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Prenatal exposure to metal mixtures and childhood temporal processing in the PROGRESS Birth Cohort Study: Modification by childhood obesity

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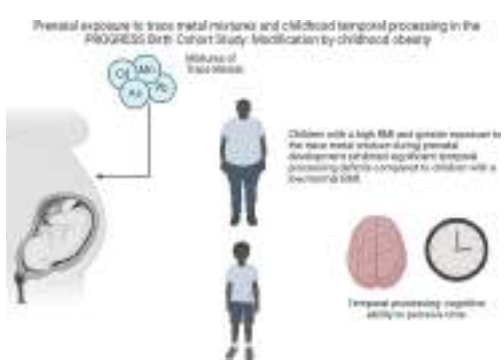
HIGHLIGHTS

- Obesity's inflammatory and metabolic features may interact, potentially amplifying metal exposure effects on neurodevelopment.
- Child BMI phenotypes modify the association between prenatal exposure to trace metal mixtures and temporal processing.
- High BMI children with increased prenatal trace metal exposure showed notable temporal processing deficits versus normal BMI peers.
- High BMI may amplify the effect of trace metals on children's temporal processing.
- Metal co-exposure may significantly impact the development of dynamic brain regions, influencing time perception.

GRAPHICAL ABSTRACT



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ABSTRACT

Children are frequently exposed to various biological trace metals, some essential for their development, while others can be potent neurotoxicants. Furthermore, the inflammatory and metabolic conditions associated with obesity may interact with and amplify the impact of metal exposure on neurodevelopment. However, few studies have assessed the potential modification effect of body mass index (BMI). As a result, we investigated the role of child BMI phenotype on the relationship between prenatal exposure to metal mixtures and temporal processing. Leveraging the PROGRESS birth cohort in Mexico City, children ($N = 563$) aged 6–9 years completed a Temporal Response Differentiation (TRD) task where they had to hold a lever down for 10–14 s. Blood and urinary metal (As, Pb, Cd, and Mn) measurements were collected from mothers in the 2nd and 3rd trimesters. Child BMI z-

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scores were dichotomized to normal (between −2 and +0.99) and high (≥1.00). Covariate-adjusted weighted quantile sum (WQS) regression models were used to estimate and examine the combined effect of metal biomarkers (i.e., blood and urine) on TRD measures. Effect modification by the child's BMI was evaluated using 2-way interaction terms. Children with a high BMI and greater exposure to the metal mixture during prenatal development exhibited significant temporal processing deficits compared to children with a normal BMI. Notably, children with increased exposure to the metal mixture and higher BMI had a decrease in the percent of tasks completed (β = −10.13; 95 % CI: −19.84, −0.42), number of average holds (β = −2.15; 95 % CI: −3.88, −0.41), longer latency (β = 0.78; 95 % CI: 0.13, 1.44), and greater variability in the standard deviation of the total hold time (β = 2.08; 95 % CI: 0.34, 3.82) compared to normal BMI children. These findings implicate that high BMI may amplify the effect of metals on children's temporal processing. Understanding the relationship between metal exposures, temporal processing, and childhood obesity can provide valuable insights for developing targeted environmental interventions.

1. Introduction

Children are often simultaneously exposed to several trace metals that may harm a complex network of brain areas (e.g., cerebellum, basal ganglia, hippocampus, and temporal lobe) (Fontes et al., 2016; Meck, 2005; Mondok and Wiener, 2023; Wittmann, 1999; Rehman et al., 2018). Trace metals can be potent neurotoxicants (e.g., arsenic [As], lead [Pb], and cadmium [Cd]), are widespread in the environment, and some are essential nutrients (e.g., manganese [Mn]) needed for human growth and development. For these reasons, it is crucial to assess both the positive and negative effects of metal elements on children's neurodevelopmental outcomes. Metal mixture exposure during pregnancy can adversely disrupt normal neurodevelopment across childhood, impacting several neurocognitive functions (Shah-Kulkarni et al., 2020), causing learning deficits (Merced-Nieves et al., 2022a), maladaptive executive functioning (Fruh et al., 2021), and neurobehavioral abnormalities (de Water et al., 2022). Research indicates that joint mixture exposures to various essential and nonessential metals have been associated with the dysregulation of cognitive performance on tasks that measure children's IQ (Levin-Schwartz et al., 2021), attention and inhibitory control (Levin-Schwartz et al., 2019), visuospatial learning (Rechtman et al., 2020), and internalizing behavioral outcomes (Horton et al., 2018). According to the heavy metal subdivision of the Agency for Toxic Substances and Disease Registry in 2022, As, Pb, and Cd are the most hazardous substances among metals, ranked first, second, and seventh on the Superfund priority list (Agency for Toxic Substances and Disease Registry, n.d.). In contrast, Mn is an essential micronutrient for human growth and brain development, but both deficiency and excess levels can be harmful to the brain.

The harmful effects of prenatal metals on general cognition are well-known, but their impact on temporal processing (e.g. the ability to perceive time) remains largely unknown. Temporal processing is a crucial skill necessary for various human behaviors (Matthews and Meck, 2016), including verbal time estimation, time reproduction, time management, and time orientation. It holds considerable importance in many cognitive and behavioral functions (Foster et al., 2013) relating to memory performance, language development, and executive functions (Nobre and Van Ede, 2018; Nowak et al., 2016; Tallal et al., 1993). It is crucial for children as it allows them to plan (e.g., I will study for my test) and execute tasks efficiently (e.g., I will finish in 10 min) and serves as a foundation for higher-level cognition, knowledge-building, sensory, and emotional processing (Paton and Buonomano, 2018; Waugh et al., 2015). To effectively perceive time intervals, children must be able to predict and anticipate events. Several cognitive control faculties associated with coordination, task initiation, and planning are considered time-dependent and require compliance with temporal limitations (Carelli et al., 2008).

