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Child and Adolescent Manganese Biomarkers and Adolescent Postural Balance in Marietta CARES Cohort Participants

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Background: Manganese (Mn) plays a significant role in both human health and global industries. Epidemiological studies of exposed populations demonstrate a dose-dependent association between Mn and neuromotor effects ranging from subclinical effects to a clinically defined syndrome. However, little is known about the relationship between early life Mn biomarkers and adolescent postural balance.

Objectives: This study investigated the associations between childhood and adolescent Mn biomarkers and adolescent postural balance in participants from the longitudinal Marietta Communities Actively Researching Exposures Study (CARES) cohort.

Methods: Participants were recruited into CARES when they were 7–9 y old, and reenrolled at 13–18 years of age. At both time points, participants provided samples of blood, hair, and toenails that were analyzed for blood Mn and lead (Pb), serum cotinine, hair Mn, and toenail Mn. In adolescence, participants completed a postural balance assessment. Greater sway indicates postural instability (harmful effect), whereas lesser sway indicates postural stability (beneficial effect). Multivariable linear regression models were conducted to investigate the associations between childhood and adolescent Mn biomarkers and adolescent postural balance adjusted for age, sex, height–weight ratio, parent/caregiver intelligence quotient, socioeconomic status, blood Pb, and serum cotinine.

Results: CARES participants who completed the adolescent postural balance assessment ($n = 123$) were 98% White and 54% female and had a mean age of 16 y (range: 13–18 y). In both childhood and adolescence, higher Mn biomarker concentrations were significantly associated with greater adolescent sway measures. Supplemental analyses revealed sex-specific associations; higher childhood Mn biomarker concentrations were significantly associated with greater sway in females compared with males.

Discussion: This study found childhood and adolescent Mn biomarkers were associated with subclinical neuromotor effects in adolescence. This study demonstrates postural balance as a sensitive measure to assess the association between Mn biomarkers and neuromotor function. https://doi.org/10.1289/EHP13381

Introduction

Manganese (Mn) is an element that exists ubiquitously in the environment, often in combination with other elements.[1] Mn plays a significant role in both human health and global industries.[1] Mn is an essential nutrient in trace quantities needed to sustain many health processes in the body, such as the formation of healthy cartilage and bone, as well as digestion, reproduction, and the antioxidant defense system, immune response, energy production, and neuronal regulation.[2] The general population is exposed to sufficient quantities of Mn through diet given that Mn is present in a wide variety of foods, including shellfish, nuts, grains, legumes, dark chocolate, and pineapple, among others.[3] Mn deficiency is rare and has been associated with skeletal abnormalities and an impaired oxidant defense system.[4] Owing to its versatile physical and chemical properties, Mn is used in a number of applications that benefit our daily lives, including iron and steel manufacturing, aluminum alloys for beverage cans, welding, and dry cell and electric-vehicle batteries, as well as a component of some fungicides.[1] Industrial processing of Mn can emit Mn compounds into the air, creating occupational exposure for workers and environmental exposure for residents living in the surrounding communities.[5–8]

The route of exposure and the amount (i.e., dose) are a key determinants in how Mn affects the body as either an essential nutrient or a neurotoxicant.[9] Ingested Mn enters the body through the gastrointestinal tract and is subjected to a delicate homeostatic process of Mn transport across enterocytes of the intestinal wall and removal by the liver.[10] Mn is absorbed into the body at rates of 1%–5% to sustain the essential levels needed to fulfill the nutritional requirements of the body.[11] Conversely, inhaled airborne Mn particulate matter can enter the body at unregulated levels through the nose, where it is not subjected to the same homeostatic regulations as ingested Mn.[12] From the nose, inhaled Mn can be directly transported into the brain and lung through two main pathways: *a*) via olfactory or trigeminal presynaptic nerve endings located in the nasal mucosa, traveling along the olfactory neuronal pathway, where Mn crosses the blood-brain barrier and

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accumulates in the brain[12,13]; and *b*) via transport across the respiratory epithelial lining of the lung and depositing into the lymphatic system or blood to circulate throughout the body. When the intake of inhaled Mn exceeds elimination, Mn preferentially accumulates in the brain regions responsible for neuromotor function control, such as the basal ganglia, frontal cortex, and cerebellum.[14–17] This accumulation can lead to neurotoxicity in a dose-dependent manner described as a "continuum of dysfunction," ranging from subclinical neuropsychological and neuromotor decrements to a clinically defined syndrome, manganism, which resembles the symptoms of Parkinson's disease (PD), although etiologies differ between diseases.[18] Because cessation of exposure may not result in restored motor function, it is critical to identify preclinical signs of neurotoxic Mn accumulation.[19,20]

Mn-exposed workers in industries such as welding, mining, and refining were the first populations to show Mn poisoning resulting from high occupational exposures.[21–23] In a summary of occupational Mn exposure studies, the Agency for Toxic Substances and Disease Registry (ATSDR) reported that workers exposed to higher levels of occupational Mn, ranging from 2,000 to 22,000 $\mu g/m^3$, demonstrated overt symptoms of manganism that included tremors, difficulty walking, and facial muscle spasms.[6] Workers exposed to lower levels of occupational Mn exposure, ranging from 70 to 970 $\mu g/m^3$, demonstrated subclinical neuromotor decrements related to eye–hand coordination, hand steadiness, reaction time, postural stability, motor efficiency and speed, and tremor.[6,18,24] Environmental Mn exposures occur at concentrations two or three orders of magnitude lower than even the occupational levels. The US Environmental Protection Agency (EPA) reported ambient annual Mn concentrations in US EPA Region 5 from 26 monitoring sites: 5 sites in commercial areas, 11 sites in industrial areas, and 10 sites in residential areas. Industrial sites reported higher annual ambient Mn concentrations (10th percentile: 0.032 $\mu g/m^3$, 90th percentile: 0.376 $\mu g/m^3$) compared with residential sites (10th percentile: 0.009 $\mu g/m^3$, 90th percentile: 0.085 $\mu g/m^3$) and commercial sites (10th percentile: 0.048 $\mu g/m^3$, 90th percentile: 0.192 $\mu g/m^3$).[25] The ATSDR has set the minimal risk level for chronic inhalation exposure to Mn at 0.30 $\mu g/m^3$.[6]

Given that the relationship between Mn exposure and neurotoxicity is dose dependent, investigating subclinical neuromotor effects of Mn in environmentally exposed adults and children is a relevant public health concern. It is important to study motor outcomes because it can inform motor limitations and potential for injury. In addition, motor function is an important neurological domain because it has a significant influence on psychological well-being.[26] Related to exposure in adults, Ruiz-Azcona et al. recently published a systemic review and meta-analysis of published studies on environmentally exposed adults and cognitive and motor functions.[27] Their pooled analysis included 11 studies with reported data susceptible for meta-analysis through pooled correlation or a standardized means difference (SMD) approach between exposed and nonexposed groups.[18,28–37] The pooled correlation revealed statistically significant negative correlations between adult Mn levels and motor scores. The SMD approach revealed statistically significantly worse motor scores in the exposed adults compared with nonexposed adults.[27]

In children, the beneficial and neurotoxic effects of Mn exposure may be unique due to the developmental timing of exposure and neuromotor function assessment (i.e., prenatal, postnatal, early childhood, childhood, adolescence, adulthood).[38,39] For instance, the prenatal developmental time point is considered a time point of increased demand for Mn as an essential nutrient to support healthy development of the central nervous system and fetus morphology, which is the initiation of development of neuromotor function.[3,9] This role of Mn as essential and neurotoxic is supported by multiple studies that found prenatal Mn exposure demonstrated an inverse U-shaped association where both low and high Mn concentrations were associated with deficits in neonatal behavioral neurological assessments at 3 d of age[40] and deficits in Bayley Scales of Infant Development (BSID)-11 measures at 6 months of age.[41,42] Other prenatal Mn exposure studies have found inverse linear[43–45] and null[46] associations with motor function during infant years 0–2, a time point when postural reflexes and rudimentary movement skills are developed. During the early childhood years 3–5, general fundamental skills such as locomotion, balance, and manipulation continue to develop. Starting in the childhood years 5–9, combinations of fundamental skills are developed into transitional skills (i.e., jumping rope, bicycling, kickball).[26] By the late childhood years 10–12, specific skills of combinations of fundamental and transitional skills are developing (i.e., soccer kicking, gymnastics, hitting a ball), and by the adolescent years 13–18, specialized motor skills, such as achieving excellence in a sport, mature. Prospective studies found prenatal Mn exposure was not associated with motor outcomes from the McCarthy Scales of Children's Abilities at 4 or 5 years of age.[47,48] Chiu et al. found higher prenatal Mn exposure was associated with better body stability in 11- to 14-y-old adolescent males compared with females.[49] Similarly, Mora et al. reported higher postnatal Mn exposure was associated with better motor outcomes at 7 and 10.5 years of age for males compared with females.[50] Cross-sectional studies conducted during childhood and adolescence have reported mixed findings. For example, some studies found Mn exposure results in inverse linear associations with motor function at 7–9,[51] 9–15,[52] and 11–14 years of age,[53] whereas other studies found no associations at 7–12[54] and 12–16 years of age.[55] Many questions remain related to the long-term impact of early childhood Mn exposure on neurodevelopment in general and on adolescent neuromotor function in particular.

The present study directly addresses this knowledge gap by leveraging our well-established longitudinal pediatric Marietta Communities Actively Researching Exposure Study (CARES) cohort, which was developed to address resident concern about Mn emissions from the longest-operating ferromanganese refinery in North America.[56,57] In the present study, we report on investigating the associations between childhood and adolescent biomarkers of Mn exposure, indicated by blood, hair, and toenail Mn concentrations, and adolescent neuromotor function, as measured by postural balance. We hypothesized that both childhood and adolescent Mn biomarkers will be significantly and positively associated with adolescent postural balance variables, indicating greater sway or postural instability.

Methods

Study Design and Population

Marietta CARES participants were invited to complete the adolescent postural balance sub-study through their enrollment in CARES. CARES eligibility included participants who were 13–17 y old, had resided in Marietta or Cambridge, Ohio, and their surrounding communities throughout their entire lives with no plans to move for at least 1 y and had completed a childhood clinic visit between 2008 and 2013 when they were 7–9 y old[58] and were scheduled for the adolescent clinic visit within 8 wk of the adolescent postural balance assessment dates. CARES adolescent participants were recruited through mailed letters and phone calls. Adolescent balance sub-study exclusion criteria included any health condition that may impact the postural test result, such as uncorrected vision problems, vestibular or musculoskeletal disorders, or were >250 lb (113.4 kilograms) in weight. The postural balance assessment was conducted over eight weekends between May 2017 and September 2018. The University of Cincinnati Institutional Review Board

approved this study. All participants and their parents or caregivers signed an informed consent, and the adolescents also signed an assent.

Internal Dose Markers of Exposure

Participants completed a childhood (7–9 years of age) and adolescent (13–17 years of age) clinic visit where they provided biospecimens of whole blood, hair, and toenails that were subsequently analyzed for Mn after each time point. Whole blood was also analyzed for blood lead (Pb) and serum cotinine, a marker of environmental tobacco smoke.[59] The methods of collection and analysis were the same across both time points unless otherwise specified and are detailed below.

Whole blood. A nurse trained in pediatric phlebotomy collected venous whole-blood specimens from the antecubital vein. One 3-mL purple-top [dipotassium salt of ethylenediaminetetraacetic acid (K_2EDTA)] tube of whole blood was collected for trace element analysis. A standard red-top tube (no preservative) was also collected, and serum was harvested off the clot for cotinine measurements. Whole-blood samples (for Mn and Pb analysis) were refrigerated at 4°C and serum samples (for cotinine analysis) were frozen at −20°C until shipped monthly to the New York State Department of Health's Wadsworth Center, Albany, New York. For samples collected in the childhood years 7–9 between 2008 and 2013, whole blood was analyzed for Mn by graphite furnace atomic absorption spectrometry (GFAAS)[60] and for Pb by inductively coupled plasma–mass spectrometry (ICP-MS).[61] The analytical methods used for analyzing childhood samples were optimized and validated for biomonitoring techniques, and the results are traceable to international standards.[62,63] Blood samples collected in the adolescent years 13–18 between 2017 and 2018 were analyzed for Pb and Mn using an updated method optimized for a newer ICP-MS instrument (Tables S1 and S2). The new method was well validated for four toxic metals (Tables S3–S5), and a robust method comparison was performed that showed good agreement with the prior ICP-MS method and with the GFAAS methods used for Mn in whole blood (Figure S1). Comparability and performance between the two ICP-MS instruments were monitored throughout the entire study period by analyzing the same internal quality control samples used previously (Table S4) and by participation in four international external quality assurance schemes for trace elements in whole blood (Table S5). Ongoing measurement accuracy was assured by routinely including blood-based National Institute of Standards and Technology Standard Reference Materials (NIST SRM 955c and SRM 1401) with certified values for several trace elements, including Pb and Mn (Table S3).[60,64] The limit of detection (LOD) for blood Mn was <2.1 μg/L by GFAAS, whereas by ICP-MS it varied from <0.85 μg/L to <1.4 μg/L. The LOD for blood Pb was <0.34 μg/dL on the older ICP-MS instrument compared with <0.04 μg/dL on the newer ICP-MS instrument.

