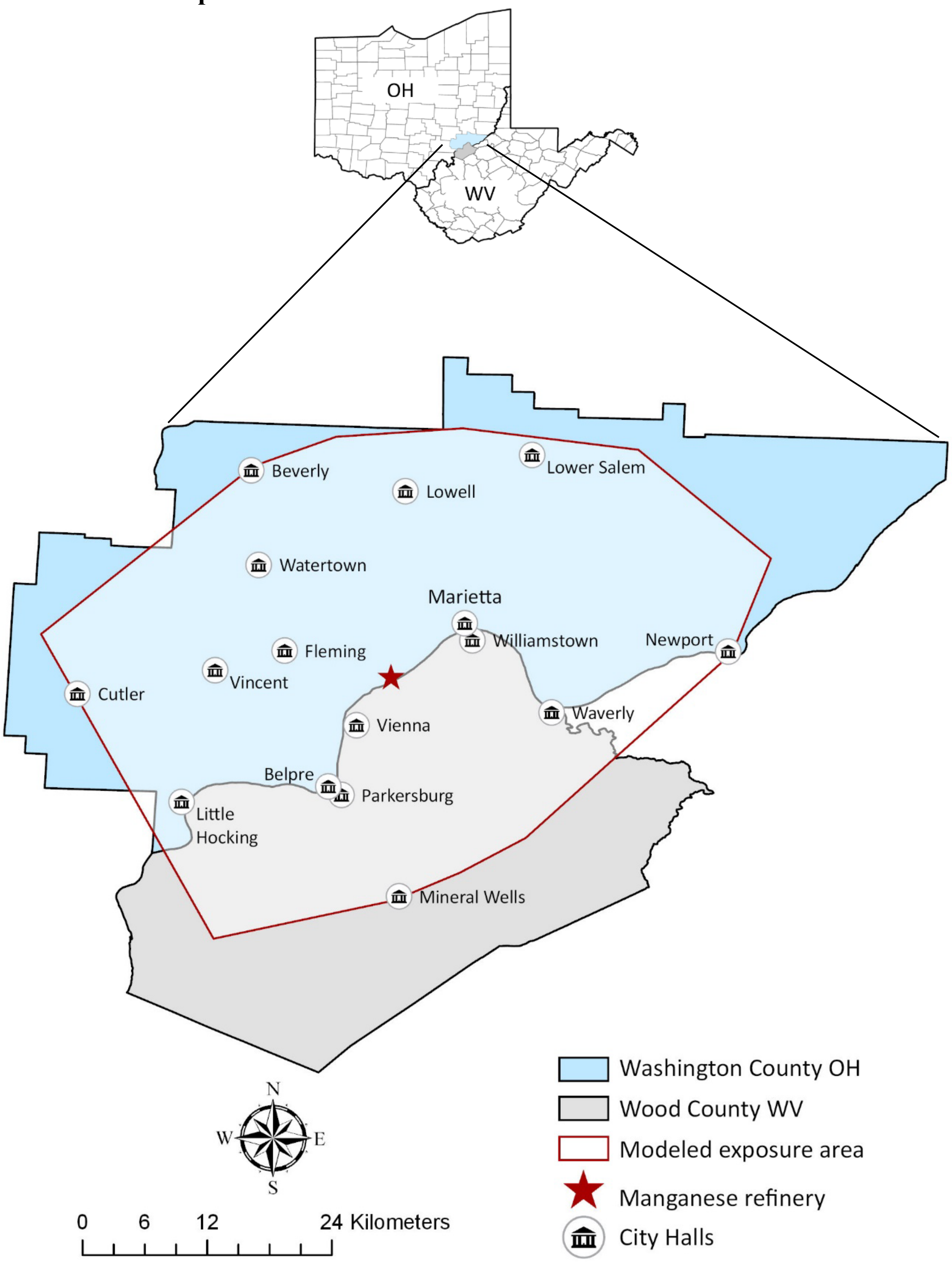


Figure 2. Modeled Average Ambient Air Mn by Year for Participant Homes and Schools