Epidemiological evidence from children's studies suggests that body mass index (BMI) could contribute to the mechanistic relationship between the neurotoxic effect of prenatal metals exposure and neurodevelopment (Ramírez et al., 2022), given that a high BMI is characterized by inflammatory and metabolic conditions, it is likely to interact and potentially amplify the effects of metal exposures on neurodevelopment. However, evidence is sparse, inconsistent, and primarily concentrates on BMI as a primary predictor of neurodevelopment (Dennis et al., 2022; Liang et al., 2014; Mehari et al., 2020) or an outcome in the association with metal exposures (Huang et al., 2022; Liu et al., 2022; Signes-Pastor et al., 2021) rather than a modifier in this relationship. We suggest that child BMI may serve as a moderator Moreover, conventionally, children's studies focus on general cognitive functions, using global or indirect (survey-based) cognition assessment methods and, more importantly, analyzing individual metal exposures through general linear models. Most studies fail to consider the cumulative impact of multiple metals that occur in real-life conditions, influencing physiological and biological mechanisms in a complex, interconnected manner. Thus, due to the potential impact of metals on BMI and the interconnection of BMI and neurodevelopment, we hypothesize that child BMI modifies the association between the mixture effect of prenatal metal exposure and children's temporal process performance. The present study leverages a computational mixture analysis-weight quantile sum (WQS) regression to investigate the cumulative effect emerging from prenatal metal exposure on temporal processing and whether child BMI phenotype modifies this association.

2. Methods

2.1. Participants

The Programming Research in Obesity, GRowth, Environment and Social Stressors study (PROGRESS) is an ongoing 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. Although continuing, we analyze children up to 6–9 age, as data are now complete for this visit. Initially, we enrolled 948 mothers enrolled in the 2nd trimester who delivered a live birth at Hospital de Ginecología y Obstetricia (la Clínica Numero 4) in Mexico City from 2008 to 2011. Mothers had two prenatal visits, in their 2nd and 3rd trimester, with inclusion criteria selecting for 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 three 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, and the National Institute of Perinatology Mexico. Children ($N = 563$) included in this analysis were those who completed the operant test battery (OTB) measures at 6–9 years of age.

2.2. Body mass index

Child weight was measured using a digital scale (BWB-800, Tanita) accurate to 0.01 kg (calibrated daily), and standing height was measured using a stadiometer with head in Frankfort plane. Child BMI categories based on BMI z-scores for age and sex were determined using weight and height according to the WHO Growth Standards and Reference. A high BMI (overweight/obese) was classified as having a z-score of 1 or greater, while a normal BMI was classified as having a z-score between −2 and +0.99 (Monasor-Ortolá et al., 2021). The study did not include participants with a z-score below −2 due to a low number of observations ($n = 8$).

2.3. Metal assessments

Maternal venous whole blood and urine samples were collected in the 2nd (between the 16th and 20th gestational weeks) and 3rd trimesters (between the 30th and 34th gestational weeks) of pregnancy. Blood specimens were stored at 4 °C; urine specimens were stored at −80 °C before being shipped to the Icahn School of Medicine at Mount Sinai for metal analysis. The current analysis included both blood and urine biomarkers, focusing on four trace elements – As, Cd, Pb, and Mn. The limits of detection (LOD) and the % metals above the LOD are presented in Table 1. Measurements were taken in five replicates and reported as an average. Quality control standards were recovered at 90–110 %. Blinded quality control samples, sourced from the Maternal and Child Health Bureau and the Wisconsin State Laboratory of Hygiene Cooperative Blood Lead Proficiency Testing Program, exhibited good precision and accuracy. Each metal for each time point was measured in blood and urine and analyzed with a triple quadrupole dynamic reaction cell-inductively coupled plasma mass spectrometer (ICP-MS; Elan 6100; PerkinElmer, Norwalk, CT) using previously described techniques and quality control procedures (Claus Henn et al., 2010).

2.4. Temporal response differentiation

Children ages 6–9 years were administered an OTB consisting of a series of behavioral tasks that provoke responses conditional upon distinctive cognitive and neurobehavioral functions (Paule et al., 1999). Further details on the description of the apparatus have been previously provided (Paule et al., 1988). During the tasks, the child was seated across from a testing panel installed in a wooden cabinet (Fig. 1). The testing panel had circular press-plates and response levers that the child could press, stimulus lights that could indicate a correct or incorrect response, and a row of 6 lights that could indicate which lever to press for one of the behavioral tasks. Located at the bottom of the apparatus was a container where the apparatus delivered nickels following a correct response. After completing the study visit, children traded the earned nickels for a toy of their choosing.

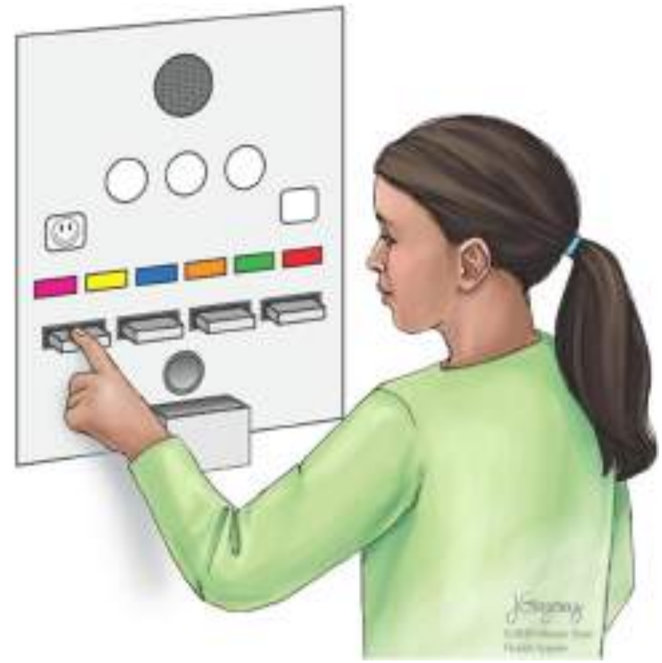

Fig. 1. Diagram of child positioning and the operant test panel. Illustration by Jill Gregory used with permission of ©Mount Sinai Health System. Starting at the top of the panel, there is a speaker and below that, there are three circular press-plates. Below the circular press-plates, there are two different types of stimulus lights – correct and incorrect response indicator lights (smiley face) and serial position indicator lights (colored rectangles). At the bottom of the apparatus, there was a container where a dispenser mounted inside the wooden cabinet delivered nickels.