Serum cotinine was analyzed by liquid chromatography/tandem mass spectrometry (LC-MS/MS) using a modification of the techniques used by the Centers for Disease Control and Prevention (CDC) for the National Health and Nutrition Examination Survey (NHANES)[65] and the New York State Wadsworth Laboratories for the New York City Health and Nutrition Examination Survey studies.[66] Each serum specimen underwent the following process: It was equilibrated with a trideuterated cotinine internal standard solution, extracted using a 96-well Bond Elut Plexa Solid Phase Extraction plate (Varian). The acetonitrile sample extract was evaporated to dryness and then reconstituted in a solution containing 96% acetonitrile and 4% water. Subsequently, the reconstituted sample was analyzed using LC-MS/MS with electrospray ionization. To ensure quality control, three different pools were employed, each having varying target cotinine concentrations (0.173, 1.61, and 15.7 μg/L) at low, medium, and high levels. The final results were blank corrected using the mean batch blank value. The same method and LC-MS/MS instrument were used for serum cotinine throughout childhood and adolescence. The LOD for serum cotinine was 0.05 μg/L.[58] For values below the LOD, machine readings provided by the laboratory were used in statistical analysis,[67] and for values <0, concentrations imputed with the LOD divided by the square root of 2 were used in statistical analysis[68,69]

Hair. Participants were asked in advance for hair to be free of all gels, oils, and hair creams or sprays prior to sample collection. Hair samples were not collected if the participant had chemically treated hair. Collection was completed by a research team member trained in proper collection procedures with a clean environment. Approximately 20 strands of hair from the occipital region were cut with ceramic scissors as close to the scalp as possible. If the hair was long, it was trimmed to 6 cm. The hair sample was taped toward the nonscalp-side of the hair shaft onto an index card with an arrow pointing in the direction of the scalp end, placed into a prelabeled envelope, and stored at room temperature until shipped for analysis. Childhood hair samples were shipped to Channing Trace Metals Laboratory at the Brigham and Women's Hospital, Harvard School of Public Health for analysis, and adolescent hair samples were sent to the lab relocation to the Molecular Environmental Health Laboratory at the Mount Sinai Hospital. Hair samples were first washed in a 1% (vol/vol) Triton X-100 solution, digested using concentrated nitric acid and then acid digestates were analyzed for Mn by ICP-MS.[51] The LOD for Mn in hair was <2 ng/g.[58]

Toenails. Parents/caregivers were asked to bring collected clippings of their child toenails inside a labeled envelope to the childhood and adolescent clinic visits. The toenails were to be clipped after growing for at least 2 wk, removing all nail polish, and washing feet with soap and water. Toenail samples were stored at room temperature until shipped to the Microbiology and Environmental Toxicology Department at the University of California Santa Cruz for analysis. Toenails were analyzed for Mn by magnetic sector ICP-MS, and the LOD for Mn in toenails was <0.03 μg/g.

Parent/Caregiver Intellectual Function and Socioeconomic Status

Full-scale intelligence quotient (IQ) of the parent/caregiver as measured by the Wechsler Abbreviated Scale of Intelligence (WASI) at the childhood clinic visit was used in this study.[58,70] Adult IQ is considered relatively stable over time; therefore, we did not reassess this caregiver measure at the adolescent visit.[71] Socioeconomic status (SES) of the parent/caregiver was measured at the adolescent clinic visit using the Barratt Simplified Measure of Social Status (BSMSS), which was completed by the parent/caregiver.[72] Although the caregiver had previously completed this measure of social status at the childhood clinic visit, the BSMSS was readministered at the adolescent clinic visit because it is based on factors that may change with time. For analysis, we used the parent/caregiver responses at the adolescent clinic visit. The BSMSS includes educational attainment scores and occupational prestige scores of the parent/caregiver and the parent/caregiver's mother, father, and spouse/partner. These questions yielded a calculated ordinal score that ranged from 8 to 66. A higher number reflects more advanced SES.

Postural Balance Assessment

Daily setup for balance testing involved a standardized protocol to maintain identical test conditions. The experimental setup required the connection of a Hall-effect force plate, Accusway-O (model Accusway-O, Advanced Mechanical Technology Inc.) and laptop installed with Balance Clinic software (Advanced

Mechanical Technology Inc.) and KineLysis software (University of Cincinnati). Before testing and halfway through testing, a standard 18-kg weight was analyzed on the force plate at five specific locations to confirm calibration to <3% error for the field studies.[73] This experimental setup quantifies the movement pattern of the body's center of pressure associated with body sway captured at a frequency of 50 Hz. The software programs use the raw data collected from the force plate during testing to generate a "fingerprint" of body sway called a stabilogram.[74] For each stabilogram, the following four postural balance/sway (the terms balance and sway are interchangeable) measures were quantified: sway area, sway length, medio–lateral excursion, and anterior–posterior excursion.[75] Sway area (in centimeters squared) is defined as the area encompassed by the *x*–*y* plot of the excursion of the center of pressure. Sway length (in centimeters squared) is defined as the total distance traveled by the center of pressure. Medio–lateral (in centimeters squared) and anterior–posterior (in centimeters squared) excursion are the net deviations of the center of pressure in the medio–lateral and anterior–posterior directions, respectively. Figure S2 represents the experimental setup, including the reference coordinate system for the force platform used to quantify a participant's postural sway and the connected laptop used to generate the stabilogram.

The maintenance of upright postural balance requires the integration of three sensory afferents: visual (eyes), vestibular (inner ear organs that act as an accelerometer and gyroscope),[76] and proprioceptive (conscious and unconscious awareness of joint position)[77] systems, which are weighted differently according to specific tasks.[78–81] Our research team administered a postural balance test protocol of six test conditions designed to challenge the visual, vestibular, and proprioceptive afferent systems required for the maintenance of postural balance, as detailed in Figure 1, which was adapted from Bhattacharya et al.[82] Each test lasted 30 s. The progression of the six-test protocol was designed for each subsequent condition to be more difficult, as reflected by an expected increase in sway area: *a*) stand with eyes open on the force plate; *b*) stand with eyes closed on the force plate; *c*) stand with eyes open on 0.10 meter thick foam pad placed on the force plate; *d*) stand with eyes closed on 0.10 meter thick foam pad placed on the force plate; *e*) stand with eyes open for 12 s, then on verbal command, bend torso at the waist and stay in that position for 5 s and return to the upright position and stand for the remainder of the 30-s test; *f*) same as *e* but with eyes closed. Repeat trials were conducted for the static tests with eyes open and eyes closed to establish a representative baseline before adding the foam and bending tests. The average of each condition was used for statistical analyses.

Other Study Covariates

Participant height was measured with a stadiometer at the adolescent clinic visit, and participant weight was measured with a scale at the adolescent postural balance assessment. Height and weight were combined into a height–weight ratio to be used for all statistical analysis. The height–weight ratio was used as a direct correlation with the physical proportions of the participant and has been used as a covariate in our previous postural balance analyses.[37,51] Birthday and biological sex at birth were established at the childhood clinic visit. Age at the balance assessment was calculated using birthday and date of postural balance assessment to be used for all statistical analysis.

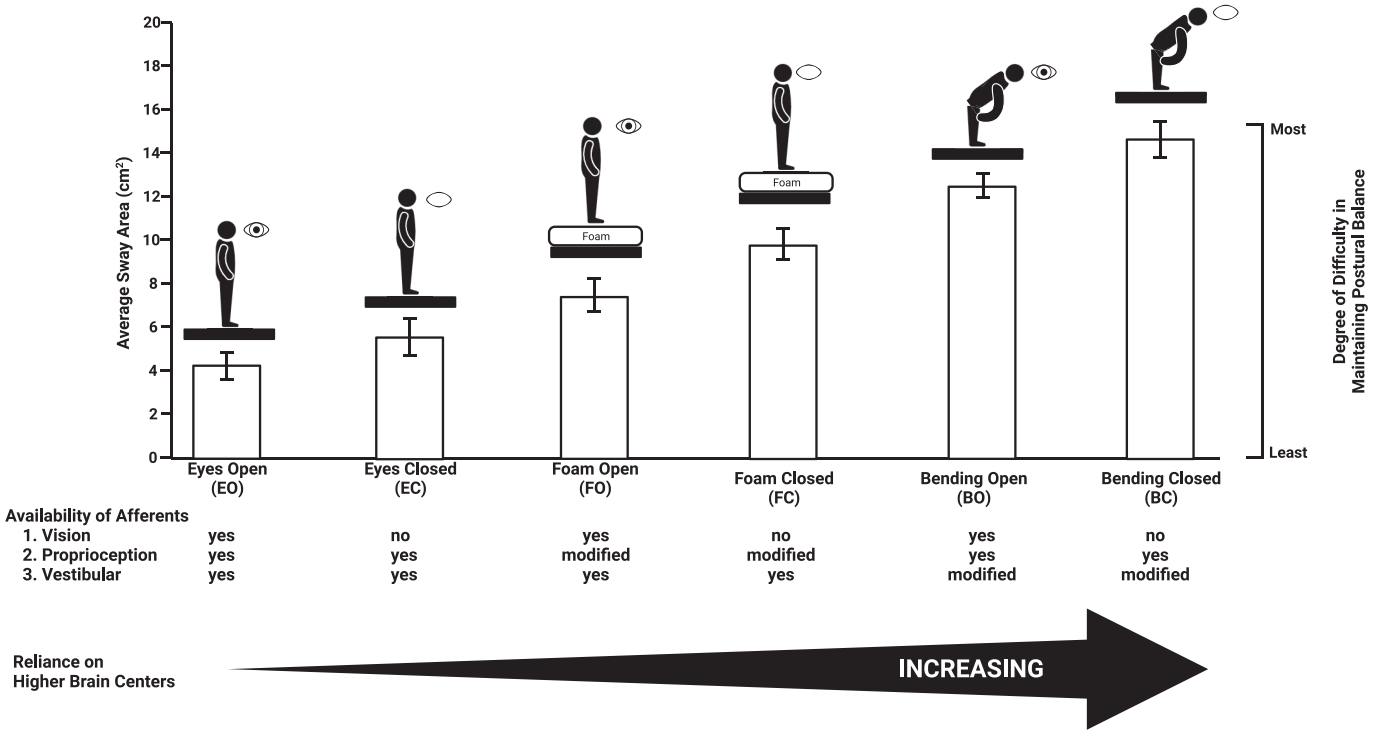

Figure 1. Schematic representation of the effect of the postural balance test protocol on sway area, afferents, and brain centers; *x*-axis describes the postural balance test protocol of six test conditions designed to challenge the visual, vestibular, and proprioceptive afferent systems required for the maintenance of postural balance; modified afferent under foam open (FO) and foam closed (FC) tests mean proprioceptors are not receiving the actual pressure under the feet because the participant is standing on a foam surface that is soft; modified afferent under bending open (BO) and bending closed (BC) tests mean vestibular system of inner ear organs have modified accelerometer and gyroscope input due to bending motion; *y*-axis describes the average sway area (the area encompassed by the *x*–*y* plot of the excursion of the participant's center of pressure) in the bars, the lines represent confidence intervals for standard deviations; the progression of the six-test protocol was designed for each subsequent test condition to be more difficult, as reflected by an expected increase in sway area. Created in biorender.com.

