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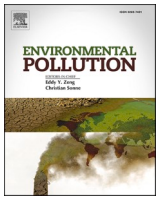

Sex-specific association between prenatal manganese exposure and working memory in school-aged children in Mexico city: An exploratory multi-media approach☆

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ABSTRACT

It remains unclear whether manganese (Mn) exposure affects working memory (WM) in a sexually dimorphic manner. Further, no gold standard media exists to measure Mn, suggesting a combined blood and urinary Mn index may better capture the totality of exposure. We investigated the modification effect of child sex on the influence of prenatal Mn exposure on WM in school-age children, exploring two methodological frameworks to integrate exposure estimates across multiple exposure biomarkers. Leveraging the PROGRESS birth cohort in Mexico City, children ($N = 559$) ages 6–8 completed the between errors and strategy measures of the CANTAB Spatial Working Memory (SWM) task. Mn levels were assayed in blood and urine of mothers during the 2nd and 3rd trimesters and in umbilical cord blood from mothers and children at delivery. Weighted quantile sum regression estimated the association of a multi-media biomarker (MMB) mixture with SWM. We applied a confirmatory factor analysis to similarly quantify a latent blood Mn burden index. We then used an adjusted linear regression to estimate the Mn burden index with SWM measures. Interaction terms were used to estimate the modification effect by child sex for all models. Results showed that the between-errors-specific MMB mixture (i.e., this model demonstrates the impact of the MMB mixture on the between-error scores.) was associated ($\beta = 6.50$, 95% CI: 0.91, 12.08) with fewer between errors for boys and more between errors for girls. The strategy-specific MMB mixture (i.e., this model demonstrates the impact of the MMB mixture on the strategy scores) was associated ($\beta = -1.36$, 95% CI: 2.55, - 0.18) with less efficient strategy performance for boys and more efficient strategy performance for girls. A higher Mn burden index was associated ($\beta = 0.86$, 95% CI: 0.00, 1.72) with more between errors in the overall sample. The vulnerability to prenatal Mn biomarkers on SWM differs in the directionality by child sex. An MMB mixture and composite index of body burden are stronger predictors than a single biomarker for Mn exposure on WM performance.

1. Introduction

Manganese (Mn) is a ubiquitous, essential mineral found naturally in the environment with measurable blood and urine levels throughout the general population. The brain is susceptible to excess and deficient Mn exposure, as evidenced by in-utero and postnatal studies (Henn et al., 2010; Chiu et al., 2017; Zhou et al., 2020). Although Mn is an essential micronutrient critical to human growth and brain development (Erikson & Aschner, 2006; Horning et al., 2015), excessive exposure can adversely affect the brain, causing neurotoxicity (Haynes et al., 2015). Mn accumulates in mitochondria tissues and the basal ganglia and crosses the blood-brain barrier (Inoue, 2007). If present in excessive

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amounts, Mn levels in the brain may disrupt neurotransmitter systems and their activity. This can increase the sensitivity of neuron activations, alter neurite length and integrity (Stanwood et al., 2009), and exhibit neurotoxic effects on specific neural systems, such as cholinergic neurons, during brain development (Lai et al., 1984; Spadoni et al., 2000). In addition, Mn's neurotoxic effects can adversely impact neurodevelopment and neurobehavioral functions relating to impaired motor, learning, psychomotor, and behavioral functions in infant and school-age populations (Andiarena et al., 2020; Carvalho et al., 2014; Chung et al., 2015; de Water et al., 2018; Haynes et al., 2015; Irizar et al., 2021; Long et al., 2014; Yu et al., 2014). Sources of nutritional Mn exposure are typically food (e.g., whole grains, green leafy vegetables, nuts, tea), with excess exposure occurring through nonfood exposure such as inhalation (e.g., high traffic density areas and tobacco smoke) and contaminated water consumption (e.g., municipal and groundwater sources; Wright & Baccarelli, 2007).

Growing evidence indicates prenatal Mn may promote or dysregulate neurodevelopmental and neurobehavioral phenotypes through impacts on brain growth and development, depending on the exposure level (Claus Henn et al., 2017; de Water et al., 2018; Irizar et al., 2021). Increasingly, researchers are addressing the sexually dimorphic impact of the environment on health, and we sought to address whether Mn effects may occur in a sex-specific manner for complex behaviors such as executive functions. Most literature to date has examined general cognition or motor function. For example, a birth cohort study found that elevated prenatal urinary Mn exposure was associated with higher performance-IQ in girls but not boys (Zhou et al., 2020). Studies measuring Mn levels in prenatal dentine in deciduous teeth found an association between higher prenatal Mn exposures and improved childhood cognitive, visuospatial, and verbal memory performance (Mora et al., 2015) and neuromotor functions (Chiu et al., 2017) in boys compared to girls. A prospective study in France observed that only boys had poorer hand skills scores when exposed to higher cord blood Mn concentrations (Takser et al., 2003). Little work on Mn has addressed higher-order executive functioning, such as working memory (WM). WM is a core domain of the human executive function and is a higher-order system for assessing, processing, containing, and manipulating information over a short period (Diamond, 2013). Healthy development of WM is critical during school-age years, given its role in learning, as it is central to following complicated instructions involved in decision-making, comprehension, reasoning, and behavioral responses (Cartwright, 2012; Cowan, 2014). WM development increases rapidly from ages 4–8 years and continues to evolve steadily up to roughly age 12 years (Gathercole, 1999). Overall, WM is vital for children's ability to store information, learn, and perform everyday tasks while simultaneously engaging in several other high-level cognitive processes.

Most research investigating the effect of prenatal Mn exposure on neurodevelopment has used either blood or urine measurements but not both. Recently, we have shown that by integrating the two biomarkers (i.e., urine Mn and blood Mn levels), greater detail on body burden levels of internal dose across individuals is attained (Levin-Schwartz et al., 2021), increasing study power. In this study, we used statistical methods to integrate biomarkers across different media biomarkers to achieve an index related to prenatal Mn body burden that should reduce measurement error and increase power. We also integrated blood and urinary Mn levels at different prenatal windows (2nd and 3rd trimesters) to better integrate prenatal Mn exposure on WM. We used this index to assess the main effects of Mn on WM and effect modification by sex. In addition, we explore two methodological frameworks: (1) a supervised approach using weighted quantile sum (WQS) regression, a data-driven mixture analysis framework, which simultaneously estimates the effects of the multi-media biomarker (MMB) mixture on the outcome, and (2) an unsupervised approach to create an Mn burden index using confirmatory factor analysis (CFA), a method based on causal theory, which allows the Mn burden index to remain constant no matter the outcome.