A trained psychologist administered all behavioral tasks, and before each task, children watched video instructions in Spanish. After the children acknowledged they understood the video instructions, the psychologist left the study room and continuously monitored the children's behavior through a one-way mirror. Children completed a TRD

Table 1
Distributions of metal concentrations among the study population (N = 563) including the range of limits of detection (LOD) and the percent of metals above the LOD.

	LOD range	% > LOD	Overall ($N = 563$) Median (25th–75th)	Normal BMI ($n = 403$) Median (25th–75th)	High BMI ($n = 160$) Median (25th–75th)
Trace metals					
Mn biomarkers					
Blood Mn at 2nd trimester (μg/L)	0.02–0.08	100.00	1.37 (1.11–1.71)	1.38 (1.12–1.73)	1.35 (1.09–1.67)
Blood Mn at 3rd trimester (μg/L)	0.02–0.08	99.79	1.84 (1.49–2.24)	1.86 (1.50–2.27)	1.80 (1.44–2.19)
Urine Mn at 2nd trimester (μg/L)	0.27–0.43	100.00	1.23 (1.02–1.66)	1.22 (1.02–1.67)	1.25 (1.02–1.63)
Urine Mn at 3rd trimester (μg/L)	0.27–0.43	100.00	1.20 (0.91–1.66)	1.18 (0.91–1.70)	1.21 (0.92–1.57)
Pb biomarkers					
Blood Pb at 2nd trimester (μg/L)	0.003–0.21	100.00	2.89 (1.93–4.44)	3.05 (1.96–4.46)	2.66 (1.91–4.33)
Blood Pb at 3rd trimester (μg/L)	0.003–0.21	99.79	3.10 (2.01–4.92)	3.22 (2.05–5.00)	2.84 (1.89–4.54)
Urine Pb at 2nd trimester (μg/L)	0.04–0.06	100.00	2.83 (1.55–5.41)	2.93 (1.60–5.61)	2.73 (1.35–4.91)
Urine Pb at 3rd trimester (μg/L)	0.04–0.06	100.00	2.90 (1.76–5.10)	2.95 (1.77–5.53)	2.57 (1.76–4.34)
As biomarkers					
Blood As at 2nd trimester (μg/L)	0.02–0.06	97.74	0.07 (0.06–0.09)	0.08 (0.06–0.10)	0.07 (0.06–0.09)
Blood As at 3rd trimester (μg/L)	0.02–0.06	96.42	0.07 (0.06–0.10)	0.08 (0.06–0.10)	0.07 (0.06–0.10)
Urine As at 2nd trimester (μg/L)	0.09–0.17	100.00	12.30 (7.53–18.83)	12.80 (7.59–19.65)	11.90 (7.35–18.15)
Urine As at 3rd trimester (μg/L)	0.09–0.17	100.00	13.50 (8.77–20.80)	14.00 (9.05–21.28)	13.30 (8.19–19.70)
Cd biomarkers					
Blood Cd at 2nd trimester (μg/L)	0.003–0.01	99.62	0.02 (0.17–0.03)	0.03 (0.02–0.03)	0.02 (0.02–0.03)
Blood Cd at 3rd trimester (μg/L)	0.003–0.01	99.16	0.02 (0.02–0.03)	0.02 (0.02–0.03)	0.02 (0.02–0.03)
Urine Cd at 2nd trimester (μg/L)	0.04–0.07	96.95	0.19 (0.11–0.32)	0.20 (0.11–0.32)	0.17 (0.10–0.27)
Urine Cd at 3rd trimester (μg/L)	0.04–0.07	94.77	0.17 (0.12–0.27)	0.17 (0.12–0.27)	0.17 (0.11–0.27)

test that assesses time perception where they had to hold the far-left lever down for 10–14 s (Fig. 2). Once the child released the response lever, whether the response was correct or incorrect, they could promptly initiate the subsequent trial. The task persisted until either 30 correct responses were achieved or 10 min had passed. The duration of the lever hold is divided into timing holds (holds greater than or equal to 2 s in duration) and bursts (holds <2 s in duration). The variables for this task included percent of tasks completed; average holds; average latency; standard deviation of the average latency; average timing holds; timing holds; standard deviation of the total hold time; total holds; total holds excluding holds <2 s; standard deviation of the total holds excluding holds <2 s; and total holds of timing accuracy. Table 2 presents the description of each TRD behavioral task the current study used as primary outcomes.

2.5. Statistical analysis

All statistical analyses were conducted using RStudio 4.0.3 software using the lm function. The interquartile range (IQR) method was used to identify outliers in the TRD variables, with limits of 1.5 IQR from the first and third quartiles. Data points falling outside these limits were subsequently removed. The overall average of observations excluded across all TRD tasks was approximately 7.18 %. Descriptive statistics (means, standard deviations (SDs), frequencies, and percentages) were calculated for all variables (see Table 3).