Statistical Analyses

All statistical analyses were conducted using SAS statistical software (version 9.4 for Windows; SAS Institute Inc.) unless otherwise specified. All biomarkers and postural balance outcomes were natural log-transformed (ln) to approximate normal distributions for statistical analyses. Descriptive statistics were calculated to describe the demographic and biomarker variables of the study participants. Demographic variables are presented as the mean ± standard deviation (SD), and biomarker variables are presented as the geometric mean(GM) ± geometric standard deviation (GSD). Pearson's bivariate correlations were examined between the biomarkers of child and adolescent environmental exposures. Pearson's correlation was defined as low if the correlation coefficient was <0.29, medium if the correlation coefficient was between 0.30 and 0.49, and high if the correlation coefficient was >0.50. Multivariable linear regression models were conducted to investigate the associations between childhood and adolescent Mn biomarkers and adolescent postural balance while adjusting for covariates. Independent variables included childhood blood Mn, childhood hair Mn, childhood toenail Mn, adolescent blood Mn, adolescent hair Mn, and adolescent toenail Mn levels. Dependent variables included sway area, sway length, medio–lateral sway, and anterior–posterior sway for each of the six postural balance test conditions: eyes open, eyes closed, foam open, foam closed, bending open, and bending closed. Covariates were the same across all models and included age, sex, height–weight ratio, parent/caregiver IQ, parent/caregiver SES, ln blood Pb, and ln serum cotinine. These covariates were chosen *a priori* based on our previous studies and factors known to impact postural balance.[37,51] Individual factors of age, sex, and height–weight ratio[83,84] and environmental exposures of blood Pb[85] and environmental tobacco smoke, measured by serum cotinine,[86] have been associated with postural balance. Both parent/caregiver IQ and parent/caregiver SES were included given the unique roles they demonstrate with neuromotor development.[51,87] Regression coefficients (βs), 95% confidence intervals (CIs), and *p*-values were reported from multivariable regression models for the Mn biomarker coefficient (i.e., blood, hair, or toenail). To interpret the β coefficient, a positive value reflects greater sway or postural instability (i.e., harmful effect), and a negative value reflects less sway or postural stability (i.e., beneficial effect). For all regression models, any participant with a missing value for any of the variables was excluded from the analytical sample.

Supplemental analyses were conducted to investigate different associations between Mn biomarkers and motor outcomes by sex by including a sex × Mn (blood, hair, toenail) interaction term in all models. Regression coefficients (β) and 95% CIs are reported separately for males and females, and *p*-values are reported from multivariable regression models for Mn × sex interaction coefficient. Statistical significance was set at $p < 0.05$. To adjust for multiple comparisons, we applied the Benjamini–Hochberg procedure[88] to the *p*-values from all of the regression models using R (version 4.1.3; R Developmental Core Team).

Additional supplemental analyses were conducted to further investigate our findings from the adjusted multivariable linear regression models between childhood and adolescent Mn biomarkers and adolescent postural balance. To explore potential different findings due in part to different sample sizes for each biomarker, a supplemental analysis was conducted using a restricted sample comprising participants with complete data on all biomarkers at both time points (childhood blood Mn and Pb, childhood serum cotinine, childhood hair Mn, childhood toenail Mn, adolescent blood Mn and Pb, adolescent serum cotinine, adolescent hair Mn, and adolescent toenail Mn levels) on the adjusted multivariable linear regression models. In another supplemental analysis aimed to understand whether there was confounding by exposure at the other time point (childhood or adolescence), multiple informant models using generalized estimating equations (MIM GEEs) were employed to test for differences in associations across Mn exposure time point (childhood, adolescence).[89–91]

Results

Participant Characteristics

CARES participants who completed the adolescent postural balance assessment ($n = 123$) were 98% White and 53% female, with a mean age of 16.1 y (range: 13–18.1 y) (Table 1). All participants consented and enrolled before they were 18 y, but due to scheduling of balance, one participant turned 18 within the 8 week time frame between consenting and balance assessment. Their childhood and adolescent biomarker concentrations of blood Mn, blood Pb, serum cotinine, hair Mn, and toenail Mn are reported as GM ± GSD and ranges in Table 2. Missing childhood blood Mn and blood Pb values ($n = 17$) were due to participant refusing blood draw ($n = 7$) and research nurse unable to collect sample ($n = 10$). Missing childhood serum cotinine values ($n = 15$) were due to participant refusing blood draw ($n = 7$), research nurse unable to collect sample ($n = 7$), and lab unable to analyze sample ($n = 1$). Missing childhood hair Mn values ($n = 4$) were due to lab unable to analyze sample ($n = 4$). Missing childhood toenail Mn values ($n = 12$) were due to parent/caregiver not providing sample ($n = 10$) and lab unable to analyze sample ($n = 2$). Missing adolescent blood Mn and Pb values ($n = 14$) were due to participant not completing adolescent clinic visit ($n = 2$), participant refusing blood draw ($n = 7$), participant refusing blood draw of one tube ($n = 1$), and research nurse unable to collect sample ($n = 4$). Missing adolescent serum cotinine values ($n = 13$) were due to participant not completing adolescent clinic visit ($n = 2$), participant refusing blood draw ($n = 7$), and research nurse unable to collect sample ($n = 4$). Missing adolescent hair Mn values ($n = 4$) were due to participant not completing adolescent clinic visit ($n = 2$) and research nurse unable to collect sample ($n = 2$). Missing adolescent values ($n = 13$) were due to participant not completing adolescent clinic visit ($n = 2$) and parent/caregiver not providing sample ($n = 11$).

In childhood years 7–9, the GM ± GSD concentrations for blood Mn ($n = 106$) was 9.7 ± 1.3 μg/L (range: 5.30–18.8), blood Pb ($n = 106$) was 0.79 ± 1.5 μg/dL (range: 0.36–2.7), serum

Table 1. Demographic characteristics of Marietta CARES adolescent balance participants, 2017–2018.

Adolescent characteristics	*n* (%)	Mean ± SD	Range
Age (y)	123 (100)	16.1 ± 1.2	13–18.1
Sex			
Female	66 (53)	—	—
Male	57 (46)	—	—
Ethnicity			
White	120 (97.5)	—	—
Asian	2 (0.016)	—	—
Black	1 (0.008)	—	—
Height–weight ratio (determined in lbs)[a]	121 (98)	2.55 ± 0.580	1.57–4.27
Parent/caregiver characteristics			
Parent/caregiver IQ (WASI)[b]	123 (100)	107 ± 13.8	65.0–132
Parent/caregiver SES (BSMSS)[c]	121 (98)	38.3 ± 10.2	15.3–57.3

Note: —, not applicable; BSMSS, Barratt Simplified Measure of Social Status; CARES, Communities Actively Researching Exposures Study; IQ, intelligence quotient; SD, standard deviation; SES, socioeconomic status; WASI, Wechsler Abbreviated Scale of Intelligence.
[a]Missing values ($n = 2$) due to participant did not complete adolescent clinic visit ($n = 2$).
[b]Higher scores are indicative of higher IQ score.
[c]Higher scores are indicative of more advanced SES. Missing values ($n = 2$) due to participants refused consent ($n = 2$).

Table 2. Biomarker concentrations of environmental exposures in Marietta CARES adolescent balance participants during childhood (2008–2013) and adolescence (2017–2018), $n = 123$.

	Childhood			Adolescence		
Biomarkers	n	GM ± GSD	Range	n	GM ± GSD	Range
Blood Mn (μg/L)	106[a]	9.7 ± 1.3	5.30–18.8	109[b]	10 ± 1.3	5.0–30
Blood Pb (μg/dL)	106[a]	0.79 ± 1.5	0.36–2.7	109[b]	0.42 ± 1.7	0.18–6.8
Serum cotinine (μg/L)	108[c]	0.044 ± 6.6	0.00060–6.1	110[d]	0.10 ± 9.8	0.00700–180
Hair Mn (ng/g)	119[e]	407 ± 2.51	63.19–7,379	119[f]	189 ± 2.69	29.90–3,330
Toenail Mn (μg/g)	111[g]	0.65 ± 2.7	0.060–9.7	110[h]	0.35 ± 2.5	0.040–2.4

Note: CARES, Communities Actively Researching Exposures Study; GM, geometric mean; GSD, geometric standard deviation; LOD, limit of detection; Mn, manganese; Pb, lead.
[a]Missing values ($n = 17$) due to participant refused blood draw ($n = 7$) and research nurse unable to collect sample ($n = 10$).
[b]Missing values ($n = 14$) due to participant did not complete adolescent clinic visit ($n = 2$), participant refused blood draw ($n = 7$), participant refused blood draw of one tube ($n = 1$), and research nurse unable to collect sample ($n = 4$).
[c]For values below LOD and >0 ($n = 70$), machine readings provided by the laboratory were used, and for values <0 ($n = 1$), concentrations were imputed with the LOD divided by the square root of 2. Missing values ($n = 15$) due to participant refused blood draw ($n = 7$), research nurse unable to collect sample ($n = 7$), and lab unable to analyze sample ($n = 1$).
[d]For values below LOD ($n = 57$) below LOD, machine readings provided by the laboratory were used. Missing values ($n = 13$) due to participant did not complete adolescent clinic visit ($n = 2$), participant refused blood draw ($n = 7$), and research nurse unable to collect sample ($n = 4$).
[e]Missing values ($n = 4$) due to lab unable to analyze sample ($n = 4$).
[f]Missing values ($n = 4$) due to participant did not complete adolescent clinic visit ($n = 2$) and research nurse unable to collect sample ($n = 2$).
[g]Missing values ($n = 12$) due to parent/caregiver did not provide sample ($n = 10$) and lab unable to analyze sample ($n = 2$).
[h]Missing values ($n = 13$) due to participant did not complete adolescent clinic visit ($n = 2$) and parent/caregiver did not provide sample ($n = 11$).

cotinine ($n = 108$) was 0.044 ± 6.6 μg/L (range: 0.00060–6.1), hair Mn ($n = 119$) was 407 ± 2.51 ng/g (range: 63.19–7,379), and toenail Mn ($n = 111$) was 0.65 ± 2.7 μg/g (range: 0.060–9.7). For childhood serum cotinine, 71 (66%) values were below the LOD. In adolescent years 13–18, the GM ± GSD concentrations for blood Mn ($n = 109$) was 10 ± 1.3 μg/L (range: 5.0–30), blood Pb ($n = 109$) was 0.42 ± 1.7 μg/dL (range: 0.18–6.8), serum cotinine ($n = 110$) was 0.10 ± 9.8 μg/L (range: 0.000700–180), hair Mn ($n = 119$) was 189 ± 2.69 ng/g (range: 29.90–3,330), and toenail Mn ($n = 110$) was 0.35 ± 2.5 μg/g (range: 0.040–2.4). For adolescent serum cotinine, 57 (52%) of values were below the LOD, and for these values, machine readings provided by the laboratory were used. The GM ± GSD and ranges of childhood and adolescent biomarker concentrations by sex are reported in Table 3.

Pearson's correlations among the biomarkers of environmental exposure at both time points are reported in Table 4. A high degree of correlation was demonstrated between childhood ln blood Mn and adolescent ln blood Mn (Pearson's $r = 0.75$, $p < 0.001$) and also between childhood ln serum cotinine and adolescent ln serum cotinine (Pearson's $r = 0.59$, $p < 0.001$).

Stabilograms from two participants are presented in Figure 2 to illustrate the differences in center of pressure movement sway patterns associated with blood Mn. The participant with lower

Table 3. Biomarker concentrations of environmental exposures in Marietta CARES adolescent balance participants during childhood (2008–2013) and adolescence (2017–2018) by sex, $n = 123$.