2. Methods

2.1. Participants

The Programming Research in Obesity, GRowth, Environment and Social Stressors study (PROGRESS) is a longitudinal birth cohort managed in partnership with the National Institute of Public Health and the National Institute of Perinatology in Mexico that has followed children from pregnancy to ages 13–15 years. Initially, we enrolled 958 mothers receiving prenatal care in the early 2nd trimester from one of four Mexican Social Security Institute's (IMSS) primary care clinics in Mexico City from 2006 to 2009. The protocol asked them to present to our study center called "La Casita" at the 2nd, 3rd trimester, and at delivery for blood and data collection. Of these pregnant, 948 delivered a live birth at an IMSS hospital. Mother-child pairs were followed after birth, completing follow-up assessments in which neurobehavioral tests were conducted, and biological samples were collected. The retention between each visit (2nd trimester, 3rd trimester, delivery, age 2 years, age 4 years, age 6 years) was >75% on average, which is a high rate for a longitudinal study of young children. Before any procedure was conducted, the study protocol was thoroughly explained to the women during each visit, and they provided informed consent. Inclusion criteria included healthy ≥18 years old women who were no more than 20 weeks pregnant, with no cardiovascular or kidney disease, had telephone access and intended to live in Mexico City for at least 3 years. Further details on the inclusion criteria have been previously described (Braun et al., 2014). All study protocols were approved by the institutional review boards of the Icahn School of Medicine at Mount Sinai, the Harvard T.H. Chan School of Public Health, the National Institute of Public Health Mexico, the National Institute of Perinatology Mexico, and the Mexican Social Security System.

2.2. Blood and urinary manganese measurement

Maternal blood and urine samples were collected from mothers in the 2nd trimester (between the 16th and 20th gestational weeks) and 3rd trimester (between the 30th and 34th gestational weeks) of pregnancy. Mn levels were also measured in venous umbilical cord blood collected from mothers on the day of delivery through a venipuncture. The child's cord blood was collected post-birth by inserting a catheter into the umbilical vein of the umbilical cord and using a syringe to withdraw a total of five ccs of blood. Mn for each time point was analyzed with a triple quadrupole dynamic reaction cell-inductively coupled plasma mass spectrometer (ICP-MS; Elan 6100; PerkinElmer, Norwalk, CT) using previously explained techniques and quality control procedures (Henn et al., 2010). Blood Mn concentrations were highly correlated across time points, and to avoid multi-collinearity, each was analyzed in separate models.

2.3. Neurodevelopment assessment of working memory

Children ages 6–8 were administered the Cambridge Neuropsychological Test Automated Battery (CANTAB) Spatial Working Memory (SWM) test (Fray & Robbins, 1996; Luciana & Nelson, 2002; Sandberg, 2011), which measures children's visuospatial memory ability and use of strategy (i.e., indicative of executive function). The test requires children to seek out blue tokens by selecting colored boxes. Children cannot return to a previously selected box where a token was found—the level of difficulty increases as the number of colored boxes increases. As primary outcome measures, we used (1) between errors, the total number of times a child incorrectly returns to a previously selected empty box, and (2) strategy, which assesses whether children begin new searches randomly or in a pattern. For both SWM measures, higher scores are reflective of poorer performance and vice versa. $N = 559$ completed the CANTAB tasks and had complete data for the analysis.

2.4. Covariates

Prior literature suggests several covariates are associated with WM in youth. Therefore, covariate-adjusted models included child gender and age at CANTAB assessment, maternal educational attainment (< high school, high school, and >high school), and socioeconomic status (SES) index. Our SES index was calculated based on an index created by the Asociación Mexicana de Agencias de Investigación de Mercados y Opinión Pública (AMAI). We used 13 variables derived from a questionnaire to classify participant families into six levels, which we simplified into a relative three-level index of low, medium, and high SES (Carrasco, 2002). Creatinine levels in children's urinary concentration were used as a covariate to adjust for differences in hydration status at the time of collection in the urine Mn models.

2.5. Statistical analysis

All statistical analyses were conducted using RStudio 4.0.3 software using the lm function and lavaan and gWQS (Renzetti et al., 2019) packages. Outliers were defined by the 1.5 interquartile range (IQR) method and removed before analysis. Descriptive statistics (means, standard deviations, frequencies, and percentages) were calculated for all variables, followed by bivariate correlations for each Mn biomarker. Multiple linear regression models estimated the association between Mn biomarkers at each time point with SWM measures. For each model, two-way interaction terms were used to estimate the modification effect of child sex. All statistical models were adjusted for selected covariates.

To account for the multiplex correlational structure among Mn biomarkers and times of measurement, we used a covariate-adjusted weighted quantile sum (WQS) regression to estimate and examine the MMB mixture effect of combined Mn biomarkers on the CANTAB SWM measures. WQS models included interaction terms to estimate modification by child sex to assess sexually dimorphic effects. All Mn biomarkers measured in blood, cord blood, and urine were included in the mixture. Further details of WQS regression have been previously described (Carrico et al., 2014; Levin-Schwartz et al., 2021). Briefly, the WQS regression is a multivariate regression model that empirically estimates a set of weights, ω_i with the following regression equation: $E[y] = \beta_0 + \beta_1 (\sum_{i=1}^{c} \omega_i q_i) + z^T \varphi$, where y is the outcome variable; β_0 is the intercept, and β_1 is the regression coefficient for the weighted sum of the quantile exposures; q_i i is the number of exposures, $z = [z_1 \ldots z_C]$ is the set of covariates; and φ is the set of regression coefficients corresponding to z. Lastly, the weights are constrained with the purpose of $0 \leq \omega_i \leq 1$ and $\sum_{i=1}^{c} \omega_i = 1$ (Carrico et al., 2015). The WQS implementation involves two steps: (1) a weighted index representing the association between each specific biomarker, and the outcome is estimated across 100 bootstrap datasets, and (2) this weighted index was then tested in a linear regression model estimating the association between the MMB mixture and the SWM outcome. WQS models were ranked into quintiles to balance the inclusion of all values below the LOD, essential for accurate exposure assessment while maintaining resolution and the direction of the association was constrained to be positive.