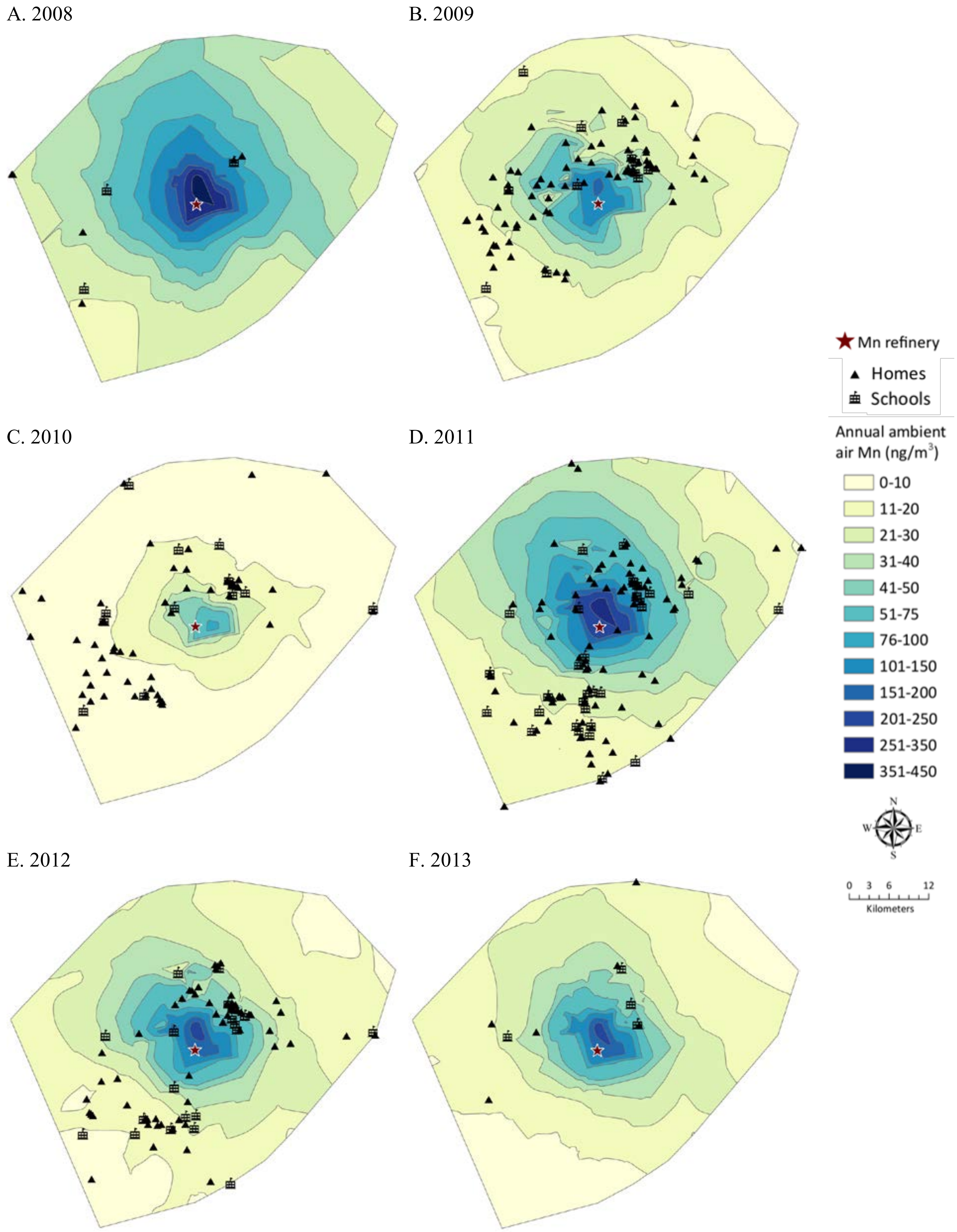
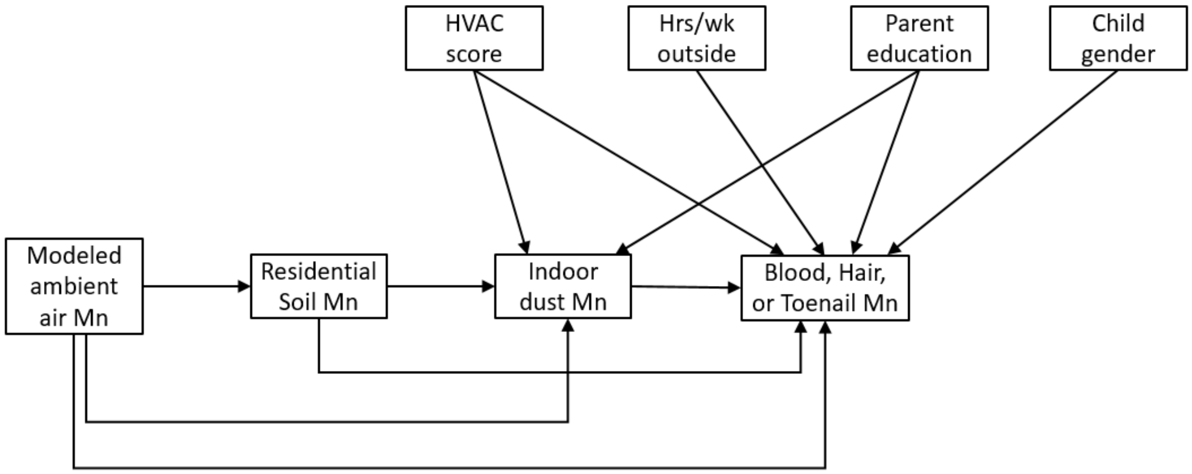


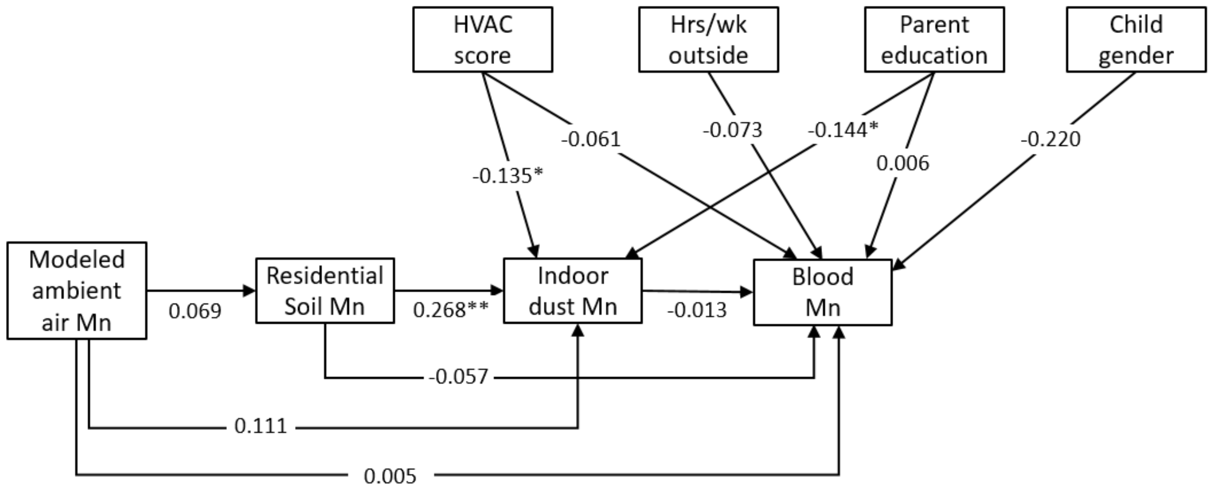
Figure 3. Hypothesized Model for Pathways of Exposure from Ambient Air Mn to Blood Mn, Hair Mn, or Toenail Mn