	Females			Males		
Biomarkers	n	GM ± GSD	Range	n	GM ± GSD	Range
Blood Mn (μg/L)						
Childhood	55[a]	10 ± 1.3	5.30–17.4	51[b]	9.4 ± 1.3	5.80–18.8
Adolescent	57[c]	10 ± 1.3	6.2–22	52[d]	9.8 ± 1.3	5.0–30
Blood Pb (μg/dL)						
Childhood	55[a]	0.76 ± 1.5	0.36–2.0	51[b]	0.82 ± 1.6	0.37–2.7
Adolescent	57[c]	0.35 ± 1.7	0.18–6.8	52[d]	0.53 ± 1.6	0.23–1.6
Serum cotinine (μg/L)						
Childhood	57[e]	0.044 ± 6.6	0.0011–6.1	51[f]	0.043 ± 6.8	0.00060–3.6
Adolescent	57[c]	0.074 ± 7.3	0.00934–180	53[g]	0.139 ± 12.7	0.00700–176
Hair Mn (ng/g)						
Childhood	66	339 ± 2.20	75.59–2,288	53[h]	513 ± 2.78	63.19–7,379
Adolescent	65[i]	147 ± 2.54	29.9–2,820	54[j]	256 ± 2.67	52.60–3,330
Toenail Mn (μg/g)						
Childhood	59[k]	0.58 ± 2.4	0.060–6.7	52[l]	0.73 ± 3.1	0.086–9.7
Adolescent	59[m]	0.32 ± 2.5	0.060–2.5	51[n]	0.40 ± 2.6	0.0400–2.36

Note: CARES, Communities Actively Researching Exposures Study; GM, geometric mean; GSD, geometric standard deviation; Mn, manganese; Pb, lead.
[a]Missing values ($n = 11$) due to participant refused blood draw ($n = 4$) and research nurse unable to collect sample ($n = 7$).
[b]Missing values ($n = 6$) due to participant refused blood draw ($n = 3$) and research nurse unable to collect sample ($n = 3$).
[c]Missing values ($n = 9$) due to participant did not complete adolescent clinic visit ($n = 1$), participant refused blood draw ($n = 5$), and research nurse unable to collect sample ($n = 3$).
[d]Missing values ($n = 5$) due to participant did not complete adolescent clinic visit ($n = 1$), participant refused blood draw ($n = 2$), participant refused blood draw of one tube ($n = 1$), and research nurse unable to collect sample ($n = 1$).
[e]Missing values ($n = 9$) due to participant refused blood draw ($n = 4$) and research nurse unable to collect sample ($n = 5$).
[f]Missing values ($n = 6$) due to participant refused blood draw ($n = 3$), research nurse unable to collect sample ($n = 2$), and lab unable to analyze sample ($n = 1$).
[g]Missing values ($n = 4$) due to participant did not complete adolescent clinic visit ($n = 1$), participant refused blood draw ($n = 2$), and research nurse unable to collect sample ($n = 1$).
[h]Missing value ($n = 4$) due to lab unable to analyze ($n = 4$).
[i]Missing value ($n = 1$) due to participant did not complete adolescent clinic visit ($n = 1$).
[j]Missing values ($n = 3$) due to participant did not complete adolescent clinic visit ($n = 1$) and lab unable to analyze ($n = 2$).
[k]Missing values ($n = 7$) due to parent/caregiver did not provide sample ($n = 6$) and lab unable to analyze sample ($n = 1$).
[l]Missing values ($n = 5$) due to parent/caregiver did not provide sample ($n = 4$) and lab unable to analyze sample ($n = 1$).
[m]Missing values ($n = 7$) due to participant did not complete adolescent clinic visit ($n = 1$) and parent/caregiver did not provide sample ($n = 6$).
[n]Missing values ($n = 6$) due to participant did not complete adolescent clinic visit ($n = 1$) and parent/caregiver did not provide sample ($n = 5$).

Table 4. Pearson's correlations (r) and p-values among the biomarkers of environmental exposures in Marietta CARES adolescent balance participants during childhood (2008–2013) and adolescence (2017–2018), $n = 123$.

	Child blood Pb	Child serum cotinine	Child hair Mn	Child toenail Mn	Adolescent blood Mn	Adolescent blood Pb	Adolescent serum cotinine	Adolescent hair Mn	Adolescent toenail Mn
Child blood Mn	−0.26, 0.0073	−0.17, 0.087	0.059, 0.56	−0.13, 0.19	0.75, ≤0.00010	−0.18, 0.085	−0.18, 0.079	−0.28, 0.0038	−0.21, 0.039
Child blood Pb		0.28, 0.0042	0.16, 0.11	0.094, 0.36	−0.30, 0.0028	0.48, ≤0.00010	0.34, 0.00060	0.31, 0.0017	0.23, 0.025
Child serum cotinine			0.16, 0.10	0.027, 0.79	−0.10, 0.32	0.041, 0.69	0.59, ≤0.0001	0.35, 0.0003	0.015, 0.89
Child hair Mn				0.44, <0.0001	0.058, 0.56	0.23, 0.020	0.14, 0.16	0.16, 0.079	0.012, 0.90
Child toenail Mn					−0.029, 0.77	0.16, 0.11	0.027, 0.79	0.12, 0.21	0.19, 0.052
Adolescent blood Mn						−0.11, 0.24	−0.17 , 0.072	−0.20, 0.034	0.022, 0.83
Adolescent blood Pb							0.17, 0.076	0.20, 0.035	0.25, 0.012
Adolescent serum cotinine								0.25, 0.0095	0.075, 0.46
Adolescent hair Mn									0.20, 0.036

Note: CARES, Communities Actively Researching Exposures Study; Mn, manganese; Pb, lead. p-Values are reported from Pearson's correlations analyses; statistical significance is set at $p < 0.05$.

blood Mn has smaller postural sway measures than the participant with higher blood Mn, demonstrating the effects of blood Mn under the static test condition, eyes open.

Associations of Mn Biomarkers with Postural Balance

Adjusted linear regression models were conducted between childhood and adolescent biomarkers of Mn (blood, hair, toenail) and postural balance outcomes measured during adolescence. The results are summarized in Tables 5 and 6.

Higher childhood hair Mn concentrations were consistently associated with greater adolescent sway measures under the test condition of eyes open standing on foam above the force plate. Under foam open, for each nanogram-per-gram increase childhood ln hair Mn, adolescent ln sway area increased 0.14 cm^2 [(95% CI: 0.039, 0.24), $p = 0.0073$]; ln sway length increased 0.050 cm [(95% CI: 0.0054, 0.095), $p = 0.029$]; and ln anterior–posterior sway increased 0.078 cm [(95% CI: 0.019, 0.14), $p = 0.010$]. Higher childhood blood Mn and childhood toenail Mn concentrations also demonstrated significant associations with adolescent sway. Under foam open, for each microgram-per-gram increase childhood ln toenail Mn, adolescent ln sway area increased 0.099 cm^2 [(95% CI: 0.0065, 0.19), $p = 0.036$]. Under bending open, for each microgram-per-gram increase childhood ln toenail Mn, adolescent ln anterior–posterior sway increased 0.076 cm [(95% CI: 0.02, 0.13), $p = 0.0038$]. Under foam closed, for each microgram-per-liter increase childhood ln blood Mn, adolescent ln anterior–posterior sway increased 0.32 cm [(95% CI: 0.05, 0.60), $p = 0.023$] (Table 5).

Higher adolescent blood Mn concentrations were consistently associated with greater sway measures under the static test conditions eyes open and eyes closed on the force plate. Under eyes open, for each microgram-per-liter increase adolescent ln blood Mn, adolescent ln sway area increased 0.45 cm^2 [(95% CI: 0.063, 0.83), $p = 0.022$]; ln medio–lateral excursion increased 0.27 cm [(95% CI: 0.018, 0.52), $p = 0.036$]; and ln anterior–posterior excursion increased 0.24 cm [(95% CI: 0.026, 0.46), $p = 0.029$]. Under eyes closed, for each microgram-per-liter increase adolescent ln blood Mn, adolescent ln sway area increased 0.44 cm^2 [(95% CI: 0.039, 0.85), $p = 0.032$] and ln anterior–posterior excursion increased 0.37 cm [(95% CI: 0.15, 0.59), $p = 0.001$]. Higher blood Mn concentrations were also significantly associated with increased sway under the semi-dynamic test conditions. Under both bending eyes open and bending eyes closed on the force plate, for each microgram-per-liter increase adolescent ln blood Mn, adolescent medio–lateral sway increased 0.21 cm [(95% CI: 0.0064, 0.41), $p = 0.043$] and 0.23 cm [(95% CI: 0.020, 0.43), $p = 0.032$], respectively. No significant associations were found between adolescent hair or toenail Mn and concurrent postural balance measures (Table 6). Supplemental analyses revealed sex-specific associations between childhood biomarkers of Mn exposure and adolescent postural balance (Table 7). Generally, males with higher childhood Mn biomarker concentrations had significantly smaller adolescent sway measures (i.e., postural stability), whereas females with higher childhood Mn concentrations had significantly greater adolescent sway measures (i.e., postural instability). For males in childhood, under the test condition eyes open standing on foam above the force plate, for each microgram-per-liter increase ln blood Mn, adolescent ln sway area and anterior–posterior sway decreased −0.77 cm^2 [(95% CI: −1.36, −0.18), $p = 0.011$] and −0.61 cm [(95% CI: −0.95, −0.27), $p = 0.0006$], respectively. In contrast, for females, ln sway area and anterior–posterior sway increased 0.49 cm^2 [(95% CI: 0.011, 0.97), $p = 0.045$] and 0.29 cm [(95% CI: 0.018, <0.0001), $p = 0.037$], respectively. The p-values for interaction for these models were 0.0013 and <0.0001, respectively. This same pattern between males and females was

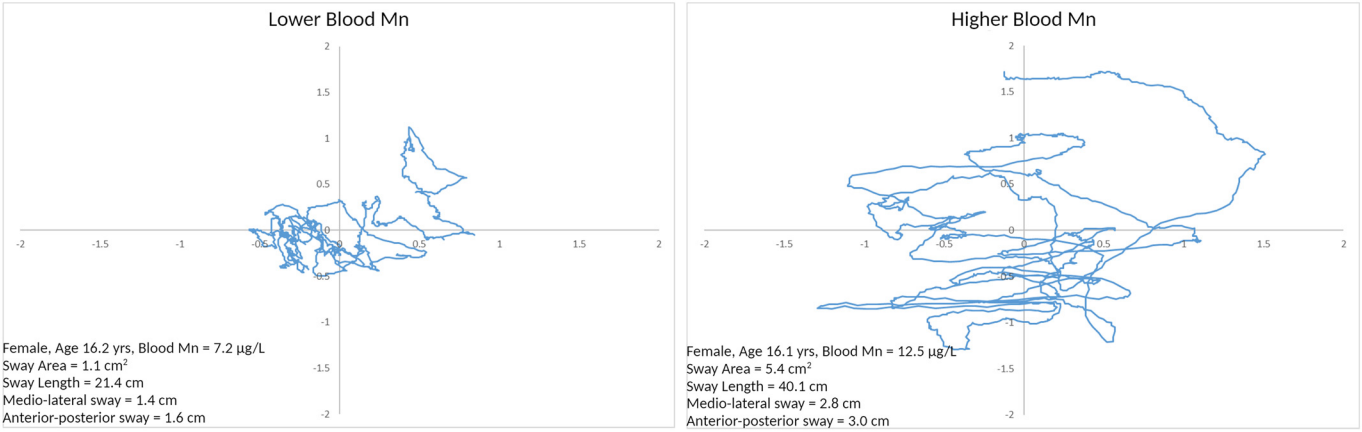

Figure 2. Stabilograms to illustrate adolescent balance performance with lower blood Mn concentrations associated with smaller sway values compared with higher blood Mn concentrations associated with higher sway values under the test condition eyes open. Created in biorender.com. Note: Mn, manganese.

identified under the test condition bending open with all childhood Mn biomarker (blood, hair, toenail) models. There were no significant sex-specific associations between adolescent biomarkers of Mn exposure and postural balance (Table 8).

After application of the Benjamini–Hochberg procedure[88] to control for multiple comparisons, adjusted *p*-values are reported in Tables S6 and S7. Of all of the multivariable linear regression models between childhood and adolescent Mn biomarkers and adolescent postural balance, only the association between adolescent blood Mn and adolescent anterior–posterior sway under eyes closed remained significant. From the supplemental analyses of the multivariable linear regression models between childhood and adolescent Mn biomarkers and adolescent postural balance, including a Mn × sex interaction term, the sex interaction term remained significant for the associations between childhood blood Mn and adolescent sway area and anterior–posterior sway under foam open.

There were 76 participants with complete data on all biomarkers at both time points. The descriptive characteristics and biomarker concentrations of this restricted sample are described in Tables S8 and S9. The results from the supplemental analysis

Table 5. Regression coefficients from linear regression models between childhood Mn biomarkers (2008–2013) and adolescent postural balance (2017–2018) among 123 participants in the Marietta CARES cohort.