We used a covariate-adjusted WQS regression to estimate and examine the combined effect of metal biomarkers on TRD measures, taking into account their multiplex correlational structure and times of measurement. Our WQS models included interaction terms to estimate modification by child BMI to assess BMI phenotype effects. All metals measured in blood and urine were included in the mixture. For more information, please see previous descriptions of the WQS regression method (Levin-Schwartz et al., 2019; Carrico et al., 2015). The WQS regression is a multivariate regression empirically estimating a set of weights, ω_i with the following regression equation: $\mathrm{E}[y] = \beta_0 + \beta_1\left(\sum_{i=1}^{c}\omega_i q_i\right) + z^T\phi$, 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: a weighted index representing the association between each specific metal biomarker, and the outcome is estimated across 1000 bootstrap datasets, and (2) this weighted index was then tested in a linear regression model estimating the association between the mixture and the TRD outcome. To ensure accurate exposure assessment and maintain resolution, the WQS models were ranked into quintiles while still incorporating all values below the LOD. The estimated weights for each component of the metal mixture contributing to the integrated effect on TRD performances among children pertain to the main effect. Given that we are assessing metal exposures, whose adverse directionality might imply both positive or negative constraints in the model, we decided to fit two WQS models for each of the outcomes – one constrained in a positive direction and the other in a negative one. Finally, we chose the model with a lower Akaike information criterion (AIC) value for each outcome. Given the same number of parameters in each model, a lower AIC implies a higher likelihood of the underlying model. Consequently, all the WQS models constrained to the positive direction had lower AIC values than those constrained negatively.

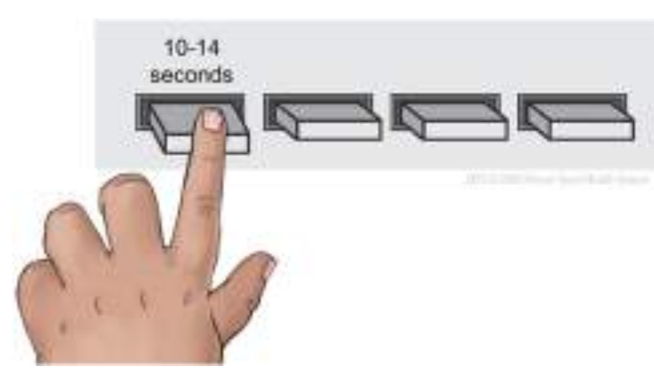

Fig. 2. Diagram of child holding the hold the far-left lever down for 10–14 s during the Temporal Response Differentiation (TRD). Illustration by Jill Gregory used with permission of ©Mount Sinai Health System.

Table 2
Description of each TRD behavioral task.

TRD outcome measures	Description of tasks
Percent of task completed %	Number of nickels earned/total possible – i.e., lower percentage indicate poorer completion performance
Average holds	Average length of time between the press and release of the response lever – i.e., lower average holds indicate poorer performance
Average latency	Average length of time between the release of the lever and the next lever press – i.e., longer latency imply slower response time and poorer performance
Average latency (SD)	Variability of the length of time between the release of the lever and the next lever press – i.e., greater variability indicate poorer performance
Average timing holds	Average length of time between the press and release of the response lever (holds ≥ 2 s) – i.e., shorter timing holds indicate poorer performance
Timing holds	The number of timing holds – i.e., decrease holds indicate poorer performance
Timing hold time (SD)	Variability of the length of time between the press and release of the lever for holds – i.e., greater variability indicate poorer performance
Total holds	The number of times the child pressed and released the lever – i.e., decrease holds indicate poorer performance
Total holds (excluding holds <2 s)	The number of times the child pressed and released the lever excluding 2 s or less –i.e., decrease holds indicate poorer performance
Total holds (SD; excluding holds <2 s)	Variability of the length between the number of times the child pressed and released the lever excluding 2 s or less – i.e., greater variability indicate poorer performance
Total holds (timing accuracy)	Average length of time between the press and release of the response lever – i.e., decrease holds indicate poorer accuracy performance

2.6. Sensitivity analyses

A sensitivity analysis was implemented, and we performed regression models, including a quadratic term for each metal biomarker to investigate nonlinear associations between metals at each trimester and TRD performance. Subsequently, we utilized covariate-adjusted WQS models that included participants ($n = 8$) with a z-score below −2. For these models, we added these observations to the normal BMI group.

2.7. Covariates

Prior literature suggests several covariates are associated with neurodevelopmental outcomes in youth. Models were adjusted for child sex, child age at time of testing, maternal educational attainment (<high school, high school, and >high school), maternal age in the 2nd trimester, 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).

Table 3
Overall and BMI-stratified social-demographics characteristics, BMI Z-scores, and TRD tasks (N = 563).

Children's characteristics	Overall	Normal BMI	High BMI
	(*N* = 563)	(n = 403)	(n = 160)
	Mean ± *SD* or n (%)	Mean ± *SD* or n (%)	Mean ± SD or n (%)
Age (years)	6.74 ± 0.60	6.71 ± 0.56	6.84 ± 0.68
Sex			
Boys	283 (50.27 %)	200 (49.63 %)	83 (51.88 %)
Girls	280 (49.73 %)	203 (50.37 %)	77 (48.12 %)
Maternal education			
<High school	226 (40.14 %)	165 (40.94 %)	61 (38.13 %)
High school	204 (36.24 %)	147 (36.48 %)	57 (35.62 %)
>High school	133 (23.62 %)	91 (22.58 %)	42 (26.25 %)
Maternal SES			
Low	301 (53.46 %)	215 (53.35 %)	86 (53.75 %)
Medium	204 (36.24 %)	145 (35.98 %)	59 (36.88 %)
High	58 (10.30 %)	43 (10.67 %)	15 (9.37 %)
Child BMI			
BMI *Z*-scores	0.46 ± 1.27	−0.18 ± 0.67	2.10 ± 0.92
TRD measures			
Percent of tasks completed (%)	20.53 ± 19.41	19.97 ± 19.20	21.93 ± 19.90
Average holds	8.30 ± 4.55	8.23 ± 4.57	8.48 ± 4.53
Average latency	2.51 ± 1.64	2.49 ± 1.62	2.56 ± 1.71
Average latency (SD)	4.43 ± 4.10	4.40 ± 4.06	4.95 ± 4.07
Average timing holds	12.35 ± 5.56	12.31 ± 5.53	12.45 ± 5.66
Timing holds	33.15 ± 16.01	32.41 ± 15.78	34.99 ± 16.48
Total holds	47.51 ± 20.63	47.17 ± 20.53	48.38 ± 20.95
Total hold time (SD)	7.74 ± 5.10	7.65 ± 5.01	7.97 ± 5.25
Total holds (excluding holds <2 s)	16.23 ± 12.75	16.06 ± 12.82	16.67 ± 12.65
Total holds (SD; excluding holds <2 s)	7.97 ± 5.64	7.88 ± 5.53	8.20 ± 5.92
Total holds (timing accuracy)	11.62 ± 10.78	11.36 ± 10.61	12.28 ± 11.19