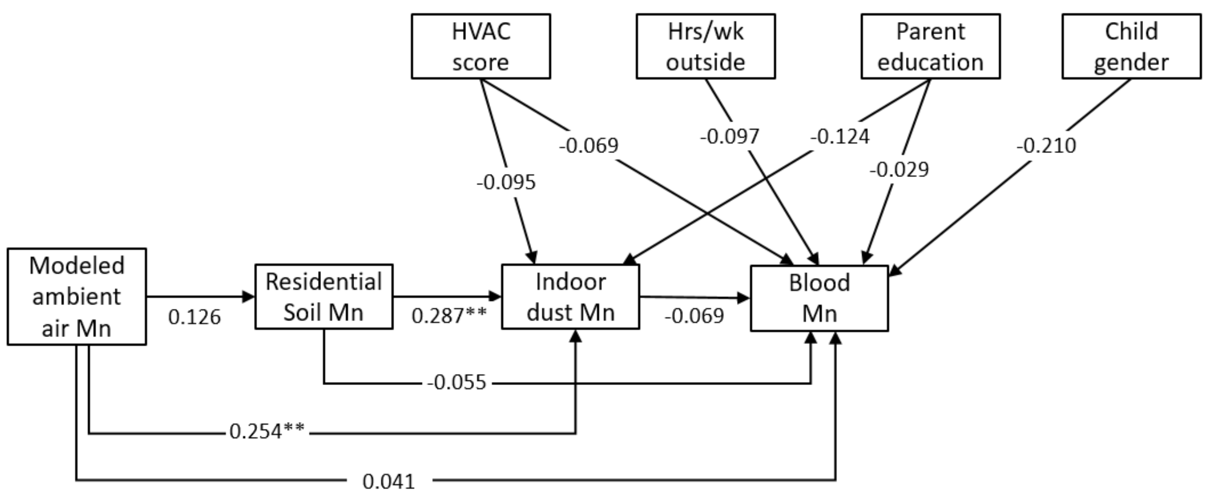
Abbreviation: Hrs/wk, hours/week

Figure 4A-B. Structural Equation Models for Pathways from Ambient Air Mn Exposure to Blood Mn