Postural balance outcomes	Blood Mn; β (95% CI), *p*-value	Hair Mn; β (95% CI), *p*-value	Toenail Mn; β (95% CI), *p*-value
n	104	100	95
Eyes open			
Sway area	0.12 (−0.32, 0.55), 0.60	0.052 (−0.065, 0.17), 0.38	−0.0071 (−0.11, 0.099), 0.89
Sway length	0.062 (−0.11, 0.24), 0.48	0.032 (−0.014, 0.078), 0.17	−0.010 (−0.051, 0.032), 0.64
Medio–lateral sway	0.10 (−0.19, 0.38), 0.49	0.043 (−0.034, 0.12), 0.27	0.019 (−0.051, 0.089), 0.59
Anterior–posterior sway	0.045 (−0.21, 0.30), 0.72	0.0027 (−0.065, 0.071), 0.94	−0.0055 (−0.069, 0.058), 0.86
Eyes closed			
Sway area	0.14 (−0.31, 0.59), 0.54	0.061 (−0.059, 0.18), 0.32	−0.0019 (−0.11, 0.11), 0.97
Sway length	0.14 (−0.095 , 0.37), 0.24	0.041 (−0.021, 0.10), 0.19	−0.036 (−0.094, 0.021), 0.21
Medio–lateral sway	0.07 (−0.22 , 0.35), 0.64	0.038 (−0.038, 0.11), 0.32	0.0056 (−0.063 , 0.075), 0.87
Anterior–posterior sway	0.17 (−0.076, 0.41), 0.17	0.024 (−0.042, 0.089), 0.47	−0.012 (−0.073, 0.050), 0.71
Foam open			
Sway area	−0.012 (−0.40, 0.38), 0.95	0.14 (0.039, 0.24), 0.0073	0.099 (0.0065, 0.19), 0.036
Sway length	0.067 (−0.11, 0.24), 0.44	0.050 (0.0054, 0.095), 0.029	0.0038 (−0.038, 0.046), 0.86
Medio–lateral sway	0.11 (−0.14, 0.36), 0.39	0.063 (−0.0051, 0.13), 0.069	0.039 (−0.020, 0.098), 0.20
Anterior–posterior sway	−0.066 (−0.30, 0.17), 0.58	0.078 (0.019, 0.14), 0.010	0.042 (−0.012, 0.096), 0.13
Foam closed			
Sway area	0.25 (−0.22, 0.72), 0.30	0.10 (−0.026, 0.23), 0.12	0.032 (−0.084, 0.15), 0.58
Sway length	0.14 (−0.10, 0.37), 0.25	0.027 (−0.034, 0.089), 0.38	−0.032 (−0.092 , 0.027), 0.28
Medio–lateral sway	0.15 (−0.15 , 0.45), 0.31	0.075 (−0.0034, 0.16), 0.060	0.022 (−0.051, 0.095), 0.55
Anterior–posterior sway	0.32 (0.05, 0.60), 0.023	0.025 (−0.051, 0.10), 0.52	−0.0026 (−0.073, 0.068), 0.94
Bending open			
Sway area	0.11 (−0.20, 0.42), 0.49	0.026 (−0.058, 0.11), 0.54	0.033 (−0.039, 0.11), 0.36
Sway length	−0.01 (−0.14, 0.13), 0.93	0.015 (−0.020, 0.049), 0.40	0.0045 (−0.027, 0.036), 0.78
Medio–lateral sway	−0.08 (−0.31, 0.15), 0.49	−0.030 (−0.091, 0.032), 0.34	−0.044 (−0.10, 0.012), 0.13
Anterior–posterior sway	0.07 (−0.14, 0.28), 0.51	0.036 (−0.020, 0.092), 0.21	0.076 (0.025, 0.13), 0.0038
Bending closed			
Sway area	−0.05 (−0.31, 0.21), 0.68	−0.00025 (−0.070, 0.069), 0.10	−0.029 (−0.093, 0.034), 0.36
Sway length	0.01 (−0.15, 0.16), 0.94	0.0078 (−0.033, 0.048), 0.70	−0.015 (−0.053, 0.023), 0.43
Medio–lateral sway	0.10 (−0.13, 0.33), 0.40	0.020 (−0.042, 0.082), 0.52	−0.019 (−0.077, 0.039), 0.52
Anterior–posterior sway	−0.14 (−0.32, 0.04), 0.12	−0.00090 (−0.049, 0.048), 0.97	−0.013 (−0.058, 0.033), 0.58

Note: The discrepancy between the analytical sample ($n = 123$) and the observations used for each model are the result of missing observations for at least one of the variables in the model. Childhood biomarkers of Mn and outcomes of postural balance were natural log (ln) transformed. All models were adjusted for the same covariates: adolescent age, sex, adolescent height–weight ratio, parent/caregiver IQ, parent/caregiver SES, childhood ln blood Pb, and childhood ln serum cotinine. CARES, Communities Actively Researching Exposures Study; CI, confidence interval; IQ, intelligence quotient; Mn, manganese; SES, socioeconomic status. *p*-Values are reported from multivariable linear regression models for the Mn biomarker coefficient (i.e., blood, hair, or toenail). Statistical significance is set at $p < 0.05$.

Table 6. Regression coefficients from linear regression models between adolescent Mn biomarkers and adolescent postural balance (2017–2018) among 123 participants in the Marietta CARES cohort.

Postural balance outcomes	Blood Mn; β (95% CI), *p*-value	Hair Mn; β (95% CI), *p*-value	Toenail Mn; β (95% CI), *p*-value
n	109	107	99
Eyes open			
Sway area	0.45 (0.063, 0.83), 0.022	−0.041 (−0.17, 0.088), 0.53	−0.051 (−0.17, 0.072), 0.41
Sway length	0.12 (−0.045, 0.29), 0.15	−0.011 (−0.065, 0.044), 0.70	−0.0060 (−0.058, 0.046), 0.82
Medio–lateral sway	0.27 (0.018, 0.52), 0.036	−0.023 (−0.11, 0.06), 0.58	−0.040 (−0.12, 0.041), 0.33
Anterior–posterior sway	0.24 (0.026, 0.46), 0.029	−0.013 (−0.086, 0.060), 0.73	−0.016 (−0.085, 0.053), 0.64
Eyes closed			
Sway area	0.44 (0.039, 0.85), 0.032	−0.053 (−0.19, 0.082), 0.44	−0.0077 (−0.14, 0.12), 0.91
Sway length	0.13 (−0.078, 0.34), 0.22	−0.032 (−0.10, 0.036), 0.36	−0.026 (−0.092, 0.041), 0.44
Medio–lateral sway	0.094 (−0.16, 0.35), 0.46	−0.013 (−0.10, 0.070), 0.76	−0.0062 (−0.086, 0.074), 0.88
Anterior–posterior sway	0.37 (0.15, 0.59), 0.001	−0.032 (−0.11, 0.042), 0.39	−0.0022 (−0.073, 0.069), 0.95
Foam open			
Sway area	0.18 (−0.18, 0.53), 0.33	0.016 (−0.10, 0.13), 0.78	0.055 (−0.057, 0.17), 0.33
Sway length	0.071 (−0.091, 0.23), 0.39	0.014 (−0.039, 0.068), 0.59	−0.014 (−0.064, 0.037), 0.59
Medio–lateral sway	0.18 (−0.050, 0.41), 0.12	0.038 (−0.038, 0.11), 0.33	0.023 (−0.05, 0.10), 0.54
Anterior–posterior sway	0.010 (−0.20, 0.22), 0.93	−0.015 (−0.084, 0.054), 0.67	0.031 (−0.036, 0.097), 0.36
Foam closed			
Sway area	0.38 (−0.061, 0.82), 0.091	0.012 (−0.13, 0.16), 0.87	−0.095 (−0.23, 0.043), 0.17
Sway length	0.10 (−0.12, 0.31), 0.37	0.019 (−0.052, 0.089), 0.60	−0.054 (−0.12, 0.013), 0.11
Medio–lateral sway	0.20 (−0.066, 0.47), 0.14	−0.017 (−0.11, 0.072), 0.70	−0.075 (−0.16, 0.0081), 0.08
Anterior–posterior sway	0.22 (−0.045, 0.48), 0.10	0.025 (−0.062, 0.11), 0.57	−0.038 (−0.12, 0.046), 0.38
Bending open			
Sway area	0.27 (−0.015, 0.55), 0.06	−0.056 (−0.15, 0.036), 0.23	−0.0055 (−0.092, 0.081), 0.90
Sway length	0.063 (−0.054, 0.18), 0.29	−0.018 (−0.057, 0.021), 0.36	0.019 (−0.019, 0.056), 0.32
Medio–lateral sway	0.21 (0.0064, 0.41), 0.043	−0.0082 (−0.075, 0.058), 0.81	−0.0052 (−0.068, 0.058), 0.87
Anterior–posterior sway	0.043 (−0.15, 0.24), 0.66	−0.0096 (−0.072, 0.053), 0.76	0.01 (−0.05, 0.08), 0.68
Bending closed			
Sway area	0.16 (−0.070, 0.38), 0.18	−0.042 (−0.11, 0.030), 0.25	−0.013 (−0.078, 0.066), 0.87
Sway length	0.076 (−0.061 , 0.21), 0.27	−0.026 (−0.070, 0.019), 0.26	0.013 (−0.031, 0.058), 0.55
Medio–lateral sway	0.23 (0.020, 0.43), 0.032	−0.025 (−0.093, 0.044), 0.48	−0.0028 (−0.068, 0.062), 0.93
Anterior–posterior sway	−0.040 (−0.21, 0.13), 0.65	−0.013 (−0.068, 0.042), 0.64	0.0016 (−0.052, 0.055), 0.95

Note: The discrepancy between the analytical sample ($n = 123$) and the observations used for each model are the result of missing observations for at least one of the variables in the model. Adolescent biomarkers of Mn and outcomes of postural balance were natural log (ln) transformed. All models were adjusted for the same covariates: adolescent age, sex, adolescent height–weight ratio, parent/caregiver IQ, parent/caregiver SES, adolescent ln blood Pb, and adolescent ln serum cotinine. CARES, Communities Actively Researching Exposures Study; CI, confidence interval; IQ, intelligence quotient; Mn, manganese; SES, socioeconomic status. *p*-Values are reported from multivariable linear regression models for the Mn biomarker coefficient (i.e., blood, hair, or toenail). Statistical significance is set at $p < 0.05$.

of the adjusted linear regression models between childhood and adolescent Mn biomarkers (blood, hair, toenail) and adolescent postural balance outcomes using the restricted sample comprising of the 76 participants with complete biomarker data are summarized in Tables S10 and S11. When the sample was restricted to participants with data available on all biomarkers at both time points, additional significant associations were discovered, but none of the significant associations initially identified in Tables 5 and 6 were lost. This may be attributed to differences in variability in the environmental exposures or postural balance outcomes between the analytical sample ($n = 123$) and the restricted sample ($n = 76$). One exception that lost significance in the restricted analyses was the association between adolescent blood Mn exposure and adolescent medio–lateral sway under bending open.

For the supplemental analysis using MIM GEEs, results are reported for the *p*-value of the Mn (blood, hair, toenail) × time point (childhood, adolescence) interaction term in Table S12. There were two significant interactions, which represent associations where the regression coefficient changes direction between childhood and adolescence: for blood Mn, under bending open, for medio–lateral sway, the regression coefficient in childhood was −0.08 and in adolescence was 0.21 ($p = 0.003$). For hair Mn, under foam open, for anterior–posterior sway, the regression coefficient in childhood was 0.078, and in adolescence, it was −0.015 ($p = 0.038$).

Discussion

The goal of this CARES substudy was to investigate the associations between childhood and adolescent Mn biomarkers, measured in blood, hair, and toenails, and adolescent postural balance. This study found that Mn biomarkers measured at both time points, childhood and adolescence, were significantly associated with adolescent postural instability. This study also found sex-specific associations between childhood Mn biomarkers and adolescent postural balance, with females demonstrating greater sway than males.