Additionally, a first-order confirmatory factor analysis (CFA; Brown, 2015) using R's lavaan package was used to verify that four blood Mn observed indicators (maternal blood Mn at the 2nd and 3rd trimester and maternal and child cord blood Mn at delivery) cluster on and quantify a latent blood Mn burden index. CFA is a statistical method used to test a hypothesized measurement model based on theoretical principles (Brown, 2015). The model fits were estimated using the chi-square (χ^2) test of model fit, root mean square error of approximation (RMSEA; Clemens et al., 2014), standardized root mean square residual (SRMR), goodness of fit (GFI), comparative fit index (CFI), normed fit index (NFI), and incremental fit index (IFI). An excellent model fit was determined by a χ^2 statistic value greater than 0.05, RMSEA less than 0.08, SRMR less than 0.07, GFI greater than 0.95, and CFI, NFI, and IFI greater than 0.90 (Kline, 2011; Meyers et al., 2013). Lastly, multiple linear regression models were used to estimate the associations of CFA-derived Mn burden index with SWM measures controlling for selected covariates with an interaction term to estimate the modification effect of child sex.

2.6. Sensitivity analysis

We ran several sensitivity analyses. First, we used the covariate-adjusted WQS regression models to assess maternal blood and urine lead exposure during the 2nd and 3rd trimesters as a covariate, as lead is an important neurotoxin, and to ensure our results were robust. Second, we conducted a first-order CFA that included six Mn observed indicators (maternal blood and urine Mn at the 2nd and 3rd trimesters and maternal and child cord blood Mn at delivery). Third, we conducted a second-order CFA, which included a higher-order factor (blood Mn and urine Mn factors) and two lower-order factors (blood Mn factor with four indicators and urine Mn factor with two indicators) to establish a latent Mn burden index.

3. Results

3.1. Demographics

Table 1 presents the overall and sex-stratified socio-demographic characteristics, concentrations of Mn biomarkers, and SWM characteristics. The sample consisted of 559 boys (50.6%) and girls (49.4%) between the ages of 6 and 8 years, with a mean age of nearly 7 years. In PROGRESS, maternal education was well distributed across three levels (40% with less than a high school diploma, 36% with a high school diploma, and 24% with more than a high school diploma), and over half (52.8%) were from low SES backgrounds. The mean ± standard deviation (SD) for children between error and strategy measures at stage 72 were 63.13 ± 11.72 and 39.07 ± 3.02. The mean ± SD for blood Mn in

Table 1
Overall and sex-stratified socio-demographic characteristics, Mn biomarkers, and SWM tasks (N = 559).

Children's characteristics	*Overall* (*N* = 559) Mean ± *SD* or %	*Boys* (*n* = 283) Mean ± *SD* or %	Girls (*n* = 276) Mean ± *SD* or %
Age (years)	6.70 ± 0.50	6.71 ± 0.51	6.69 ± 0.50
Maternal Education			
< High School	39.9%	44.2%	35.5%
High School	36.3%	31.8%	40.9%
> High School	23.8%	24.0%	23.6%
Maternal SES			
Low	52.8%	53.7%	51.8%
Medium	37.2%	36.0%	38.4%
High	10.0%	10.3%	9.8%
Mn Biomarkers			
Blood Mn at 2nd trimester (μg/L)	14.18 ± 4.38	14.36 ± 4.43	13.99 ± 4.32
Blood Mn at 3rd trimester (μg/L)	18.62 ± 5.39	18.81 ± 5.62	18.43 ± 5.15
Maternal Cord Blood Mn at delivery (μg/L)	23.95 ± 8.04	23.65 ± 7.99	24.28 ± 8.09
Child's Cord Blood Mn at delivery (μg/L)	44.47 ± 14.66	45.08 ± 15.02	43.70 ± 14.23
Urine Mn at 2nd trimester (μg/L)	1.34 ± 0.41	1.33 ± 0.40	1.34 ± 0.42
Urine Mn at 3rd trimester (μg/L)	1.21 ± 0.42	1.22 ± 0.42	1.21 ± 0.41
SWM Measures			
Between Errors	63.13 ± 11.72	62.75 ± 12.71	63.53 ± 10.62
Strategy	39.07 ± 3.02	38.77 ± 3.08	39.37 ± 2.92

the 2nd trimester, 3rd trimester, maternal cord blood at delivery, and child cord blood at delivery were 14.18 μg/L ± 4.38, 18.62 μg/L ± 5.39, 23.95 μg/L ± 8.04, and 44.47 μg/L ± 14.66, respectively. In the 2nd and 3rd trimesters, the mean for urinary Mn was 1.34 μg/L ± 0.41 and 1.21 μg/L ± 0.42, respectively.

3.2. Prenatal Mn exposure and between error scores

There was no significant association between error scores for blood Mn and urine Mn in the 2nd and 3rd trimesters. Similarly, there was no evidence that maternal and children's cord blood Mn concentrations at delivery were significantly associated with between error scores. Further, there was no significant difference between child sex and sex-based interaction with Mn exposures in either trimester or at delivery and between error performances (Table 2).

3.3. Prenatal Mn exposure and strategy scores

In the 2nd trimester, there was no significant association between blood Mn concentrations and strategy scores. We found a marginally significant association between child sex and strategy scores (β = 1.49, 95% *CI*: 0.27, 3.26), with girls having 1.49 higher strategy scores, indicating less efficient strategizing for girls compared to boys. There was no interaction effect between blood Mn in the 2nd trimester and child sex. For prenatal Mn levels in the 3rd trimester, there was a marginally significant interaction between blood Mn exposure and child sex (β = −0.09, 95% *CI*: 0.20, 0.01), with Mn being positively associated with strategy in boys and negatively associated with strategy in girls. There was a significant association between child sex and strategy scores (β = 2.42, 95% *CI*: 0.35, 4.50), with girls having 2.42 higher scores on the strategy tasks, indicating less efficient strategizing for girls compared to boys. Further, there was no significant association between blood Mn concentrations in 3rd trimesters and strategy scores (Table 3).

There were no significant associations between prenatal urine Mn in the 2nd and 3rd trimesters and maternal and children's cord blood Mn concentrations at delivery with strategy scores. Similarly, there was no significant effect with child sex and no sex-based interactions with exposures at either trimester or delivery and strategy performance.