A. Hypothesized Model Including All Years



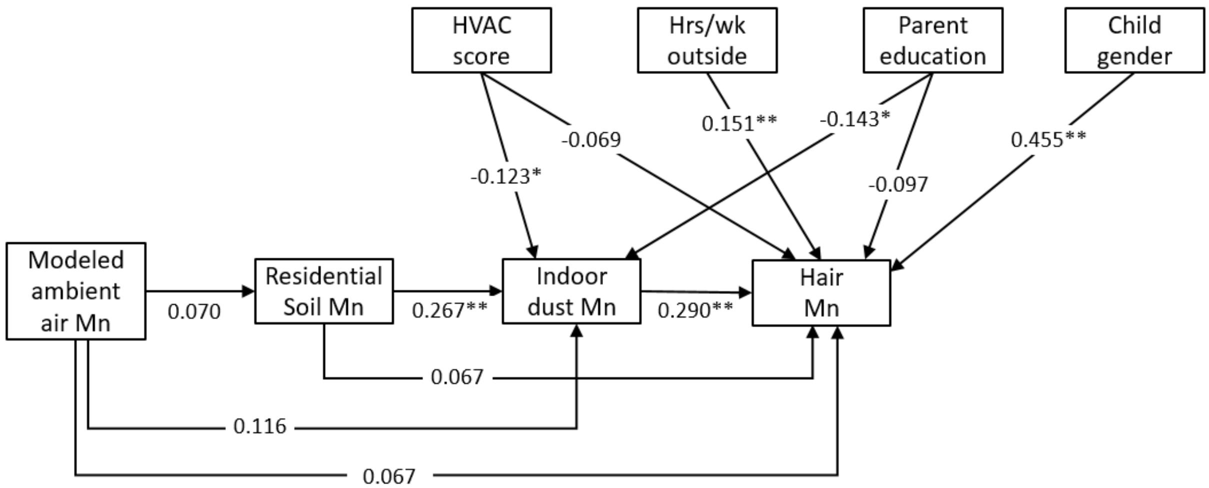
B. Model with 2010 Excluded



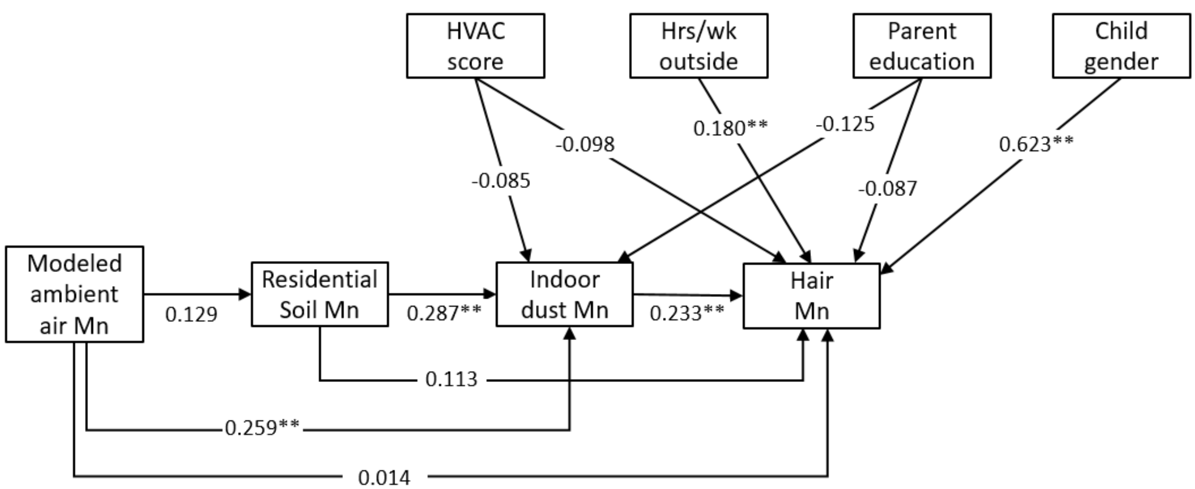
*P<0.05, **P<0.01. Values are standardized coefficients. All variables except gender are standardized on Y and X; gender is standardized on Y. Abbreviation: Hrs/wk, hours/week.

Figure 5A-B. Structural Equation Models for Pathways from Ambient Air Mn Exposure to Hair Mn

A. Hypothesized Model Including All Years



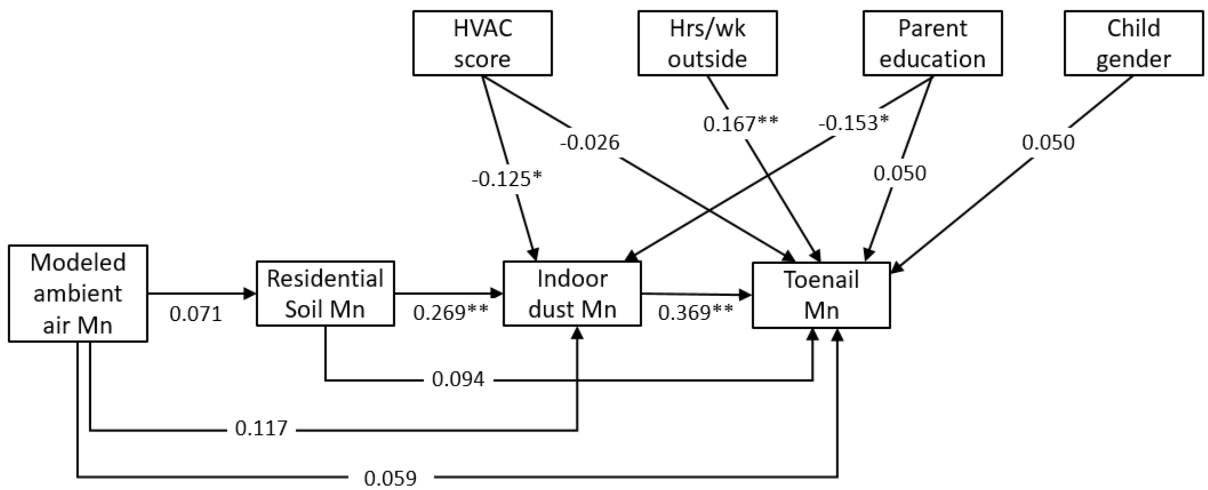
Model with 2010 Excluded



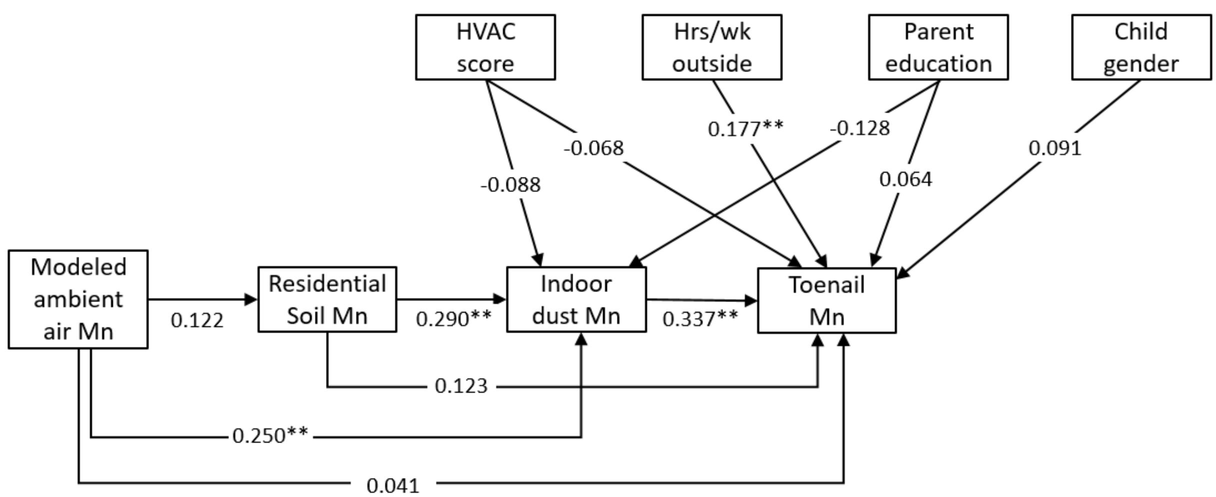
*P<0.05, **P<0.01. Values are standardized coefficients. All variables except gender are standardized on Y and X; gender is standardized on Y. Abbreviation: Hrs/wk, hours/week.