Within our cohort, participants with higher childhood blood Mn concentrations had significantly greater adolescent postural sway measures under the foam open test condition, and participants with higher childhood hair and toenail Mn concentrations had significantly greater postural sway measures under the foam closed test conditions. These results are consistent with our previous findings in a subset of 55 CARES children 7–9 years of age located in the Marietta community. Rugless et al. reported that participants with higher childhood hair Mn concentrations had significantly greater childhood postural sway measures under the foam open and foam closed test conditions.[51] The present study found a significant association between childhood hair and toenail Mn and foam open in the adolescent postural balance assessment. Foam open involves standing on foam to challenge the proprioceptive receptors on the feet, forcing dependence on the visual and vestibular sensory afferents. Increased sway under the foam open tests implies that the participants with higher childhood hair Mn and toenail Mn concentrations are increasing muscular activity and body velocity to compensate when forced to depend on the visual and vestibular sensory afferents. Foam closed further removes visual cues and forces reliance on the vestibular sensory afferent. Thus, increased sway under the foam closed balance tests implies that the participants with higher childhood blood Mn are

Table 7. Regression coefficients from linear regression models between childhood Mn biomarkers (2008–2013) and adolescent postural balance with sex × Mn interaction term (2017–2018) among 123 participants in the Marietta CARES cohort.

Postural balance outcomes	Blood Mn ($n=104$); β (95% CI), p-value			Hair Mn ($n=100$); β (95% CI), p-value			Toenail Mn ($n=95$); β (95% CI), p-value		
	Male	Female	$p_{interaction}$	Male	Female	$p_{interaction}$	Male	Female	$p_{interaction}$
Eyes open									
Sway area	−0.40 (−1.1, 0.27), 0.24	0.46 (−0.090, 1.0), 0.10	0.052	0.027 (−0.13, 0.18), 0.73	0.086 (−0.094, 0.27), 0.34	0.62	−0.040 (−0.18, 0.10), 0.57	0.042 (−0.13, 0.21), 0.62	0.46
Sway length	−0.12 (−0.39, 0.16), 0.39	0.18 (−0.042, 0.41), 0.11	0.095	0.040 (−0.020, 0.10), 0.19	0.021 (−0.050, 0.093), 0.55	0.69	−0.012 (−0.066, 0.042), 0.66	−0.0064 (−0.073, 0.060), 0.85	0.90
Medio–lateral sway	−0.18 (−0.63, 0.27), 0.44	0.28 (−0.084, 0.65), 0.13	0.12	−0.0036 (−0.10, 0.10), 0.94	0.11 (−0.010, 0.23), 0.07	0.15	−0.0026 (−0.094, 0.089), 0.95	0.051 (−0.061, 0.16), 0.37	0.47
Anterior–posterior sway	−0.18 (−0.58, 0.21), 0.36	0.20 (−0.13, 0.52), 0.23	0.14	−0.0066 (−0.10, 0.083), 0.88	0.016 (−0.090, 0.12), 0.77	0.75	−0.023 (−0.11, 0.060), 0.58	0.021 (−0.081, 0.12), 0.68	0.50
Eyes closed									
Sway area	−0.26 (−0.97, 0.45), 0.46	0.41 (−0.17, 0.98), 0.16	0.15	0.034 (−0.12, 0.19), 0.67	0.098 (−0.088, 0.28), 0.30	0.61	−0.041 (−0.18, 0.10), 0.57	0.057 (−0.12, 0.23), 0.52	0.40
Sway length	0.046 (−0.32, 0.41), 0.80	0.20 (−0.10, 0.49), 0.20	0.53	0.043 (−0.037, 0.12), 0.29	0.037 (−0.058, 0.13), 0.44	0.92	−0.031 (−0.11, 0.044), 0.41	−0.044 (−0.14, 0.049), 0.35	0.84
Medio–lateral sway	−0.19 (−0.64, 0.26), 0.40	0.24 (−0.13, 0.61), 0.20	0.15	0.0073 (−0.092, 0.11), 0.88	0.081 (−0.036, 0.20), 0.17	0.34	−0.024 (−0.11, 0.065), 0.59	0.051 (−0.060, 0.16), 0.36	0.30
Anterior–posterior sway	−0.024 (−0.41, 0.36), 0.90	0.30 (−0.018, 0.61), 0.064	0.20	−0.0019 (−0.088, 0.084), 0.97	0.059 (−0.042, 0.16), 0.25	0.36	−0.052 (−0.13, 0.027), 0.19	0.050 (−0.048, 0.15), 0.32	0.11
Foam open									
Sway area	−0.77 (−1.36, −0.18), 0.011	0.49 (0.011, 0.97), 0.045	0.0013	0.11 (−0.025, 0.24), 0.11	0.18 (0.028, 0.34), 0.02	0.46	0.071 (−0.049, 0.19), 0.24	0.14 (−0.0082, 0.29), 0.06	0.48
Sway length	−0.049 (−0.32, 0.22), 0.72	0.14 (−0.078, 0.37), 0.20	0.28	0.065 (0.0066, 0.12), 0.30	0.029 (−0.040, 0.098), 0.41	0.43	0.012 (−0.043, 0.067), 0.66	−0.0090 (−0.077, 0.059), 0.79	0.63
Medio–lateral sway	−0.17 (−0.57, 0.23), 0.40	0.30 (−0.028, 0.62), 0.073	0.074	0.0067 (−0.081, 0.095), 0.88	0.14 (0.038, 0.25), 0.01	0.051	0.015 (−0.061, 0.092), 0.69	0.074 (−0.021, 0.17), 0.12	0.35
Anterior–posterior sway	−0.61 (−0.95, −0.27), 0.00060	0.29 (0.018, 0.57), 0.037	<0.0001	0.083 (0.0054, 0.16), 0.036	0.071 (−0.020, 0.16), 0.13	0.85	0.027 (−0.044, 0.097), 0.45	0.066 (−0.022, 0.15), 0.14	0.50
Foam closed									
Sway area	−0.070 (−0.82, 0.68), 0.85	0.46 (−0.15, 1.07), 0.14	0.28	0.082 (−0.083, 0.25), 0.33	0.12 (−0.071, 0.32), 0.21	0.74	0.049 (−0.10, 0.20), 0.52	0.0076 (−0.18, 0.20), 0.94	0.74
Sway length	0.11 (−0.26, 0.48), 0.57	0.16 (−0.14, 0.46), 0.30	0.84	0.049 (−0.032, 0.13), 0.23	−0.0025 (−0.098, 0.093), 0.96	0.42	−0.00035 (−0.077, 0.076), 0.99	−0.081 (−0.18, 0.014), 0.09	0.20
Medio–lateral sway	−0.029 (−0.50, 0.44), 0.90	0.27 (−0.11, 0.66), 0.16	0.33	0.088 (−0.015, 0.19), 0.093	0.057 (−0.065, 0.18), 0.36	0.69	0.054 (−0.042, 0.15), 0.27	−0.026 (−0.14, 0.092), 0.66	0.30
Anterior–posterior sway	0.08 (−0.36, 0.51), 0.73	0.48 (0.13, 0.84), 0.0076	0.15	0.016 (−0.084, 0.12), 0.75	0.036 (−0.082, 0.15), 0.55	0.80	0.0076 (−0.085, 0.10), 0.87	−0.018 (−0.13, 0.10), 0.76	0.73
Bending open									
Sway area	−0.21 (−0.70, 0.28), 0.39	0.32 (−0.075, 0.72), 0.11	0.10	−0.026 (−0.14, 0.084), 0.64	0.097 (−0.032, 0.23), 0.14	0.15	0.024 (−0.070, 0.12), 0.61	0.047 (−0.070, 0.16), 0.43	0.77
Sway length	−0.16 (−0.37, 0.040), 0.11	0.10 (−0.067, 0.27), 0.24	0.050	0.0093 (−0.036, 0.054), 0.68	0.022 (−0.031, 0.075), 0.41	0.72	0.0053 (−0.036, 0.047), 0.80	0.0034 (−0.048, 0.055), 0.89	0.96
Medio–lateral sway	−0.16 (−0.52, 0.21), 0.40	−0.030 (−0.33, 0.27), 0.84	0.60	−0.097 (−0.17, −0.019), 0.016	0.064 (−0.028, 0.16), 0.17	0.010	−0.091 (−0.16, −0.018), 0.02	0.026 (−0.064, 0.12), 0.57	0.050
Anterior–posterior sway	−0.25 (−0.58, 0.073), 0.13	0.28 (0.018, 0.55), 0.037	0.013	0.054 (−0.020, 0.13), 0.15	0.011 (−0.076, 0.098), 0.80	0.45	0.095 (0.029, 0.16), 0.01	0.047 (−0.034, 0.13), 0.25	0.37
Bending closed									
Sway area	−0.010 (−0.42, 0.40), 0.96	−0.082 (−0.42, 0.25), 0.63	0.79	−0.0071 (−0.10, 0.084), 0.88	0.0093 (−0.099, 0.12), 0.86	0.82	−0.035 (−0.12, 0.048), 0.40	−0.020 (−0.12, 0.083), 0.70	0.82
Sway length	−0.06 (−0.31, 0.18), 0.60	0.052 (−0.14, 0.25), 0.60	0.46	0.020 (−0.033, 0.074), 0.45	−0.0096 (−0.072, 0.053), 0.76	0.47	−0.011 (−0.061, 0.038), 0.65	−0.020 (−0.081, 0.041), 0.51	0.83
Medio–lateral sway	0.25 (−0.11, 0.61), 0.17	−0.0030 (−0.30, 0.29), 0.98	0.28	0.031 (−0.050, 0.11), 0.45	0.0046 (−0.091, 0.10), 0.92	0.68	−0.0078 (−0.083, 0.067), 0.84	−0.036 (−0.13, 0.057), 0.45	0.65
Anterior–posterior sway	−0.16 (−0.44, 0.13), 0.27	−0.13 (−0.36, 0.10), 0.27	0.88	0.0037 (−0.060, 0.068), 0.91	−0.0073 (−0.083, 0.068), 0.85	0.82	−0.0073 (−0.067, 0.052), 0.81	−0.021 (−0.094, 0.053), 0.57	0.78

Note: The discrepancy between the analytical sample ($n=123$) and the observations used for each model are the result of missing observations for at least one of the variables in the model. Childhood biomarkers of Mn and outcomes of postural balance were natural log (ln) transformed. All models were adjusted for the same covariates: adolescent age, sex, adolescent height–weight ratio, parent/caregiver IQ, parent/caregiver SES, childhood ln blood Pb, and childhood ln serum cotinine. CARES, Communities Actively Researching Exposures Study; CI, confidence interval; IQ, intelligence quotient; Mn, manganese; SES, socioeconomic status. p-Values are reported from multivariable linear regression models for the Mn biomarker (i.e., blood, hair, or toenail) × sex interaction coefficient. Statistical significance is set at $p<0.05$.

Table 8. Regression coefficients from linear regression models between adolescent Mn biomarkers and adolescent postural balance with sex × Mn interaction term (2017–2018) among 123 participants in the Marietta CARES cohort.