3.4. MMB mixture effect of combined Mn biomarkers on SWM measures

3.4.1. Between error scores

There was a negative association (i.e., main effect) for the MMB mixture (β = −4.59, 95% *CI*: 8.55, −0.63) and for child sex (β = −12.82, 95% *CI*: 24.82, −0.84) with between error scores (Table 4). However, there was also a significant interaction between the MMB mixture and child sex (β = 6.50, 95% *CI*: 0.91, 12.08), with the MMB mixture being positively associated with between error performance in girls (i.e., higher Mn levels were associated with more errors) and negatively associated with between error performance in boys (i.e., higher Mn levels were associated with fewer errors; Fig. 1). This interaction is the focus of the paper. Between error scores reduced by 4.59 for every 1-unit increase of the MMB mixture exposed during pregnancy, and girls had 12.82 fewer errors than boys, indicating better WM performance. Urinary Mn in the 2nd trimester, child cord blood Mn, and maternal cord blood Mn were the most significant weights to the MMB mixture effect (30.6%, 22.7%, and 21.2%; Fig. 2).

3.4.2. Strategy scores

There was a positive association (i.e., main effect) for the MMB mixture (β = 1.35, 95% *CI*: 0.52, 2.18) and for child sex (β = 3.55, 95% *CI*: 1.01, 6.08) with strategy scores (Table 4). However, the analysis showed a significant interaction between the MMB mixture and child sex (β = −1.36, 95% *CI*: 2.55, −0.18), for strategy performance (i.e., higher Mn levels were associated with using more efficient strategies for girls and higher Mn levels were associated with using less efficient strategies for boys; Fig. 3). Strategy scores increased by 1.35 for every 1-unit increase of the MMB mixture exposed during pregnancy, and girls had 3.55 higher strategy scores than boys, indicating poorer performance. In

Table 2
Association between single blood or urine Mn biomarkers in pregnancy with between error task.

		Main Effect Mn	Main Effect (Child Sex)	Interaction
Outcome measures	Exposure	β (95% CI)	β (95% CI)	β (95% CI)
Between Error[a]	Blood Mn at 2nd Trimester (μg/L)	−0.17 (−0.49, 0.15)	−4.59 (−11.51, 2.32)	0.36 (−0.10, 0.83)
	Blood Mn at 3rd Trimester (μg/L)	−0.16 (−0.45, 0.12)	1.85 (−6.32, 10.01)	−0.04 (−0.46, 0.38)
	Maternal Cord Blood Mn at delivery (μg/L)	−0.01 (−0.20, 0.19)	−0.69 (−7.84, 6.46)	0.09 (−0.19, 0.37)
	Child's Cord Blood Mn at delivery (μg/L)	0.03 (−0.10, 0.15)	0.18 (−8.63, 8.99)	0.00 (−0.19, 0.19)
	Urine Mn at 2nd Trimester (μg/L)	−1.75 (−5.68, 2.19)	−4.26 (−11.85, 3.33)	3.56 (−1.92, 9.04)
	Urine Mn at 3rd Trimester (μg/L)	−3.08 (−6.93, 0.78)	−3.10 (−10.19, 4.00)	3.38 (−2.06, 8.83)

Note. Child sex (Males served as the reference group). Controls are child age, maternal age, maternal education (less than high school served as the reference group), SES (low SES served as the reference group), and creatinine levels in children's urinary concentration (only in urine Mn models). *B* = Unstandardized Regression Weight; *CI* = Confidence Interval. *$p < .05$, † marginal significance.
[a]Greater scores indicate lower performance.

Note. Child sex (Males served as the reference group). Controls are child age, maternal age, maternal education (less than high school served as the reference group), SES (low SES served as the reference group), and creatinine levels in children's urinary concentration (only in urine Mn models). *B* = Unstandardized Regression Weight; *CI* = Confidence Interval. *$p < .05$, † marginal significance.
[b]Greater scores indicate lower performance.

Table 3
Association between single blood or urine Mn biomarkers in pregnancy with strategy task.

		Main Effect Mn	Main Effect (Child Sex)	Interaction
Outcome measures	Exposure	β (95% CI)	β (95% CI)	β (95% CI)
Strategy[b]	Blood Mn at 2nd Trimester (μg/L)	0.01 (−0.07, 0.09)	**1.49 (-0.27, 3.26)**†	−0.06 (−0.18, 0.05)
	Blood Mn at 3rd Trimester (μg/L)	0.04 (−0.03, 0.12)	**2.42 (0.35, 4.50)***	**−0.09 (-0.20, 0.01)**†
	Maternal Cord Blood Mn at delivery (μg/L)	−0.01 (−0.06, 0.04)	−0.08 (−1.93, 1.76)	0.04 (−0.04, 0.11)
	Child's Cord Blood Mn at delivery (μg/L)	0.01 (−0.02, 0.04)	0.45 (−1.79, 2.70)	0.00 (−0.05, 0.05)
	Urine Mn at 2nd Trimester (μg/L)	0.00 (−0.97, 0.97)	0.33 (−1.55, 2.20)	0.27 (−1.08, 1.62)
	Urine Mn at 3rd Trimester (μg/L)	−0.80 (−1.79, 0.20)	−0.80 (−2.62, 1.03)	1.09 (−0.30, 2.49)

Table 4
Association of MMB mixture with between error and strategy tasks.

		Main Effect (MMB)	Main Effect (Child Sex)	Interaction
Outcome measures	Exposure	β (95% CI)	β (95% CI)	β (95% CI)
Between Error[a]	MMB Mixture	−4.59 (−8.55, −0.63)*	−12.82 (−24.82, −0.84)*	6.50 (0.91, 12.08)*
Strategy[b]	MMB Mixture	1.35 (0.52, 2.18)*	3.55 (1.01, 6.08)*	−1.36 (−2.55, −0.18)*

Note. Child sex (Males served as the reference group). Controls are child age, maternal education (less than high school served as the reference group), and SES (low SES served as the reference group). *B* = Unstandardized Regression Weight; *CI* = Confidence Interval. *$p < .05$, † marginal significance. [a-b]Greater scores indicate lower performance.

this model, child cord blood Mn at delivery, urine Mn and blood Mn in the 2nd trimester were the most critical weights in the MMB mixture (40.3%, 22.6%, and 21.9%; Fig. 4).

3.5. Confirmatory factor analysis of a Mn burden index

Given the correlation structure of blood Mn biomarkers at different time points, to the exception of a significant χ2, other criteria indices suggest an acceptable fit for the CFA model (Fig. 5; χ^2 (*df*) = 12.09 (2), $p < .01$, RMSEA = 0.15, SRMR = 0.05, GFI = 0.97, CFI = 0.95, NFI = 0.94, IFI = 0.95). Based on the extracted values from the CFA models for blood Mn, we used a covariate-adjusted linear regression analysis similar to Tables 2–3. There was a direct association between the Mn burden index and higher between errors (β = 0.86, 95% *CI*: 0.00, 1.72). Although there was no association between the Mn burden index and strategy scores, we found that child sex had a main effect on strategy scores (β = 0.81, 95% *CI*: 0.03, 1.60), with girls having higher scores than boys, indicating less efficient strategy performance. Further, there was no significant effect of child sex on between error scores and no sex-based interactions with the Mn burden index on both SWM measures.