Figure 6A-B. Structural Equation Models for Pathways from Ambient Air Mn Exposure to Toenail Mn

A. Hypothesized Model Including All Years



Model with 2010 Excluded



*P<0.05, **P<0.01. Values are standardized coefficients. All variables except gender are standardized on Y and X; gender is standardized on Y. Abbreviation: Hrs/wk, hours/week.

References

Aelion CM, Davis HT, McDermott S, Lawson AB. Soil metal concentrations and toxicity: associations with distances to industrial facilities and implications for human health. Sci Total Environ 2009;407:2216-2223.

Agency for Toxic Substances and Disease Registry ATSDR, 2009. Health Consultation. Marietta Air Investigation, Marietta, Ohio. 24p. July. Retrieved February 1, 2020 from atsdr.cdc.gov/HAC/pha/marietta3/ATSDRMariettaHealthConsultationIII2009Final.pdf.

Agency for Toxic Substances and Disease Registry ATSDR, 2012. Toxicological Profile for Manganese (Final). 556p. September. Retrieved February 1, 2020 from atsdr.cdc.gov/ToxProfiles/tp151.pdf.

Akinwunmi F, Akinhanmi TF, Atobatele ZA, Adewole O, Odekunle K, Arogundade LA et al. Heavy metal burdens of public primary school children related to playground soils and classroom dusts in Ibadan North-West local government area, Nigeria. Environ Toxicol Pharmacol 2017;49:21-26.

Barratt W. The Barratt Simplified Measure of Social Status (BSMSS), 2012. Retrieved February 1, 2020 from http://socialclassoncampus.blogspot.com/2012/06/barratt-simplified-measure-of-social.html.

Boudissa SM, Lambert J, Muller C, Kennedy G, Gareau L, Zayed J. Manganese concentrations in the soil and air in the vicinity of a closed manganese alloy production plant. Sci Total Environ 2006;361:67-72.

Bowler RM, Harris M, Gocheva V, Wilson K, Kim Y, Davis SI et al. Anxiety affecting parkinsonian outcome and motor efficiency in adults of an Ohio community with environmental airborne manganese exposure. Int J Hyg Environ Health 2012;215:393-405.

Bowler RM, Kornblith ES, Gocheva VV, Colledge MA, Bollweg G, Kim Y et al. Environmental exposure to manganese in air: Associations with cognitive functions. Neurotoxicology 2015;49:139-148.

Bowler RM, Adams SW, Wright CW, Kim Y, Booty A, Colledge M et al. Medication use associated with exposure to manganese in two Ohio towns. Int J Environ Health Res 2016;26:483-496.

Bowler RM, Beseler CL, Gocheva VV, Colledge M, Kornblith ES, Julian JR et al. Environmental exposure to manganese in air: Associations with tremor and motor function. Sci Total Environ 2016;541:646-654.

Bowler RM, Adams SW, Schwarzer R, Gocheva VV, Roels HA, Kim Y et al. Validity of self-reported concentration and memory problems: Relationship with neuropsychological assessment and depression. J Clin Exp Neuropsychol 2017;39:1026-1036.

Broberg K, Taj T, Guazzetti S, Peli M, Cagna G, Pineda D et al. Manganese transporter genetics and sex modify the association between environmental manganese exposure and neurobehavioral outcomes in children. Environ Int 2019;130:104908.

Butler L, Gennings C, Peli M, Borgese L, Placidi D, Zimmerman N et al. Assessing the contributions of metals in environmental media to exposure biomarkers in a region of ferroalloy industry. J Expo Sci Environ Epidemiol 2019;29:674-687.

Callan AC, Winters M, Barton C, Boyce M, Hinwood AL. Children's exposure to metals: a community-initiated study. Arch Environ Contam Toxicol 2012;62:714-722.

Callan AC, Hinwood AL, Ramalingam M, Boyce M, Heyworth J, McCafferty P et al. Maternal exposure to metals-concentrations and predictors of exposure. Environ Res 2013;126:111-117.

Carter MR, Gaudet BJ, Stauffer DR, White TS, Brantley SL. Using soil records with atmospheric dispersion modeling to investigate the effects of clean air regulations on 60 years of manganese deposition in Marietta, Ohio (USA). Sci Total Environ 2015;515-516:49-59.

Chang JC, Hanna SR. Air quality model performance evaluation. Meteorol Atmos Phys 2004;87:167-196.

Chattopadhyay G, Lin KC, Feitz AJ. Household dust metal levels in the Sydney metropolitan area. Environ Res 2003;93:301-307.

Coetzee DJ, McGovern PM, Rao R, Harnack LJ, Georgieff MK, Stepanov I. Measuring the impact of manganese exposure on children's neurodevelopment: advances and research gaps in biomarker-based approaches. Environ Health 2016;15:91.

Colledge MA, Julian JR, Gocheva VV, Beseler CL, Roels HA, Lobdell DT et al. Characterization of air manganese exposure estimates for residents in two Ohio towns. J Air Waste Manag Assoc 2015;65:948-957.