	Blood Mn ($n = 109$); β (95% CI), p-value			Hair Mn ($n = 107$); β (95% CI), p-value			Toenail Mn ($n = 99$); β (95% CI), p-value		
Postural balance outcomes	Male	Female	$p_{interaction}$	Male	Female	$p_{interaction}$	Male	Female	$p_{interaction}$
Eyes open									
Sway area	0.24 (−0.29, 0.77), 0.37	0.68 (0.12, 1.24), 0.02	0.26	−0.069 (−0.24, 0.10), 0.42	−0.015 (−0.18, 0.15), 0.85	0.61	0.0028 (−0.16, 0.17), 0.97	−0.11 (−0.29, 0.061), 0.20	0.32
Sway length	0.048 (−0.18, 0.28), 0.68	0.20 (−0.041, 0.44), 0.10	0.37	−0.0040 (−0.077, 0.069), 0.91	−0.017 (−0.086, 0.053), 0.64	0.78	0.011 (−0.058, 0.080), 0.75	−0.026 (−0.10, 0.048), 0.49	0.45
Medio–lateral sway	0.12 (−0.23, 0.47), 0.49	0.44 (0.070, 0.80), 0.02	0.22	−0.034 (−0.15, 0.077), 0.54	−0.014 (−0.12, 0.092), 0.80	0.77	0.0046 (−0.10, 0.11), 0.93	−0.091 (−0.21, 0.024), 0.12	0.22
Anterior–posterior sway	0.17 (−0.13, 0.48), 0.26	0.32 (0.0031, 0.64), 0.05	0.51	−0.050 (−0.15, 0.047), 0.31	0.020 (−0.072, 0.11), 0.67	0.25	0.0053 (−0.087 , 0.10), 0.91	−0.041 (−0.14, 0.058), 0.41	0.48
Eyes closed									
Sway area	0.15 (−0.40, 0.71), 0.58	0.76 (0.18, 1.35), 0.01	0.14	−0.092 (−0.27, 0.087), 0.31	−0.019 (−0.19, 0.15), 0.82	0.51	0.054 (−0.12, 0.23), 0.54	−0.079 (−0.27, 0.11), 0.40	0.29
Sway length	0.0010 (−0.29, 0.29), 0.99	0.27 (−0.030, 0.57), 0.08	0.20	−0.031 (−0.12, 0.059), 0.50	−0.032 (−0.12, 0.054), 0.46	0.98	−0.0095 (−0.10, 0.079), 0.83	−0.044 (−0.14, 0.051), 0.36	0.59
Medio–lateral sway	−0.094 (−0.44, 0.25), 0.59	0.30 (−0.062, 0.67), 0.10	0.12	−0.047 (−0.16, 0.063), 0.40	0.017 (−0.087, 0.12), 0.75	0.35	0.015 (−0.092, 0.12), 0.78	−0.031 (−0.15, 0.084), 0.60	0.55
Anterior–posterior sway	0.22 (−0.080, 0.51), 0.15	0.54 (0.23, 0.85), ≤0.001	0.14	−0.048 (−0.15, 0.051), 0.34	−0.19 (−0.11, 0.075), 0.69	0.64	0.039 (−0.055, 0.13), 0.42	−0.050 (−0.15, 0.051), 0.33	0.20
Foam open									
Sway area	−0.076 (−0.56, 0.41), 0.76	0.46 (−0.058, 0.97), 0.08	0.14	0.036 (−0.12, 0.19), 0.64	−0.0013 (−0.15, 0.15), 0.99	0.70	0.12 (−0.025, 0.27), 0.10	−0.025 (−0.18, 0.13), 0.76	0.17
Sway length	0.11 (−0.12, 0.33), 0.35	0.032 (−0.20, 0.27), 0.79	0.65	0.030 (−0.041, 0.10), 0.40	0.0010 (−0.066, 0.068), 0.98	0.51	0.0067 (−0.061, 0.074), 0.84	−0.038 (−0.11, 0.035), 0.31	0.36
Medio–lateral sway	0.080 (−0.24, 0.40), 0.62	0.29 (−0.044, 0.63), 0.09	0.37	0.012 (−0.090, 0.11), 0.82	0.061 (−0.035, 0.16), 0.21	0.44	0.032 (−0.0066, 0.13), 0.52	0.012 (−0.093, 0.12), 0.82	0.78
Anterior–posterior sway	−0.11 (−0.40, 0.19), 0.47	0.14 (−0.17, 0.45), 0.37	0.26	0.0094 (−0.083, 0.10), 0.84	−0.036 (−0.12, 0.051), 0.41	0.43	0.084 (−0.0029, 0.17), 0.06	−0.032 (−0.13, 0.062), 0.50	0.068
Foam closed									
Sway area	0.16 (−0.44, 0.77), 0.60	0.62 (−0.022, 1.26), 0.06	0.31	0.0065 (−0.19, 0.20), 0.95	0.017 (−0.17, 0.20), 0.85	0.93	−0.017 (−0.20, 0.17), 0.85	−0.18 (−0.38, 0.011), 0.06	0.20
Sway length	0.10 (−0.20, 0.39), 0.52	0.10 (−0.21, 0.41), 0.54	0.99	0.047 (−0.046, 0.14), 0.32	−0.0060 (−0.094, 0.082), 0.89	0.36	−0.040 (−0.13, 0.050), 0.38	−0.072 (−0.17, 0.025), 0.14	0.62
Medio–lateral sway	0.15 (−0.22, 0.52), 0.43	0.26 (−0.13, 0.66), 0.19	0.67	−0.027 (−0.15, 0.091), 0.65	−0.0080 (−0.12, 0.10), 0.89	0.79	−0.021 (−0.13, 0.089), 0.71	−0.14 (−0.26, −0.020), 0.02	0.14
Anterior–posterior sway	−0.025 (−0.38, 0.33), 0.89	0.49 (0.11, 0.86), 0.01	0.05	0.032 (−0.084, 0.15), 0.59	0.019 (−0.09, 0.13), 0.73	0.86	−0.0026 (−0.11, 0.11), 0.96	−0.078 (−0.20, 0.042), 0.20	0.35
Bending open									
Sway area	0.19 (−0.20, 0.58), 0.33	0.35 (−0.061, 0.76), 0.09	0.58	−0.050 (−0.17, 0.073), 0.42	−0.061 (−0.18 , 0.055), 0.30	0.88	−0.0045 (−0.12, 0.11), 0.94	−0.0066 (−0.13, 0.12), 0.92	0.98
Sway length	0.0012 (−0.16, 0.16), 0.99	0.13 (−0.039, 0.30), 0.13	0.27	−0.015 (−0.067, 0.036), 0.56	−0.020 (−0.069, 0.028), 0.41	0.87	0.039 (−0.011, 0.089), 0.12	−0.0048 (−0.058, 0.048), 0.86	0.22
Medio–lateral sway	0.24 (−0.039, 0.52), 0.09	0.17 (−0.12, 0.46), 0.25	0.73	−0.020 (−0.11, 0.069), 0.66	0.0021 (−0.082, 0.086), 0.96	0.69	−0.0058 (−0.090, 0.078), 0.89	−0.0046 (−0.10, 0.086), 0.92	0.98
Anterior–posterior sway	−0.078 (−0.35, 0.19), 0.56	0.18 (−0.10, 0.46), 0.22	0.20	0.013 (−0.070, 0.10), 0.76	−0.029 (−0.11, 0.049), 0.46	0.42	−0.0031 (−0.086, 0.080), 0.94	0.032 (−0.058, 0.12), 0.48	0.56
Bending closed									
Sway area	0.17 (−0.14, 0.48), 0.28	0.14 (−0.19, 0.47), 0.41	0.89	−0.059 (−0.15, 0.036), 0.22	−0.027 (−0.12, 0.063), 0.55	0.59	−0.033 (−0.13, 0.063), 0.49	0.025 (−0.077, 0.13), 0.63	0.40
Sway length	0.040 (−0.15, 0.23), 0.68	0.12 (−0.083, 0.32), 0.25	0.58	−0.025 (−0.084, 0.034), 0.41	−0.026 (−0.082, 0.030), 0.36	0.98	0.021 (−0.038, 0.081), 0.48	0.0041 (−0.060, 0.068), 0.90	0.69
Medio–lateral sway	0.24 (−0.046, 0.53), 0.10	0.21 (−0.090, 0.51), 0.17	0.89	−0.047 (−0.14, 0.044), 0.31	−0.0050 (−0.091, 0.081), 0.91	0.46	−0.016 (−0.10, 0.07), 0.71	0.013 (−0.081, 0.11), 0.78	0.64
Anterior–posterior sway	0.040 (−0.20, 0.28), 0.74	−0.13 (−0.38, 0.12), 0.31	0.34	−0.021 (−0.095, 0.053), 0.57	−0.0063 (−0.076, 0.064), 0.86	0.75	−0.0053 (−0.077, 0.066), 0.88	0.010 (−0.068, 0.087), 0.80	0.77

Note: The discrepancy between the analytical sample ($n = 123$) and the observations used for each model are the result of missing observations for at least one of the variables in the model. Adolescent biomarkers of Mn and outcomes of postural balance were natural log (ln) transformed. All models were adjusted for the same covariates: adolescent age, sex, adolescent height–weight ratio, parent/caregiver IQ, parent/caregiver SES, adolescent ln blood Pb, and adolescent ln serum cotinine. CARES, Communities Actively Researching Exposures Study; CI, confidence interval; IQ, intelligence quotient; Mn, manganese; SES, socioeconomic status. p-Values are reported from multivariable linear regression models for the Mn biomarker (i.e., blood, hair, or toenail) × sex interaction coefficient. Statistical significance is set at $p < 0.05$.

increasing muscular activity and body velocity to compensate when forced to depend on the vestibular sensory afferent.

These results may be indicative of the pediatric developmental trajectories of postural control. During childhood, the neuromuscular mechanisms involving sensory and motor processes are immature. Researchers such as Hirabayashi and Iwasaki,[92] Cumberworth et al.,[93] Steindl et al.,[94] and Ferber-Viart et al.[95] have found that the visual sensory afferent develops much earlier than the vestibular system in children. Given that the vestibular sensory afferent is not fully developed like adulthood until 14–16 years of age,[95] our findings support that childhood Mn biomarkers may impact the developing vestibular system. Animal and epidemiological studies provide some support for the neurotoxic impact of Mn on the vestibular system.[37,96] For example, Ding et al. reported *in vivo* studies of manganese chloride ($MnCl_2$)-exposed cochlear organotype cultures on postnatal day-3 rats caused damage to the sensory hair cells, peripheral auditory nerve fibers, and spiral ganglionic neurons in cochlear implants from the vestibular system. In the 1980s, Khalkova and Kostadinova studied Bulgarian coke chemical production and ferroalloy production workers. They found pronounced changes in the hearing and vestibular indices in workers with the lowest degree of exposure. The authors proposed analysis of the vestibular system as criteria for early diagnosis of chronic Mn intoxiciation.[97] Since then, no studies have fully elucidated Mn's neurotoxic effect on the vestibular system related to neuromotor function.

Within our study's cohort, participants with higher adolescent blood Mn concentrations had significantly greater adolescent sway measures under the eyes open and eyes closed postural balance test conditions. This association was also demonstrated in our previous study of adults living in Marietta, Ohio. Standridge et al. found that higher hair Mn concentrations in 22 nonoccupationally exposed 19- to 68-old Marietta adults were significantly associated with greater sway measures under the eyes open and eyes closed test conditions.[37] Eyes open and eyes closed are the least difficult postural balance test conditions given the availability of more sensory afferents than the subsequent test conditions. Thus, increased sway under the eyes open and eyes closed balance tests implies that, despite availability of all or most sensory afferents, participants with higher adolescent blood Mn must increase muscular activity and body velocity to maintain upright postural balance. During adolescence, the pediatric development of the visual, vestibular, and proprioceptive systems has matured to healthy adult status, whereas multisensory integration strategies may not mature until young adulthood.[93,98] Our results suggest adolescent blood Mn may impact mechanisms beyond the three sensory afferents that control postural balance, which is indicative of the development of pediatric postural control. Relevant mechanisms during adolescence may include the rapid maturation of the frontal brain system,[99] dopaminergic pathways,[100–102] and complex interacting musculoskeletal processes.[103] Mn is postulated to selectively exert toxicity on dopaminergic neurons,[104] resulting in motor changes.[105] Despite maturity of postural control, brain development studies indicate adolescence is a significant period of plasticity and neurodevelopment related to patterns of gray matter thinning, white matter pathway integrity, and synapse proliferation.[106] The ongoing maturation of the adolescent brain provides support for adolescence as a unique neurodevelopmental time point.[106] Given the uniqueness of the adolescent brain development, the subclinical neuromotor effects of adolescent blood Mn on adolescent postural balance reported in this study may reflect mechanisms of neurotoxicity that persist into adulthood, as demonstrated by Standridge et al.[37]

A growing body of epidemiological and animal studies suggest Mn may impact males and females differently.[42,50,107–112] This study found significant sex differences in the associations between childhood Mn biomarkers and adolescent balance; however, this study did not find any sex differences in the associations between concurrent adolescent Mn biomarkers and balance. Specifically, this study found that childhood blood and hair Mn was associated with decreased adolescent sway in males (i.e., postural stability) and increased adolescent sway in females (i.e., postural instability) under various postural balance outcomes. These results are in opposition to several studies on sex differences in postural stability that reported male children exhibit greater sway compared with female children of similar ages.[94,113–119] Potential explanations for this may be attributed to sway parameters,[117] physical growth, and the neuromuscular system[120] developing earlier in female children compared with males. Despite support for female children to have better neuromotor function than male counterparts, other pediatric Mn exposure studies that examined sex effects have also found similar Mn effects impacting females worse than males. These same sex effects were found previously by Chiu et al., who reported higher prenatal dentin Mn was associated with decreased adolescent sway in males and increased adolescent sway in females in 11- to 14-y-old participants from the Italian Public Health Impact of Manganese Exposure cohort living near historical ferroalloy industries.[49] Similar findings were reported in another pediatric Mn cohort, the California Center for the Health Assessment of Mother and Children of Salinas (CHAMACOS) cohort study. Mora et al. found that higher prenatal and postnatal dentin Mn levels were associated with better childhood motor outcomes at 7, 9, and 10.5 years of age in males but not in females.[50] Also in the CHAMACOS cohort, Gunnier et al. reported an effect modification by sex for the association between postnatal dentin Mn levels and motor function at 6 months of age, measured by the Psychomotor Development Index of the Bayley Scales of Infant Development, where a significant adverse linear relationship was found in females only.[42]