3.6. Sensitivity analyses

The results from the covariate-adjusted WQS regression models, which considered prenatal blood and urine lead levels during the 2nd and 3rd trimesters, were consistent with the primary WQS models. These models showed significant main effects and a sex interaction effect for both between errors and strategy tasks, as detailed in Supplemental Table S1. A first-order CFA revealed that urine Mn indicators were not statistically significantly related to the latent Mn burden index and a second-order CFA showed that both blood Mn and urine Mn were insignificant and did not load onto the main latent burden factor (Supplemental Table S2 and Table S3).

4. Discussion

We investigated the association between cumulative prenatal Mn exposure on WM performance in school-age children using the multimedia biomarker approach of Levin-Schwartz et al. (2021) and the moderating effect of child sex. To our knowledge, this is the first study to investigate the association between prenatal Mn and WM using MMBs in children. We compared our MMB approach with traditional single biomarker regressions and found it better suited to finding associations. Interestingly, we found a main effect using the MMB approach and an interaction with child sex. For purposes of the discussion, we focus on the sex interactions.

Traditional single biomarker approaches demonstrated only a marginal association of increased blood Mn with improved strategy

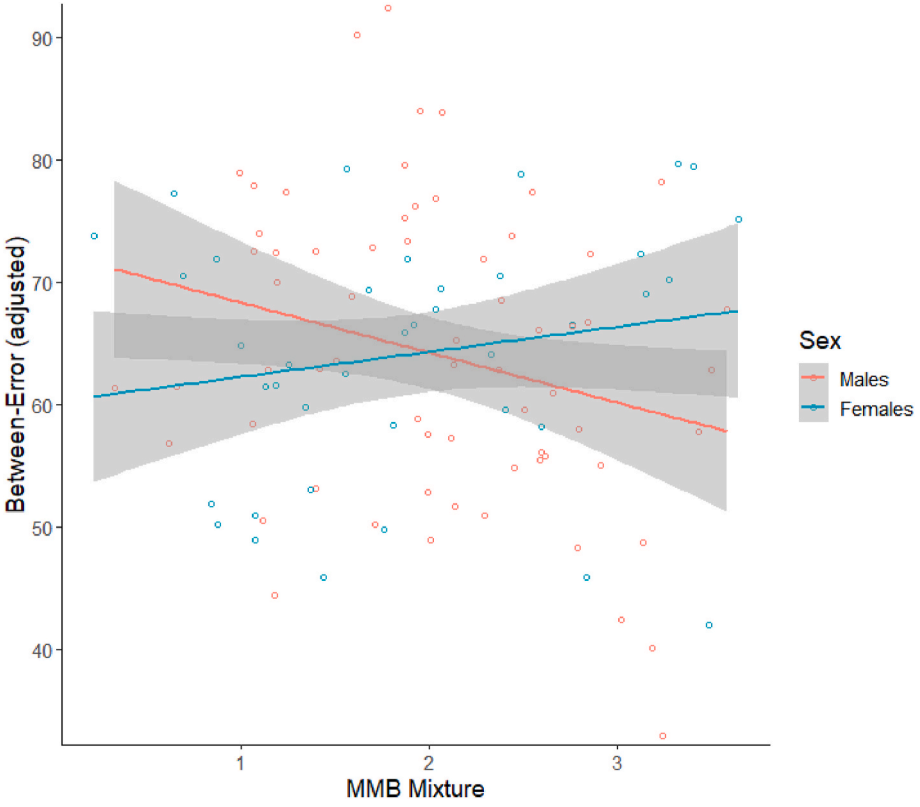

Fig. 1. Covariate-adjusted model examining the moderating effect of child sex on the association between WQS MMB mixture and between error performances among children.

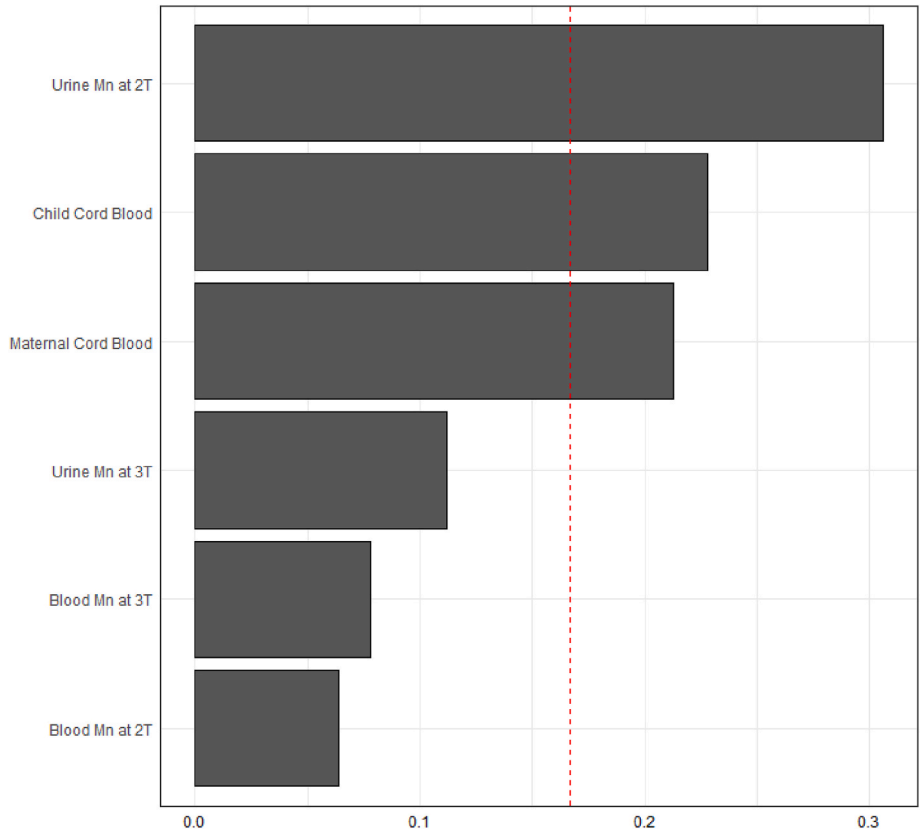

Fig. 2. Covariate adjusted estimated weights for each component of the MMB mixture contributing to the integrated effect on between error performances among children. Higher weights indicate a greater contribution. The red line indicates the cut-off value for defining the elements with significant weights in the MMB mixture. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