3. Results

3.1. Demographic data

Table 3 presents participants' overall and BMI-stratified socio-demographic characteristics, concentrations of metal biomarkers, and summary statistics for each TRD task. The study sample comprised 563 children aged between 6 and 9 years, including 283 boys and 280 girls, with an average age of almost 7 years. Approximately 28 % of the children were classified as having a high BMI (z-score ≥ 1.00). In this subsample, 40 % of mothers had less than a high school diploma, 36 % had a high school diploma, and 24 % had more than a high school diploma, with over half (53.5 %) being from low SES backgrounds. Table 3 also presents the mean ± SD for the average performance on each TRD task.

3.2. Effects modification of child BMI on metal mixture and TRD performance

The WQS analyses consistently identified significant interaction effects between child BMI and the metal mixture in several TRD tasks (Table 4). These tasks include percent of tasks completed, average holds, average latency, average timing holds, total holds, SD in the timing hold time, total holds excluding holds <2 s, and total hold–time accuracy.

A main effect was observed between child BMI status (β = 21.24; 95 % CI: 2.34, 40.15) and percent of tasks completed, indicating that children with a high BMI had a higher completion on the percent of tasks than children with a normal BMI. This model showed a significant BMI-based interaction with the metal mixture, indicating a 10.13 decrease in percent of tasks completed (95 % CI: −19.84, −0.42; Fig. 3a) with each quintile increase in the metal mixture for children with a high BMI compared to children with a normal BMI, suggesting an adverse effect of the metal mixture on children with a BMI. As in the 2nd trimester and Mn in 2nd and 3rd trimesters were the most prominent weights contributing 27.8 %, 17.4, and 16.7 %, respectively, to the mixture index (Fig. 3b). A main effect was observed in the average holds model between child BMI status (β = 4.90, 95 % CI: 1.34, 8.45) and average hold time, indicating that children with a high BMI had a better performance with a higher average hold time than children with a normal BMI. Furthermore, there was a significant BMI-based interaction, demonstrating that children with a high BMI had a 2.15 s lower average hold time (95 % CI: −3.88, −0.41; Fig. 3c) for each quintile increase in the metal mixture exposure compared to children with a normal BMI, suggesting that the metal mixture had an adverse effect on average hold time for children with a high BMI. Maternal Mn in the 3rd trimester and As and Cd in the 2nd trimester had the highest weights of the trace element mixture (37.4 %, 25.8 %, and 19.9 %; Fig. 3d). The average latency model showed a main effect between child BMI status (β = −1.63; 95 % CI: −2.95, −0.32) and average latency, indicating that children with a high BMI had a better performance on the average latency tasks than children with a normal BMI. The BMI-based interaction showed that children with a high BMI had a 0.78 s longer latency (95 % CI: 0.13, 1.44; Fig. 3e) for every quintile increase in the metal mixture compared to children with a normal BMI, suggesting an adverse effect of the metal mixture on the performance of children with a high BMI. As in the 2nd and 3rd trimesters had the highest weights contributing to the metal mixture index (56.7 % and 21.8 %; Fig. 3f). In the average timing holds model, child BMI status (β = 5.11; 95 % CI: 0.93, 9.29) was positively associated with average timing holds, indicating a better performance for children with a high BMI compared to the children with a normal BMI. In Fig. 3g, there was a significant BMI-based interaction between the metal mixture and average timing holds, indicating an adverse effect of the metal mixture on children with a high BMI exhibiting a 2.39 s shorter timing holds (95 % CI: −4.30, −0.48) with each

Table 4
Association between trace metal mixture and TRD tasks in 6 to 9-year-olds.

Outcome measures	Main effect (Trace metal mixture)	Main effect (BMI status)	Interaction
	B (95 % CI)	*B* (95 % CI)	*B* (95 % CI)
Percent of tasks completed	1.94 (−2.57, 6.45)	21.24 (2.34, 40.15)*	−10.13 (−19.84, −0.42)*
Average hold	0.46 (−0.53, 1.47)	4.90 (1.34, 8.45)*	−2.15 (−3.88, −0.41)*
Average latency	−0.31 (−0.66, 0.03)	−1.63 (−2.95, −0.32)*	0.78 (0.13, 1.44)*
Average latency (SD)	0.67 (0.05, 1.28)*	−0.09 (−2.71, 2.53)	0.53 (−0.69, 1.76)
Average timing holds	−0.16 (−1.18, 0.86)	5.11 (0.93, 9.29)*	−2.39 (−4.30, −0.48)*
Timing holds	1.21 (−1.77, 4.19)	15.03 (3.28, 26.78)*	−4.57 (−9.89, 0.76)
Total holds	1.09 (−2.17, 4.36)	11.52 (−2.53, 25.58)	−6.22 (−12.38, −0.05)*
Total hold time (SD)	−1.34 (−2.37, −0.31)*	−2.84 (−6.60, 0.92)	2.08 (0.34, 3.82)*
Total holds (excluding holds <2 s)	0.08 (−2.70, 2.86)	11.49 (1.28, 21.70)	−6.18 (−11.02, −1.35)*
Total holds (SD; excluding holds <2 s)	0.83 (−0.25, −1.92)	5.69 (1.65, 9.73)*	−1.77 (−3.61, 0.07)
Total holds (timing accuracy)	1.05 (−1.14, 3.25)	11.43 (1.99, 20.87)*	−5.66 (−10.08, −1.25)*

$p < .05$ = *.