Corathers CA. Manganese. U.S. Geological Survey 2009 Minerals Yearbook, August 2011. Retrieved February 1, 2020 from: https://www.usgs.gov/centers/nmic/manganese-statistics-and-information.

Corathers CA. Manganese. U.S. Geological Survey 2010 Minerals Yearbook, October 2012. Retrieved February 1, 2020 from: https://www.usgs.gov/centers/nmic/manganese-statistics-and-information.

Eastman RR, Jursa TP, Benedetti C, Lucchini RG, Smith DR. Hair as a biomarker of environmental manganese exposure. Environ Sci Technol 2013;47:1629-1637.

Environmental Systems Research Institute. (n.d.). Esri Data & Maps, USA census layer package. Retrieved February 1, 2020 from http://www.arcgis.com/home/group.html?q=USAcensus layerpackage&t=group&start=1&id=24838c2d95e14dd18c25e9bad55a7f82&view=list#content.

FOIA online. (n.d.). EPA-HQ-2019-004104. Retrieved February 1, 2020 from https://foiaonline.gov/foiaonline/action/public/search/ quickSearch?query=EPA-HQ-2019-004104.

Fulk F, Haynes EN, Hilbert TJ, Brown D, Petersen D, Reponen T. Comparison of stationary and personal air sampling with an air dispersion model for children's ambient exposure to manganese. J Expo Sci Environ Epidemiol 2016;26:494-502.

Fulk F, Succop P, Hilbert TJ, Beidler C, Brown D, Reponen T et al. Pathways of inhalation exposure to manganese in children living near a ferromanganese refinery: A structural equation modeling approach. Sci Total Environ 2017;579:768-775.

Gulson B, Mizon K, Taylor A, Korsch M, Stauber J, Davis JM et al. Changes in manganese and lead in the environment and young children associated with the introduction of methylcyclopentadienyl manganese tricarbonyl in gasoline-preliminary results. Environ Res 2006;100:100-114.

Gulson B, Mizon K, Taylor A, Korsch M, Davis JM, Louie H et al. Pathways of Pb and Mn observed in a 5-year longitudinal investigation in young children and environmental measures from an urban setting. Environ Pollut 2014;191:38-49.

Gunier RB, Jerrett M, Smith DR, Jursa T, Yousefi P, Camacho J, et al. Determinants of manganese levels in house dust samples from the CHAMACOS cohort. Sci Total Environ 2014;497-498:360-368.

Gutiérrez-González E, García-Esquinas E, de Larrea-Baz NF, Salcedo-Bellido I, Navas-Acien A, Lope V, et al. Toenails as biomarker of exposure to essential trace metals: A review. Environ Res 2019;179(Pt A):108787. doi: 10.1016/j.envres.2019.108787. Epub 2019 Oct 7.

Han B, Hu LW, Bai Z. Human exposure assessment for air pollution. Adv Exp Med Biol 2017;1017:27-57.

Hanna S, Chang J. Acceptance criteria for urban dispersion model evaluation. Meteorol Atmos Phys 2012;116:133-146.

Haynes EN, Heckel P, Ryan P, Roda S, Leung YK, Sebastian K et al. Environmental manganese exposure in residents living near a ferromanganese refinery in Southeast Ohio: a pilot study. Neurotoxicology 2010;31:468-474.

Haynes EN, Ryan P, Chen A, Brown D, Roda S, Kuhnell P et al. Assessment of personal exposure to manganese in children living near a ferromanganese refinery. Sci Total Environ 2012;427-428:19-25.

Haynes EN, Sucharew H, Kuhnell P, Alden J, Barnas M, et al. Manganese exposure and neurocognitive outcomes in rural school-age children: the Communities Actively Researching Exposure Study (Ohio, USA). Environ Health Perspect 2015;123:1066-1071.

Haynes EN, Sucharew H, Hilbert TJ, Kuhnell P, Spencer A, Newman NC et al. Impact of air manganese on child neurodevelopment in East Liverpool, Ohio. Neurotoxicology 2018;64:94-102.

Herring S, Huq P. A review of methodology for evaluating the performance of atmospheric transport and dispersion models and suggested protocol for providing more informative results. Fluids 2018;*3(1)*,20; https://doi.org/10.3390/fluids3010020.

Kim Y, Bowler RM, Abdelouahab N, Harris M, Gocheva V, Roels HA. Motor function in adults of an Ohio community with environmental manganese exposure. Neurotoxicology 2011;32:606-614.

Kline RB. *Principles and Practice of Structural Equation Modeling*. 4th ed. New York, NY: The Guilford Press; 2016.

Kornblith ES, Casey SL, Lobdell DT, Colledge MA, Bowler RM. Environmental exposure to manganese in air: Tremor, motor and cognitive symptom profiles. Neurotoxicology 2018;64:152-158.

Layton DW, Beamer PI. Migration of contaminated soil and airborne particulates to indoor dust. Environ Sci Technol 2009;43:8199-8205.

Ledoux F, Laversin H, Courcot D, Courcot L, Zhilinskaya EA, Puskaric E et al. Characterization of iron and manganese species in atmospheric aerosols from anthropogenic sources. Atmos Res 2006;82:622-632.

Lioy PJ, Freeman NCG, Millette JR. Dust: a metric for use in residential and building exposure assessment and source characterization. Environ Health Perspect 2002;110:969-983.

Lucas EL, Bertrand P, Guazzetti S, Donna F, Peli M, Jursa TP et al. Impact of ferromanganese alloy plants on household dust manganese levels: implications for childhood exposure. Environ Res 2015;138:279-290.