performance in girls and reduced performance in boys using either blood or urine Mn levels individually, and results were consistently weaker than with the MMB approach. Our results showed an overall Mn effect on WM when using an integrated MMB. In the WQS models, we also observed a sex-specific association between the MMB mixture and SWM tasks. Exposure to the MMB mixture was associated with fewer errors for boys and more errors for girls and was predominantly driven by urinary Mn in the 2nd trimester, child cord blood Mn, and maternal cord blood Mn. In addition, the MMB mixture was associated with less efficient strategy performance for boys and more efficient strategy performance for girls. This strategy-specific MMB mixture was predominately driven by child cord blood Mn at delivery and urine Mn and blood Mn in the 2nd trimester. Lastly, the CFA demonstrated that blood Mn indicators successfully verified the Mn burden index. In the regression models using the CFA-derived Mn burden index, we found that a higher Mn burden index was associated with more between errors, which is different from our WQS models. We also found an association of child sex with strategy scores, indicating girls had poorer strategy performance. Our results suggest that (i) vulnerability to prenatal Mn co-exposure on SWM differs in the directionality by sex, (ii) Mn exposure as an MMB mixture and burden index is more affecting than a single exposure on WM performance, and (iii) late childhood may persist in being a sensitive neurodevelopmental period.

Our findings are consistent with previous research that used teeth to reconstruct early-life Mn exposure and showed sex differences in the effects of Mn on WM facets in children, with boys benefiting more than girls. In Italian adolescents, boys had a more beneficial association between prenatal Mn and tasks of WM (Bauer et al., 2021) and visuospatial learning and memory performance (Bauer et al., 2017) than girls. Since Bauer et al. studies used a retrospective tooth biomarker, and our study is prospective, our results are an important replication of tooth biomarker research. Among school-aged children in California, a positive association was reported between prenatal Mn and visual memory performance and other cognitive tasks in boys but not girls living close to treated areas of Mn fungicide (Mora et al., 2015). We and other studies have documented the sex differences in the association between prenatal Mn exposure and general cognitive domains, such as strategy, indexing executive function, and WM capacity. We found that girls' ability to strategize benefited more than boys' when exposed to higher levels of Mn during pregnancy. Other studies have reported direct associations between higher prenatal Mn exposure and improved general-cognitive scales (e.g., McCarthy Scales of Children's Abilities, WISC-IV, and IQ scores) in girls but not boys (Irizar et al., 2021; Rahman et al., 2017; Riojas-Rodríguez et al., 2010). There may be complex reasons behind the differences in how boys and girls are affected by manganese neurotoxicity. One possibility is that there are sex-specific variations in neurochemistry and overall brain development (Cosgrove et al., 2007; Kaczkurkin et al., 2019), as well as differences in how the body regulates oxidative stress and hormones (Llop et al., 2013; Ngun et al., 2011). These differences could contribute to the varying effects of prenatal manganese exposure on neurodevelopment. More research is needed to understand these differences fully.

Further, we found no associations between cord blood Mn biomarkers and SWM tasks. However, inconsistent results are reported by Oppenheimer et al. (2022), who found a negative association between cord blood Mn and lower verbal WM in both sexes, but a more robust effect among boys than girls. The inconsistencies between our results and some prior work may be explained by several aspects, such as the use of different Mn media biomarkers (e.g., blood, urine, hair, and teeth; Leonhard et al., 2019), assessments of WM instrumentals, and critical time window of prenatal exposure assessment as opposed to child life stages measures of Mn. These results support the need to address

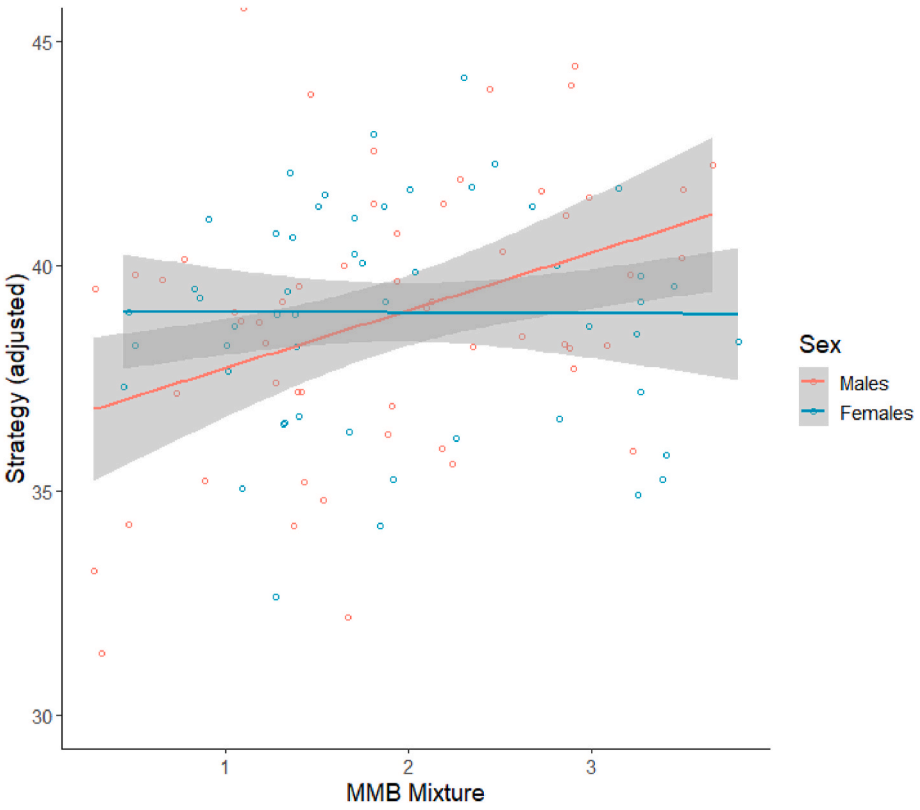

Fig. 3. Covariate-adjusted model examining the moderating effect of child sex on the association between WQS MMB mixture and strategy performances among children.

sex-specific effects as well as MMB or latent variables of Mn exposure using multiple biomarkers in future research investigating Mn exposure in children.