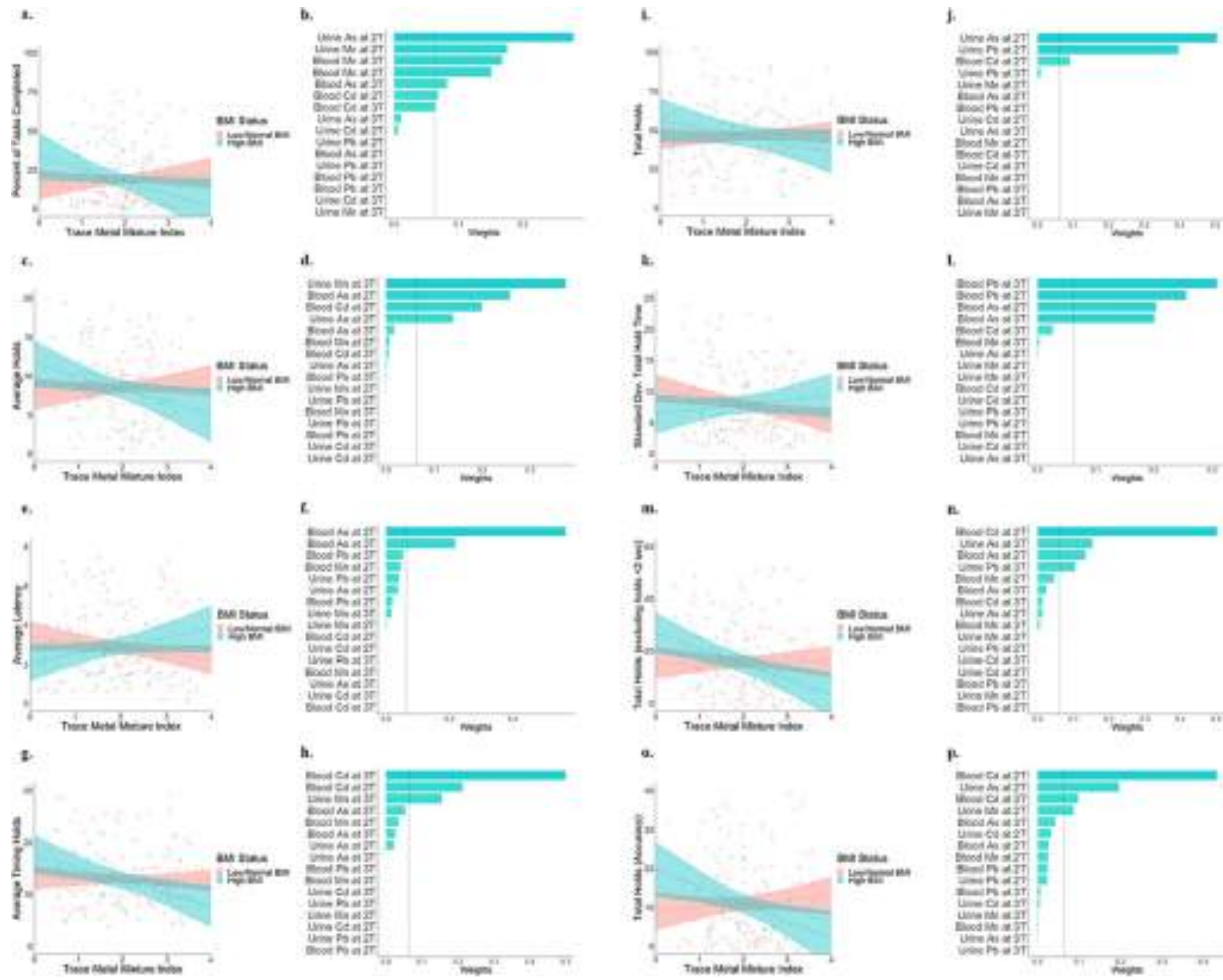

Fig. 3. Covariate-adjusted WQS models show the interaction effects of child BMI on the association between the trace metal mixture index and TRD tasks. a. Percent of tasks completed, c. average holds, e. average latency, g. average timing holds, i. total holds, k. SD in total holds time, m. total holds (excluding holds <2 s), o. total holds (accuracy). Bar plots show estimated weights for each component of the trace metal mixture contributing to the integrated effect on TRD performances (i.e., main effects) among children. Higher weights indicate a greater contribution. The dashed line (1/number of metals, assuming equal weights) indicates the cut-off value for defining the elements with significant weights in the metal mixture. Components abbreviations: The initial term denotes the matrix type (Blood or Urine), while the subsequent terms signify the specific metal (As = arsenic, Cd = cadmium, Pb = lead, and Mn = manganese) and trimester ($2T$ = 2nd trimester and $3T$ = 3rd trimester).

Note. BMI status (normal BMI status served as the reference group). Controls are child sex (males served as the reference group), maternal education (less than high school served as the reference group), SES (low SES served as the reference group) and child age at the time of testing. B = Unstandardized Regression Weight; CI = Confidence Interval. $p < .05$ = *.

quintile increase of the metal mixture than children with a normal BMI. Cd in the 2nd and 3rd trimesters and Mn in the 3rd trimester were the prominent weights in the metal mixture (50.0 %, 21.2 %, and 15.5 %; Fig. 3h).