Lucchini RG, Guazzetti S, Zoni S, Donna F, Peter S, Zacco A et al. Tremor, olfactory and motor changes in Italian adolescents exposed to historical ferro-manganese emission. Neurotoxicology 2012;33:687-696.

Lucchini RG, Zoni S, Guazzetti S, Bontempi E, Micheletti S, Broberg K et al. Inverse association of intellectual function with very low blood lead but not with manganese exposure in Italian adolescents. Environ Res 2012;118:65-71.

Lucchini RG, Guazzetti S, Zoni S, Benedetti C, Fedrighi C, Peli M et al. Neurofunctional dopaminergic impairment in elderly after lifetime exposure to manganese. Neurotoxicology 2014;45:309-317.

Lucchini R, Placidi D, Cagna G, Fedrighi C, Oppini M, Peli M et al. Manganese and developmental neurotoxicity. Adv Neurobiol 2017;18:13-34.

Lucchini RG, Aschner M, Landrigan PJ, Cranmer JM. Neurotoxicity of manganese: indications for future research and public health intervention from the Manganese 2016 conference. Neurotoxicology 2018;64:1-4.

Massaquoi LD, Ma H, Liu XH, Han PY, Zuo SM, Hua ZX et al. Heavy metal accumulation in soils, plants, and hair samples: an assessment of heavy metal exposure risks from the consumption of vegetables grown on soils previously irrigated with wastewater. Environ Sci Pollut Res Int 2015;22:18456-18468.

McDermott S, Bao W, Aelion CM, Cai B, Lawson AB. Does the metal content in soil around a pregnant woman's home increase the risk of low birth weight for her infant? Environ Geochem Health 2014;36:1191-1197.

Menezes-Filho JA, Souza KOF, Rodrigues JLG, Santos NRD, Bandeira MJ, Koin NL et al. Manganese and lead in dust fall accumulation in elementary schools near a ferromanganese alloy plant. Environ Res 2016;148:322-329.

Moya J, Bearer CF, Etzel RA. Children's behavior and physiology and how it affects exposure to environmental contaminants. Pediatrics 2004;113:996-1006.

Multi-Resolution Land Characteristics Consortium (MLRC). (n.d.). Data. Retrieved February 1, 2020 from https://www.mrlc.gov/data.

National Centers for Environmental Information. (n.d.-a). Automated Surface Observing System (ASOS). Retrieved February 1, 2020 from https://www.ncdc.noaa.gov/data-access/land-based-station-data/land-based-datasets/automated-surface-observing-system-asos.

National Centers for Environmental Information. (n.d.-b). Quick Links, 3. Integrated Surface Database (ISD), Hourly, Global. Retrieved February 1, 2020 from https://www.ncdc.noaa.gov/data-access/quick-links#dsi-3505.

National Oceanic and Atmospheric Administration. (n.d.). NOAA/ESRL Radiosonde Database. Retrieved February 1, 2020 from https://ruc.noaa.gov/raobs/.

O'Neal SL, Zheng W. Manganese toxicity upon overexposure: a decade in review. Curr Environ Health Rep 2015;2:315-328.

Otero-Pregigueiro D, Fernandez-Olmo I. Use of CALPUFF to predict airborne Mn levels at schools in an urban area impacted by a nearby manganese alloy plant. Environ Int 2018;119:455-465.

Otero-Pregigueiro D, Hernandez-Pellon A, Borge R, Fernandez-Olmo I. Estimation of PM10-bound manganese concentration near a ferromanganese alloy plant by atmospheric dispersion modelling. Sci Total Environ 2018;627:534-543.

Ozkaynak H, Baxter LK, Dionisio KL, Burke J. Air pollution exposure prediction approaches used in air pollution epidemiology studies. J Expo Sci Environ Epidemiol 2013;23:566-572.

Pavilonis BT, Lioy PJ, Guazzetti S, Bostick BC, Donna F, Peli M et al. Manganese concentrations in soil and settled dust in an area with historic ferroalloy production. J Expo Sci Environ Epidemiol 2015;25:443-450.

Pena-Fernandez A, Gonzalez-Munoz MJ, Lobo-Bedmar MC. "Reference values" of trace elements in the hair of a sample group of Spanish children (aged 6-9 years) - are urban topsoils a source of contamination?. Environ Toxicol Pharmacol 2014;38:141-152.

Racette BA. Manganism in the 21st century. Neurotoxicology 2014;45:201-207.

Reis AP, Costa S, Santos I, Patinha C, Noack Y, Wragg J et al. Investigating relationships between biomarkers of exposure and environmental copper and manganese levels in house dusts from a Portuguese industrial city. Environ Geochem Health 2015;37:725-744.

Rentschler G, Covolo L, Haddad AA, Lucchini RG, Zoni S, Broberg K. ATP13A2 (PARK9) polymorphisms influence the neurotoxic effects of manganese. Neurotoxicology 2012;33:697-702.

Rink SM, Ardoino G, Queirolo EI, Cicariello D, Mañay N, Kordas K. Associations between hair manganese levels and cognitive, language, and motor development in preschool children from Montevideo, Uruguay. Arch Environ Occup Health 2014;69:46-54.

Rodrigues JLG, Araújo CFS, Dos Santos NR, Bandeira MJ, Anjos ALS, Carvalho CF, et al. Airborne manganese exposure and neurobehavior in school-aged children living near a ferro-manganese alloy plant. Environ Res 2018;167:66-77.