4.1. Biomarkers of manganese exposure

Measuring exposure to environmental chemicals is commonly achieved using biomarkers in which the chemical concentration is measured. Several biological media have been used to measure prenatal Mn exposure, the most common being blood and urine, but other media like nails, hair, and teeth have also been used. Unlike lead, for which blood is considered the gold standard biomarker media, no definitive media exists for Mn biomarkers. The association between prenatal Mn exposure using a precise media biomarker such as blood and urine with neurodevelopment in children remains ambiguous. For example, a positive association was reported between neurodevelopment and Mn in maternal blood (Irizar et al., 2021). Studies reported negative associations (Chung et al., 2011; Hernández-Bonilla et al., 2011; Muñoz-Rocha et al., 2018) on intelligence, psychomotor, and attention indexes. However, other studies reported no associations (Menezes-Filho et al., 2014; Parvez et al., 2011; Wasserman et al., 2011), whereas some reported an inverted U-shape association between neurodevelopment outcomes and Mn in maternal blood (Chung et al., 2015; Henn et al., 2012), revealing that both under- and overexposure to Mn are associated with subclinical impairment.

Similarly, studies measuring urinary Mn concentrations have reported inconsistent results (Gunier et al., 2015; Haynes et al., 2015; Shen et al., 2021; Zhou et al., 2020). Furthermore, evidence suggests that these inconsistencies across studies of Mn as a neurotoxin may partially depend on differences in media biomarkers used. The MMB approach overcomes the absence of a definitive media biomarker to measure Mn exposure and also allows researchers to avoid choices between biomarkers, as they can integrate different biomarkers. We have shown that integrating Mn biomarkers assessed in blood and urine using statistical methods designed for complex chemical mixtures improves the power for finding associations with health outcomes. Hence, in this study, we used Mn assessed at the 2nd and 3rd trimesters in blood and urine to create an integrated mixture of prenatal Mn body burden in our analyses.

Biomarkers for Mn are physiologically complex as Mn is regulated in the blood system to be in a specific concentration range. Excess Mn is excreted in the bile and urine (Malecki et al., 1996). Although blood is commonly used to measure prenatal Mn concentrations, evidence suggests that due to its immediate hepatic clearance (O'Neal & Zheng, 2015), blood may not be the most definitive biomarker to assess total body burden and excessive exposure until levels are exceptionally high (Levin-Schwartz et al., 2021). Researchers propose urine as a noninvasive biomarker with the advantage of being solely a medium to reflect recent exposures, as Mn primarily excretes in bile with a short half-life. The immediate disadvantage of using urine as a biomarker is its insufficient excretion levels (Klaassen, 1974), making monitoring very difficult. Therefore, this limits the benefits of urine as a definitive media of Mn exposure, thus making it not highly recommended (Hoet et al., 2012; Smith et al., 2007). Our MMB approach essentially resolves these issues by using both biomarkers and creating an index of exposure.

Our analysis used two methodological approaches to integrate media biomarkers to measure prenatal Mn body burden across time points. First, the WQS regression is a data-driven mixture analysis that allows us to reevaluate the mixture as a single weighted index by estimating the integrated effect under two assumptions: (1) each Mn biomarker has no association or association with the same directionality with SWM outcomes, and (2) each Mn biomarker associations have a linear and additive effect. Second, the CFA is an underlying theoretically-driven latent variable analysis that allows us to test whether the association between Mn biomarkers (or indicators) and the underlying latent construct (i.e., Mn burden index) exists. Specifically, the CFA enables

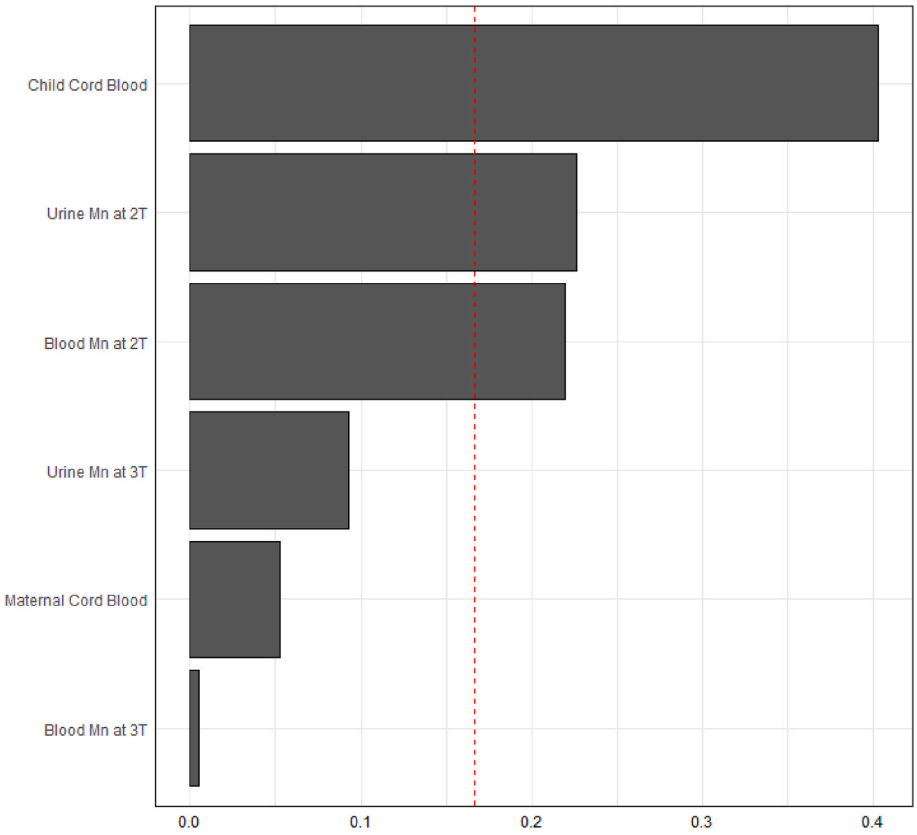

Fig. 4. Covariate adjusted estimated weights for each component of the MMB mixture contributing to the integrated effect on strategy performances among children. Higher weights indicate a greater contribution. The red line indicates the cut-off value for defining the elements with significant weights in the MMB mixture. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