In addition, a significant BMI-based interaction was observed between the metal mixture and child BMI status with total holds, revealing that children with a high BMI had a 6.22 s decrease in total holds (95 % CI: −12.38, −0.05; Fig. 3i) for each quintile increase of the metal mixture compared to children with children with a normal BMI, indicating an adverse effect of the metal mixture on performance of children with a high BMI. As and Pb in the 2nd trimester were the most prominent weights to the metal mixture index (50.5 % and 39.6 %; Fig. 3j). In the SD of the timing hold time, a main effect was observed between the metal mixture (β = −1.34, 95 % CI: −2.37, −0.31) and the SD of the total hold time. There was a significant BMI-based interaction between the metal mixture and the SD of the total hold time, indicating an adverse effect of the metal mixture on children with a high BMI having greater variability in their hold time (β = 2.08; 95 % CI: 0.34, 3.82; Fig. 3k), for each quintile increase in the metal mixture than children with a normal BMI. Pb in the 3rd and 2nd trimesters and As in the 2nd and 3rd trimesters were the most prominent weights in the metal mixture (30.9 %, 25.6 %, 20.4 %, and 20.1 %; Fig. 3l). A significant BMI-based interaction was observed between the metal mixture and total holds, excluding holds <2 s, with children with a high BMI having decreased holds (β = −6.18; 95 % CI: −11.02, −1.35; Fig. 3m) for each quintile increase in the metal mixture than children with a normal BMI, indicating an adverse effect of the metal mixture on children with a high BMI. Cd in the 2nd trimester, As in the 3rd and 2nd trimesters, and Pb in the 3rd trimester were the most prominent weights in the metal mixture (50.3 %, 15.4 %, 13.4 %, and 10.5 %; Fig. 3n). The total hold–timing accuracy model had a main effect on child BMI status (β = 11.43; 95 % CI: 1.99, 20.87), indicating that children with a high BMI performed better on the told hold–timing accuracy tasks than children with a normal BMI. There was an interaction effect, revealing that children with a high BMI had a 5.66 % decrease in timing accuracy (95 % CI: −10.08, −1.25; Fig. 3o) with each quintile increase in the metal mixture than children with a normal BMI, suggesting that the metal mixture had an adverse effect on children with a high BMI. Cd and As in the 2nd trimester were the prominent weights, contributing 43.2 % and 19.6 % to the metal mixture index (Fig. 3p).

3.3. Sensitivity analysis

The sensitivity analyses revealed no significant quadratic effects, and consequently, these results were not presented. The covariate-adjusted WQS regression models, inclusive of BMI z-scores below −2 within the normal BMI group, consistently mirrored the findings of the primary WQS models. Nevertheless, statistical significance was not evident, and these results were subsequently omitted.

4. Discussion

We investigated the modification effect of child BMI phenotype on the association between prenatal exposure to metal mixtures and children temporal processing. Our primary results revealed interactions between child BMI and the mixture of metals in several TRD tasks such that high BMI children tended to have shorter holds with increasing levels of metals. This would be consistent with higher levels of poor inhibitory control, although other explanations such as impaired time perception are possible. Given that poor inhibitory control is associated with higher risk of obesity, we believe these results are consistent with that explanation. Specifically, we observed that increased exposure to the metal mixture was associated with worse performance in children with a high BMI, while it was linked to improved performance in children with a normal BMI. This suggests that a child's BMI may influence the neuro-pathway between metal exposure and temporal processing. Children with a high BMI may face a greater challenge in their temporal processing abilities when exposed to higher levels of metals. In contrast, children with a normal BMI may be less burdened from increased exposure to metals, potentially leading to improved performance in tasks related to temporal processing. Secondly, our results show that the mixture of metals during prenatal exposure was linked to deficits in one TRD outcome measured at ages 6–9, suggesting that combined exposure to essential and nonessential metals may play a significant role in the development of several complex and dynamic brain regions serving time perception. Lastly, we observed a trend of associations between child BMI phenotype and TRD tasks. In finality, our results highlight the complex interplay between BMI, metal exposure, and temporal processing in children.

Trace metals are ubiquitous in the environment and enter the human body commonly through food (e.g., seafood, leafy vegetables, fruits, and grains), contaminated water, inhalation (e.g., air pollution, industrial emission, and pesticides), and dermal absorption (e.g., cosmetic products (Briffa et al., 2020; Chung et al., 2014; Tchounwou et al., 2012; Witkowska et al., 2021)). Subsequently, once in the body, they are absorbed in the gastrointestinal tract, transported to the liver, and accumulated in other living tissues (e.g., bones marrow and various organs) in small amounts (National Research Council (US) Committee on Diet and Health, 1989), with half-lives varying from a few days to several years (Li et al., 2020). Once metabolized, they are excreted through the kidney, bile, and skin via perspiration. While low doses of nutritionally essential trace metals (Mn, zinc [Zn], iron [Fe], selenium [Se], and chromium [Cr]) are critical to various biological processes, such as the metabolic system, imbalances in essential trace metals can lead to deficiencies or neurotoxicity depending on the time and combination of metal exposures. In contrast, any degree of exposure to nonessential trace metals (Pb, As, Cd, mercury [Hg], and strontium [Sr]) can contribute to neurodevelopmental problems (National Research Council (US) Committee on Diet and Health, 1989; Merced-Nieves et al., 2021). Metals have the ability to cross the placenta and penetrate the fetal blood-brain barriers (Gorini et al., 2014; Gundacker and Hengstschläger, 2012; Sanders et al., 2009). This can result in neurotoxic effects on specific neural systems (Gorini et al., 2014; Carmona et al., 2021; Pyatha et al., 2022), disrupt astrocyte function (Harada et al., 2016; Li et al., 2021), and increase oxidative stress (Pyatha et al., 2022; Chandravanshi et al., 2018).

The study findings are broadly consistent with prior research that has linked metal mixture exposure to decrements in cognitive and behavioral faculties (Merced-Nieves et al., 2022a; Bennett et al., 2022; Dórea, 2019; Kim et al., 2013). For example, prenatal studies found that co-exposures to metals that include essential and nonessential trace metals can adversely impact children's cognitive flexibility (Sun et al., 2023), verbal IQ (Bauer et al., 2020), visual processing (Rechtman et al., 2020), fine and gross motor abilities (Freire et al., 2018), and neurobehavioral profiles (Tung et al., 2022). In light of compelling evidence linking biological metals with adverse neurodevelopmental and behavioral outcomes in children, limited research explores the pathway between prenatal metal exposures and temporal processing. However, our findings support prior evidence from animal and human studies indicating that greater exposure to metals alters brain structure and function in regions such as the hippocampus (Takeda et al., 1994; Takeda, 2004), basal ganglia (Montgomery Jr, 1995), and cerebellum (Kozlova and Kozlov, 2023; Ramos et al., 2015), which support temporal processing (Merced-Nieves et al., 2022b). During the prenatal period, early brain development undergoes intricate and rapid growth and maturational progressive stages, including neurogenesis, neural migration, synaptogenesis, and myelin formation (Kolb and Gibb, 2011) that are susceptible to metal exposures, which can disrupt normal neuro-maturational systems, thus laying the groundwork for impaired neurodevelopmental pathways, subsequently leading to atypical temporal processing in childhood.