Rodriguez-Barranco M, Lacasana M, Aguilar-Garduno C, Alguacil J, Gil F, Gonzalez-Alzaga B et al. Association of arsenic, cadmium and manganese exposure with neurodevelopment and behavioural disorders in children: a systematic review and meta-analysis. Sci Total Environ 2013;454-455:562-577.

Rosa MJ, Benedetti C, Peli M, Donna F, Nazzaro M, Fedrighi C et al. Association between personal exposure to ambient metals and respiratory disease in Italian adolescents: a cross-sectional study. BMC Pulm Med 2016;16:6,016-0173-9.

Rugless F, Bhattacharya A, Succop P, Dietrich KN, Cox C, Alden J et al. Childhood exposure to manganese and postural instability in children living near a ferromanganese refinery in Southeastern Ohio. Neurotoxicol Teratol 2014;41:71-79.

Salem Ali Albar HM, Ali N, Musstjab Akber Shah Eqani SA, Alhakamy NA, Nazar E, Rashid MI, et al. Trace metals in different socioeconomic indoor residential settings, implications for human health via dust exposure. Ecotoxicol Environ Saf. 2020;189:109927. doi: 10.1016/j.ecoenv.2019.109927.

Smith D, Gwiazda R, Bowler R, Roels H, Park R, Taicher C, et al. Biomarkers of Mn exposure in humans. Am J Ind Med 2007;50:801-811.

Solis-Vivanco R, Rodriguez-Agudelo Y, Riojas-Rodriguez H, Rios C, Rosas I, Montes S. Cognitive impairment in an adult Mexican population non-occupationally exposed to manganese. Environ Toxicol Pharmacol 2009;28:172-178.

Tabachnick BG, Fidell LS. *Using Multivariate Statistics*. 6th ed. Boston, MA. Pearson Education, 2013.

Tong ST, Lam KC. Home sweet home? A case study of household dust contamination in Hong Kong. Sci Total Environ 2000;256:115-123.

U.S. Census Bureau. (n.d.-a). Centers of Population, 2010. Retrieved February 1, 2020 from https://www.census.gov/geographies/reference-files/time-series/geo/centers-population.html.

U.S. Census Bureau. (n.d.-b). Population and Housing Unit Estimates Tables. Retrieved February 1, 2020 from https://www.census.gov/programs-surveys/popest/data/tables.All.html.

U.S. Department of Housing and Urban Development (HUD), 1995. HUD Guidelines for the Evaluation and Control of Lead-Based Paint Hazards in Housing. Retrieved February 1, 2020 from https://www. hud.gov/program_offices/healthy_homes/lbp/hudguidelines1995.

U.S. Environmental Protection Agency, 1996. Method 3050B: Acid Digestion of Sediments, Sludges, and Soils, Revision 2. Washington, DC. Retrieved February 1, 2020 from https://www.epa.gov/esam/epa-method-3050b-acid-digestion-sediments-sludges-and-soils.

U.S. Environmental Protection Agency, 2002. IRIS Chemical Assessment Summary for Manganese (CAS No. 7439-96-5). Retrieved February 1, 2020 from https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0373_summary.pdf.

U.S. Environmental Protection Agency, 2004. User's Guide for the AMS/EPA Regulatory Model AERMOD. EPA-454/B-03-001. Retrieved February 1, 2020 from https://nepis.epa.gov.

U.S. Environmental Protection Agency, 2008. AERSURFACE User's Guide EPA-454/B-08-001. Retrieved February 1, 2020 from https://www3.epa.gov/scram001/7thconf/aermod/aersurface_userguide.pdf.

U.S. Environmental Protection Agency, 2015. Economic Impact Analysis (EIA) for the Manganese Ferroalloys RTR. Final Report. (EPA-452/R-15-004). Retrieved February 1, 2020 from https://nepis.epa.gov/Exe/ZyPDF.cgi/P100MLTY.PDF?Dockey=P100MLTY.PDF.

U.S. Environmental Protection Agency. (n.d.). National Emissions Inventory. Retrieved February 1, 2020 from https://www.epa.gov/air-emissions-inventories/national-emissions-inventory-nei.

VanderWeele TJ, Mathur MB. Some desirable properties of the Bonferroni correction: is the Bonferroni correction really so bad? Am J Epidemiol 2019;188:617-618.

Vollet K, Haynes EN, Dietrich KN. Manganese exposure and cognition across the lifespan: contemporary review and argument for biphasic dose-response health effects. Curr Environ Health Rep 2016;3:392-404.

Wahlberg KE, Guazzetti S, Pineda D, Larsson SC, Fedrighi C, Cagna G et al. Polymorphisms in manganese transporters SLC30A10 and SLC39A8 are associated with children's neurodevelopment by influencing manganese homeostasis. Front Genet 2018;9:664.

World Health Organization, 2000. Air Quality Guidelines for Europe, Second Edition. WHO regional publications, European series, No. 91. Retrieved February 1, 2020 from http://www.euro.who.int/__data/ assets/ pdf_file/0005/74732/E71922.pdf.

Zoni S, Lucchini RG. Manganese exposure: cognitive, motor and behavioral effects on children: a review of recent findings. Curr Opin Pediatr 2013;25:255-260.

Zota AR, Riederer AM, Ettinger AS, Schaider LA, Shine JP, Amarasiriwardena CJ et al. Associations between metals in residential environmental media and exposure biomarkers over time in infants living near a mining-impacted site. J Expo Sci Environ Epidemiol 2016;26:510-519.

Zou B, Wilson JG, Zhan FB, Zeng Y. Air pollution exposure assessment methods utilized in epidemiological studies. J Environ Monit 2009;11:475-490.