In contrast, Takser et al. conducted a study of mother–newborn couples from a French maternity hospital and found higher umbilical blood Mn concentration at birth was negatively associated with hand skill at 3 years of age in males only.[121] The majority of the studies suggest early life Mn exposure impacts development of motor function differently in males and females. However, because of the lack of childhood and adolescent Mn biomarker and motor studies investigating sex effects, there is not sufficient information to conclude why we might be finding significant associations related to adolescent motor function in the childhood Mn exposure time point only and not also in adolescence. A potential explanations for the sex effects we did see between childhood Mn biomarkers and adolescent balance may be attributed to biological differences between males and females in response to Mn exposure.[122] There is also evidence from animal studies in rats that Mn accumulation differs between males and females in striatal morphology across body tissues.[108,109]

Currently, there is no ideal biomarker of Mn exposure in environmental studies. This study was strengthened by our use of multiple Mn biomarkers (blood, hair, and toenails) at two time points of pediatric neurodevelopment (childhood and adolescence). Whole blood is a commonly collected biomarker of Mn exposure. Because Mn has a relatively short half-life of hours in blood, it is often used to reflect recent exposure rather than body burden.[123] However, interpreting blood Mn as a biomarker of recent exposure should be done cautiously when considering the discrepancy between the half-life of Mn in blood vs. tissue/body. In monkeys exposed to 1.5 mg Mn/m^3 for 13 wk, the half-life of elimination in soft tissues of kidney and heart was 18.3 and 27.3 d, respectively. Halftime of elimination of Mn from the monkey brain varied by region, ranging 4.9 d from the olfactory bulb; 15.7–16.7 d

from the globus pallidus, putamen, and caudate; 19.4 d from the olfactory cortex; 23.6 d from the pituitary; and 32.3 d from the cerebellum.[124] Based on animal studies conducted in rats, the half-life of Mn in hard tissue of human bone is expected to be 8–9 y.[125] Chronic exposure to Mn can lead to accumulated stores in the body, which may release Mn into the blood circulation, opening up the possibility that blood Mn may also act as a measure of more long-term exposure.[126]

It is interesting that we found adolescent blood Mn was significantly associated with greater adolescent sway when childhood blood Mn was not associated with adolescent sway, given the high correlation between blood Mn at the two time points (Pearson's $r = 0.75$, $p \leq 0.0001$). In addition, as participants aged over the decade from childhood into adolescence, the participants were exposed to increasingly less ambient Mn emitted from the local ferromanganese refinery. Over the past decade, total Mn emissions (sum of fugitive or non-point air emissions and stack or point air emissions) reported by Eramet Marietta Inc. have varied widely but, in general, decreased from 108,380 kg Mn compounds in 2008, this study's first year of child recruitment, to 14,576 kg Mn compounds in 2017, the first year of recruitment for the adolescent postural balance sub-study.[127] Despite the lower Mn emissions during the adolescent study visit years, adolescent blood Mn was uniquely associated with subclinical adolescent neuromotor effects. To interpret this adolescent cross-sectional finding, further discussion of blood as a biomarker of Mn exposure and the adolescent time point is needed. A literature-based analysis conducted by Baker et al.[128] hypothesized that blood Mn acts as an exposure biomarker for inhaled Mn at concentrations $>10\,\mu g/m^3$. The adolescents in the present study were exposed to environmental Mn well below this threshold. The pharmacokinetics of inhaled Mn at lower environmental concentrations have yet to be elucidated; however, the research that underlies the pharmacokinetic models for Mn suggests blood Mn levels serve as a viable biological indicator for inhalation exposures in controlled experimental conditions.[129] In the present study, it was beyond the scope of our analysis to interpret whether adolescent blood Mn reflects recent or chronic exposure. However, the lack of associations between adolescent hair or adolescent toenail Mn with adolescent postural balance lends support to adolescent blood Mn as a reflection of recent exposure. This is plausible given the rapid neurodevelopment occurring during the adolescent time point, despite the lower levels of environmental Mn during adolescence compared with childhood.

Hair and toenails are other commonly collected tissues of Mn exposure used to reflect chronic exposure. Many metals deposit in keratin, a protein found in hair and nails. Because the growth rate of hair and toenails are ~ 1.27 cm/month[130] and 0.35 cm/month,[131] respectively, mean hair and toenail levels are used to represent cumulative exposure over 2–4 months[132] and 7–12 months[131,133] before sampling, respectively. Hair and toenails are easy to collect because they require noninvasive collection methods and also are easy to store.[134,135] Although the mechanisms of the ambient air Mn to hair Mn pathway need to be further elucidated, several studies found significant associations between Mn levels in hair and distance to industrial point source of Mn.[136–138] Although hair Mn has been regarded by Coetzee et al. as the "most consistent and valid biomarker in pediatric epidemiology,"[139] this statement is problematic because it is based on the greater number of pediatric studies that identify significant associations between pediatric hair Mn and neurodevelopmental outcomes compared with other Mn biomarkers. Few studies include measures of both internal dose Mn and environmental Mn, and those that do yield diverse findings regarding the relationship between Mn concentrations in hair or toenails and environmental mediums. For example, in Italian children living in a community of historical ferroalloy emissions, children's hair Mn concentrations exhibited a significantly low correlation with Mn in household dust and airborne particles.[140] In Bangladeshi children exposed to elevated levels of Mn in drinking water, Skröder et al. reported no correlation between hair Mn and water Mn.[141] On the contrary, Bouchard et al. and Oulhote et al. reported that Canadian children living in homes with elevated levels of Mn in water had higher hair Mn concentrations compared with children living in homes with lower levels of Mn in water.[20,142] Regarding toenails, in Brazilian children living near a ferromanganese alloy plant, toenail Mn was significantly correlated with Mn in exterior dust and interior environment.[143] The utility of hair as a Mn biomarker is limited by the potential for external contamination and lack of standardized cleaning methods to remove exogenous Mn from hair before analysis that has led to varying hair Mn ranges across environmentally exposed children.[53,144–148] Similar limitations exist for the utility of toenails as a Mn biomarker. Generally, toenails are considered less susceptible to external contamination than hair because, for a given sample weight, toenails have a smaller surface-to-volume ratio.[149,150] However, there is also a lack of standardized cleaning methods for toenails.[151]

There was no correlation between the childhood and adolescent measures of hair Mn and toenail Mn. Compared with their childhood measurements, participants had lower hair Mn and toenail Mn concentrations during the adolescent time point. Given the decrease in emissions from the ferromanganese refinery, this difference was anticipated. We observed that participants with greater childhood hair Mn and toenail Mn concentrations had significantly greater adolescent sway measures under the foam open test condition. This finding suggests that early life Mn biomarkers may impact adolescent balance.

This study has public health, as well as occupational health and safety, relevance for Mn-exposed children and adolescents because greater sway is associated with increased risk of prospective fall.[152] Adolescents are identified as one of the most high-risk group for falls by the World Health Organization.[153] In addition, adolescence is a time when the majority of youth enter the labor force before they finish high school.[154] The CDC identifies adolescents as a high-risk group for work-related injuries owing to their unique physical and psychosocial characteristics.[154] Given the well-established relationship between greater sway and increased risk of falls,[152] adolescents in this study with higher internal Mn dose may be at increased risk of injuries, including at work, compared with adolescents with lower levels. A study conducted in Pb-exposed children provides support for potential injury trends.[155] Pb and Mn are both metals with evidence of low exposure associated with neurotoxicity in pediatric populations. Pb-exposed children who demonstrated postural instability were followed up in adolescent years. Study results indicated that falls among these subjects were the most common event leading to injury and were associated with increased blood Pb concentrations.[155] Injuries are a largely preventable public health problem; thus, balance training as a public health intervention may be useful for pediatric populations living near Mn emissions.[156]

This study had several strengths that enabled it to address gaps in understanding regarding the associations between Mn exposure at childhood and adolescent time points and adolescent neuromotor function. One strength lies in the long-standing bidirectional academic–community partnership between our research team and the Marietta community.[57] This relationship enabled the high participation rate and sample size, providing new information on the impact of Mn biomarkers during childhood and adolescence on adolescent balance. Adolescent participants in our study had a mean age of 16 y, which is older than other adolescent studies on Mn that have an average or median age of

$\sim$12 y.[52,55,157] This study was also strengthened by our choice of neuromotor assessment. Postural balance testing is a validated biomarker of neuromotor function and long-established method used in Mn exposure studies dating back to the early 1990s.[158,159(p199)] Neuromotor function is a primary outcome of interest in occupational studies owing to its role in occupational safety and prevention of injury. Increasingly, environmental exposure studies of Mn-exposed adults and children living near industrial emissions are investigating neuromotor outcomes. Across pediatric Mn exposure studies, a myriad of tests has been employed in attempts to quantify neuromotor function, contributing to the heterogeneity of study findings. Popular tests include fingertapping,[42,86,142] visual motor,[50,52,160,161] pursuit aiming,[49] pegboard,[54,86,161] and postural balance tests.[51,53] Our postural balance testing methods exceed the criteria outlined by Zoni et al. for a standardized neuromotor test to emerge that is validated, reproducible, sensitive to early neurotoxic alternations affected by Mn, and can be administered in the field under standard conditions.[162,163] The experimental setup for balance testing is portable, sensitive enough to detect $<3\%$ error in field studies, and our methods are validated[37,51,164] and sensitive enough to effectively distinguish differences between patients exhibiting manganism and PD, something which is challenging to do clinically.[165] Our findings support postural balance as the standard test of neuromotor function to aid early detection of subclinical Mn neurotoxicity.

This article is the first step in investigating the associations between childhood and adolescent Mn biomarkers and adolescent postural balance. Our results add valuable information to the limited body of knowledge surrounding pediatric Mn biomarkers and neuromotor function. The supplemental analyses strengthen the interpretation of our findings. When restricting the analytical sample to participants with data on all biomarkers at both time points ($n=76$), the significant associations initially found in the adjusted multivariable linear regression models between childhood Mn and adolescent Mn and adolescent balance ($n=123$) remained, with the exception of one. Additional associations were found. This may be attributed to differences in variability in the environmental exposures or postural balance outcomes between the analytical sample ($n=123$) and the restricted sample ($n=76$). In addition, the supplemental analyses using MIM GEEs identified the exposure time points that have the greatest impact on postural balance outcomes. Under foam open, for anterior–posterior sway, childhood hair Mn was associated with increased adolescent sway (i.e., postural instability), whereas adolescent hair Mn was associated with decreased adolescent sway (i.e., postural stability). Under bending open, for medio–lateral sway, childhood blood Mn was associated with increased adolescent sway (i.e., postural instability), whereas adolescent blood Mn was associated with decreased adolescent sway (i.e., postural stability).

This study was limited by the subset of Marietta CARES adolescents who completed the adolescent neuromotor study visit, who were predominantly White. Although this is generally representative of the Appalachian Ohio region, it did not reflect the diversity of the study catchment area, Washington County's 2.1% Black, 1.9% two or more races, 1.3% American Indian and Alaska Native, and 1.2% Hispanic population.[166] In conclusion, this study adds new knowledge about the effects of childhood and adolescent Mn biomarkers on adolescent neuromotor outcomes. Postural balance is a sensitive measure to assess the impact of neurotoxic exposure on neuromotor function. Given the association between Mn biomarkers and postural instability, future research should investigate injury trends in Mn-exposed adolescents. It is important for future research to include ambient Mn concentrations to better approximate ambient exposures with health outcomes, such as balance. This will contribute significantly to the translational efforts of our findings to public health impact for protection of adolescent workers and aid regulatory standards for ambient Mn concentrations.

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