In addition, accumulating epidemiological studies have observed both an association between metal exposure and child obesity (Huang et al., 2022; Nasab et al., 2022; Shan, 2022; Vrijheid et al., 2020) and child obesity and cognitive deficits (Kösling et al., 2022; Meo et al., 2019; Ronan et al., 2020; Tee et al., 2018), respectively. However, to our knowledge, no study addresses whether a child's BMI phenotype modifies (or mediates) the neuropathway between prenatal exposure to metal mixture concentrations and temporal processing. We found that the association between higher levels of the metal mixture during prenatal development and temporal processing was more robust in children with a high BMI than children with a normal BMI, with high BMI children exhibiting temporal processing deficits. *Obesity* is a metabolic disorder that is typically identified by measuring BMI. It is defined as having values greater than the 95th percentile for children of the same sex assigned at birth and age. Our findings may be explained by the pathophysiology of obesity, as it is considered a systematic inflammatory state that is linked to programming dysregulations in several neurodevelopment outcomes (Yang et al., 2018) and deficits in structural and functional brain alterations, including changes in white matter integrity, lower cortical volumes and thickness, morphological alterations, and reduced connectivity in brain networks in regions responsible for temporal processing (Dennis et al., 2022; Laurent et al., 2020; Kaltenhauser et al., 2023).

Notably, the mixture of metals has shown a reduced burden on children with a normal BMI. This suggests that a normal BMI might act as a protective factor in the connection between exposure to metal mixtures and temporal processing. This could be attributed to the maintenance of a balanced metabolic and hormonal profile, as well as reduced inflammation associated with a normal BMI. These factors contribute to efficient energy utilization and metabolic function, potentially reducing the burden of metal exposures on neurodevelopment. The potential protective role of a normal BMI in mitigating the impact of metal exposures on neurodevelopment remains relatively unexplored in the existing literature. Therefore, a child's BMI could significantly determine how early-life exposure to metals affects neurodevelopment due to the intricate and dynamic processes involving variations in metabolism, inflammation, oxidative stress, intestinal permeability, hormonal pathways, and metal distribution. Understanding these complex relationships is crucial for a comprehensive grasp of the nuanced effects of metal exposure on a child's neurodevelopment.

4.1. Limitations and strengths

To our knowledge, this is the first study to investigate temporal processing performance in children in reference to prenatal metal mixtures. An essential strength is the use of the TRD tasks from the OTB, which allowed for the specific assessment of temporal processing. As previously mentioned, temporal processing is an important underlying cognitive timing activity and essential for interaction with the complexity of everyday life. Estimating time plays a pivotal role in a range of cognitive and behavioral functions, such as developing language and literacy (Tallal et al., 1997), attention span, cognitive skills involving responding to time-based information (Chan et al., 2022), motor coordination enabling children to time (temporal control) their physical movements accurately (Wittmann, 1999), and social interactions (Tallal et al., 1997). The TRD tasks possess a distinct quality in their ability to offer the capability to pinpoint global cognitive deficits specifically associated with temporal processing. Another strength lies in our focus on the cumulative effect of prenatal exposure to metals. We simultaneously collected blood and urine media biomarkers from a panel of metals from the same source, ensuring consistency and a more comprehensive assessment of metal exposure. The study's evaluation of child BMI phenotype as an effect modifier was also a strength. Limited research exists on this interaction effect with prenatal metal mixture exposure and temporal processing. Our study has limitations, such as not adjusting for potential critical covariates (e.g., maternal smoking) and in terms of generalizability to other populations, as it was conducted on a relatively homogeneous Mexican cohort. Our study focused on prenatal metal levels, and we were unable to directly measure metals in the fetus due to ethical reasons. Lastly, relying exclusively on BMI may not be the most effective indicator for specifying overweight and obesity in children. Studies suggest the potential benefits of integrating additional anthropometric measurements, such as waist circumference, to account for factors like muscle mass and other characteristics (Vanderwall et al., 2017; Simmonds et al., 2015).

5. Conclusions

Our findings suggest that exposure to trace metals during critical periods of brain development may have long-lasting effects on time perception and, notably, that high BMI may amplify the effect of prenatal metals on children's temporal processing. Here we expand the literature by using child BMI as an effect modifier and including an operant behavioral metric that captures global cognitive performance specifically associated with temporal processing, which has been primarily operated in animal research. Here, we build a translational bridge for toxicological research between human and non-human studies by utilizing an OTB task to assess temporal processing in children, linking TRD performance to prenatal metal exposures. Lastly, it is essential to note that various factors, including the type and dose of metals, the timing and duration of exposure, individual susceptibility, and sexual dimorphism, may influence the effects of metal exposure on cognitive and behavioral developments. Thus, further research is needed to understand better the mechanisms underlying the effects of metal exposure on brain development, the potential implications of these interactions, and to identify environmental and cognitive health strategies for reducing exposure and mitigating its effects.

CRediT authorship contribution statement

Jamil M. Lane: Writing – review & editing, Writing – original draft, Visualization, Methodology, Formal analysis, Conceptualization. **Francheska M. Merced-Nieves:** Writing – review & editing, Conceptualization. **Vishal Midya:** Methodology. **Shelley H. Liu:** Methodology. **Sandra Martinez-Medina:** Project administration, Data curation. **Rosalind J. Wright:** Investigation, Funding acquisition. **Martha M. Téllez-Rojo:** Writing – review & editing, Resources, Project administration, Investigation, Data curation. **Robert O. Wright:** Writing – review & editing, Supervision, Resources, Project administration, Investigation, Funding acquisition, Data curation, Conceptualization.

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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