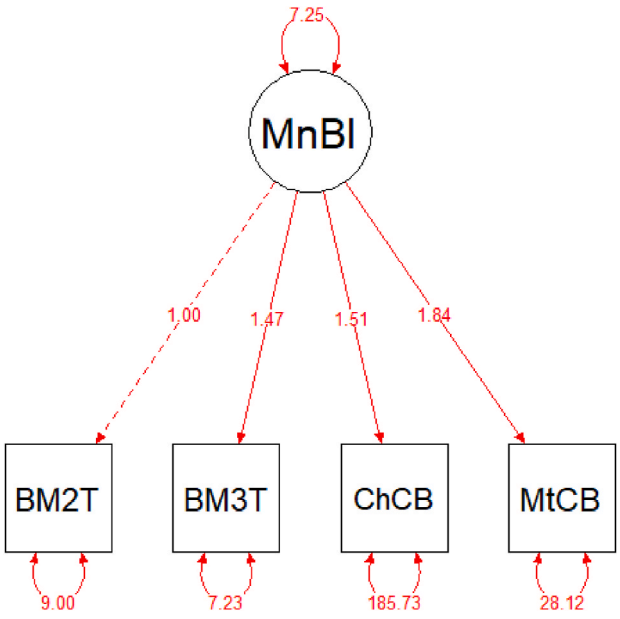

Fig. 5. Standardized estimates from the first-order CFA to quantify a Mn burden index. MnBl: Mn burden index; BM2T: Blood Mn measured in the 2nd trimester; BM3T: Blood Mn measured in the 3rd trimester; ChCB: Umbilical cord blood Mn measured in children at delivery; MtCB: Umbilical cord blood measured in mothers at delivery.

measurement error in each Mn biomarker. Inferences about the Mn body burden (latent construct) can be interpreted as if the Mn burden index were measured without error, thus allowing us to benefit from the reduced measurement error in the Mn burden index (Lahey et al., 2012).

Furthermore, the CFA differs from other unsupervised methods like principal component analysis and k-means clustering, as it adopts a theoretical approach. These other methods are designed to identify hidden patterns or structures in the data, reduce the data dimensionality, or group similar observations together without a pre-specific model or hypothesis. Applying the CFA help provides more robust and reliable results, ultimately leading to a better understanding of the underlying structure of the data. Several research studies have applied the CFA method to investigate the link between environmental exposure and health effects (Brauer et al., 2008; Grandjean and Budtz-Jørgensen, 2010; Valvi et al., 2021). It has emerged as a powerful technique for analyzing complex associations, high-dimensional data, and untangling the effects of exposure variables (Grandjean & Budtz-Jørgensen, 2007). A strength of the WQS is that it disentangles and identifies the effects of independent biomarkers in a mixture. The main difference between the two approaches and the strength of the CFA is that it holds the exposure metric constant, so the metric for evaluating between errors and strategy scores remains the same. While the WQS does not hold the exposure metric constant, and the weights depend on the chosen outcome.

4.2. Study strengths and limitations

The study has several strengths over previous studies examining the neurotoxic effect of prenatal Mn exposure in children. We measured prenatal Mn concentrations in several media from the same sample across the same time points. In addition, using an MMB approach reduces the bias often raised by selecting individual biomarkers to

measure the effect of prenatal Mn exposure (Levin-Schwartz et al., 2021). Rather than use child sex as a covariate, we investigated the role of child sex acting as an effect modifier, which enabled us to detect a sexually dimorphic effect that may shed light on sex-specific protections and regulations (Rechtman et al., 2020) relating to oxidative stress (Llop et al., 2013). We also explored two different approaches to integrate Mn exposure across media biomarkers. The WQS estimated the total effect of the mixture as a composite on the outcome and identified the prominent exposure in the mixture. At the same time, the CFA verified the underlying latent variable. Both approaches improve the opportunities of achieving a better internal body burden that can reflect an individual's total exposure and reduce measurement error. In this study, we observed evidence for the integrated effect of Mn on WM performance across several media biomarkers and that these relationships exist in a sexually dimorphic manner. Lastly, we used SWM tasks from the CANTAB test developed to target explicit executive function domains compared to other assessments (e.g., WISC-IV) that primarily measure overall composite scores of cognitive and behavioral faculties (Lucchini et al., 2019).

This study has several limitations. The measures of Mn biomarkers in this urban population in Mexico may not be entirely generalizable to US populations or communities with Mn-contaminated water or air. Such populations may see an inverse association with the MMB and WM measures, which is different from our findings in a community without known excess Mn exposure. We did not measure Mn levels in the 1st trimester and measured it during the 2nd and 3rd trimesters, which only provided a snapshot for those particular periods, limiting our ability to determine windows of susceptibility during pregnancy when exposure may be particularly harmful. Further, this limited our ability to explain any additional variability across trimesters. However, we acknowledge the significance of examining other media, such as deciduous teeth measurements, which can provide weekly variations in Mn exposure (Arora et al., 2011; Arora et al., 2012; Arora and Austin, 2013; Mora et al., 2015). These measurements can capture variations that may be missed by only measuring at a trimester level. Our WQS approach is limited to linear and additive effects; thus, other methods for using an MMB must consider multiplicative and nonlinear effects (Levin-Schwartz et al., 2021). Because of the poorer fit when using both blood and urine Mn measures, our CFA approach was based on blood Mn. Future work will explore including urine Mn in the index in a multi-dimensional framework while addressing identifiability issues of the model since there are only two urine Mn indicators.

5. Conclusion

In conclusion, our findings show an association between prenatal Mn neurotoxic effects on WM in school-aged children with higher Mn exposure biomarker levels generally regulating WM performance in a sexually dimorphic manner. Prior studies have shown that WM tests can be sexually dimorphic, and further research is needed to understand the role that Mn may play in this finding, as we found that prenatal Mn exposure as an MMB dysregulates the development of WM in children in a sexual dimorphic manner. The discrete biological mechanisms behind the sexual dimorphism in Mn neurotoxicity are still not clearly defined. Therefore, understanding the beneficial or neurotoxic sex-specific effects of prenatal Mn exposure may require a detailed assessment of age at exposure and multiple exposure biomarkers. Any interventions or prevention measures should factor in the added value of assessing blood and urine together, Mn's role as an essential nutrient and a potential neurotoxicant, as well as its sexually dimorphic effects on brain development.

Credit author statement

Jamil M. Lane: Conceptualization, Methodology, Formal analysis, Software, Writing – original draft, Writing – review & editing, Visualization.**Shelley H. Liu**: Supervision, Methodology, Formal analysis, Writing – review & editing.**Sandra Martinez-Medina**: Writing – review & editing.**Ivan Pantic**: Project administration, Data curation, Writing – review & editing.**Martha M. Téllez-Rojo**: Investigation, Resources, Project administration, Data curation, Writing – review & editing.**Chitra Amarasiriwardena**: Investigation, Data curation.**Robert O. Wright**: Investigation, Resources, Supervision, Project administration, Funding acquisition, Conceptualization, Writing – review & editing.

Declaration of competing interest

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

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envpol.2023.121965.

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