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Decreased DNA repair capacity caused by exposure to metal mixtures is modulated by the *PARP1* rs1136410 variant in newborns from a polluted metropolitan area

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ABSTRACT

Background: DNA damage caused by exposure to metal mixtures and the potential modulating role of genes involved in DNA repair and the antioxidant response have not been evaluated in newborns.
Aim: The aim was to evaluate the association between prenatal exposure to metal mixtures and DNA repair capacity (DRC) in newborns from the Metropolitan Area of Mexico City (MAMC), a heavily polluted area, and the impact of variants in genes involved in DNA repair and the antioxidant response on this association.
Methods: We analyzed cord blood samples obtained at delivery from 125 healthy newborns from the MAMC. Twenty-four elements were determined by inductively coupled plasma mass spectrometry (ICP–MS), but only 12 (Cu, I, Se, Zn, As, Ba, Cs, Mn, Sb, Sr, Pb, and Ti) were quantified in most samples. DRC was assessed by the challenge-comet assay, and *OGG1*, *PARP1*, and *NFE2L2* genotyping was performed with TaqMan probes. Metal mixtures were identified and analyzed using principal component analysis (PCA) and weighted quantile sum (WQS) regression. Independent adjusted linear regression models were used to evaluate the associations.
Results: A null DRC was observed in 46% of newborns. The metals with the highest concentrations were Mn, Sr, Ti, and Pb. Essential elements showed normal levels. Only the mixture characterized by increased As, Cs, Cu, Se, and Zn levels was inversely associated with DRC. As was the principal contributor (37.8%) in the negative direction in the DRC followed by Ba and Sb, according to the WQS regression. Newborns carrying of the derived (G) allele of the *PARP1* rs1136410 variant showed decreased DRC by exposure to some potentially toxic metals (PTMs) (As, Cs, and Ba).
Conclusion: Prenatal exposure to metal mixtures negatively affected DRC in newborns, and the *PARP1* rs1136410 variant had a modulating role in this association.

1. Introduction

The Metropolitan Area of Mexico City (MAMC) is one of the most populated metropolises in Mexico (approximately 22 million inhabitants), and it is also considered one of the most polluted areas in the country, particularly in relation to air pollution (SEDEMA, 2021a). Air pollutant concentrations in the MAMC frequently exceed the annual air quality guidelines recommended by the World Health Organization (WHO, 2016). However, a recent review reported that the concentrations of lead (Pb), cobalt (Co), mercury (Hg), manganese (Mn), cadmium (Cd), and arsenic (As) in PM_{10} collected from the MAMC decreased in the past decades, probably due to the implemented regulatory policies (Morton-Bermea et al., 2021). Environmental pollution is responsible for 9 million deaths per year worldwide, and 90% of these deaths occur in low- and middle-income countries, where few efforts have focused on preventive policies (Fuller et al., 2022). Metals/metalloids are one group of environmental pollutants of most concern, as they are widely used in various types of industries. Therefore, anthropogenic activities are the main sources of environmental contamination by metals (Tchounwou et al., 2012).

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Metals are classified as essential and nonessential. Essential metals, such as copper (Cu), selenium (Se), and zinc (Zn), contribute to maintaining cell homeostasis. On the other hand, nonessential metals/metalloids, such as As, Cd, Hg, nickel (Ni), and Pb, do not have a known biological function (Jomova et al., 2022) but antagonize the effect of essential metals affecting cellular homeostasis. Some nonessential metals/metalloids, such as As, Cd, Hg, Ni, and Pb, are considered carcinogens or probable or possible carcinogens for humans (IARC, 2022). Therefore, they are considered potentially toxic metals (PTMs) since they can be toxic even at trace concentrations (Tchounwou et al., 2012).

Some environmental pollutants, including PTMs, can cross the placental barrier and thus reach the fetus (Rager et al., 2020). Prenatal exposure to PTMs, such as As, Cd, Hg, and Pb, has been related to short-term effects in newborns, including low birth weight, low birth length, small head circumference, and alterations in gestational age (Rager et al., 2020). Prenatal PTM exposure also has long-term effects on the central nervous system and can lead to endocrine disruption and cardiovascular and metabolic diseases (Garí et al., 2022; Hawkesworth et al., 2013; Liu et al., 2020). Thus, the period from preconception to early postnatal life is considered a window of susceptibility to cellular damage caused by environmental pollutants, increasing the risk of disease development in childhood and adulthood, as established by the Developmental Origins of Health and Disease (DOHaD) (Gluckman et al., 2016). For this reason, early effect biomarkers in susceptible populations, such as newborns, can provide early warning and are therefore valuable tools (Lam and Gray, 2003). One of these biomarkers is DNA repair capacity (DRC), which is used in human studies as an indicator of genomic instability, thereby increasing the risk of cancer and premature aging (Collins and Azqueta, 2012; Maynard et al., 2015; Wu et al., 2022).

One of the mechanisms of toxicity of some PTMs is DNA damage; therefore, a differential DRC plays an important role in human disease, including cancer (Wu et al., 2022). Cells possess DNA repair pathways to maintain the integrity of genetic information (Li et al., 2021), such as the base excision repair (BER) pathway, which corrects lesions resulting from oxidative damage (Krokan and Bjoras, 2013). Several proteins are involved in this pathway, including poly-(ADP-ribose)-polymerase 1 (PARP1), 8-oxoguanine glycosylase 1 (OGG1) (Krokan and Bjoras, 2013), and nuclear factor erythroid-2 (Nrf2), which is one of the main orchestrators of the antioxidant response (Rojo de la Vega et al., 2018). It has been reported that cellular repair systems are susceptible to the effects of some toxic elements, such as As, Cd, Hg, Ni, and Pb. These elements inhibit the repair systems at different levels, causing impaired DRC, which increases the level of unrepaired damage and therefore the incidence of mutations and diseases, including cancer (Koedrith and Seo, 2011).

Genes encoding these proteins have single-nucleotide variants (SNVs), including rs1052133 in *OGG1* (Ser326Cys), rs1136410 in *PARP1* (Val762Ala), and rs6721961 in NFE2-like bZIP transcription factor 2 (*NFE2L2*) (−617C > A), that affect the activity of the encoded protein or its abundance (Marzec et al., 2007; Wang et al., 2007; Wilson et al., 2011). In agreement with the function of the proteins encoded by these genes, the SNV rs1052133 has been associated with modulation of the DNA damage response, whereas the SNVs rs1136410 and rs6721961 have been associated with increased cancer risk (Figueroa et al., 2007; Kaur and Kaur, 2020; Okano et al., 2013; Zhao and Zhao, 2022).

Few studies have evaluated the effect of exposure to metal mixtures on DRC, and even fewer studies have been performed on susceptible populations, such as newborns. Therefore, the aim of the present work was to evaluate the effect of prenatal exposure to mixtures of essential and potentially toxic metals/metalloids on DRC in newborns from the MAMC. Additionally, we also evaluated the impact of SNVs in genes involved in DNA repair and the antioxidant response on the association between DRC alterations and exposure to mixtures of metals/metalloids.

2. Material and methods

2.1. Study design

The newborns included in this work were a subsample of a cross-sectional study conducted in 2016 (Montes-Castro et al., 2019). Pregnant women aged between 18 and 35 years who delivered at a hospital from the Mexican Social Security Institute (IMSS) in Mexico City were recruited (n = 181). The inclusion criteria were no history of diabetes or hypertension before or during pregnancy, a hemoglobin concentration >11.5 g/dL in the last trimester, and at least one year of residence in the MAMC (including the duration of the pregnancy). The included women had to deliver at term (>37 weeks), and women with twin pregnancies were not considered in the study. Written informed consent was obtained from the women before enrollment in the study. After delivery, all mothers completed a questionnaire on their sociodemographic characteristics and exposure to secondhand tobacco smoke at home or at work; those who answered "yes" were classified as passive smokers. In addition, clinical records were reviewed to obtain anthropometric information, hemoglobin concentration, delivery type, gestational age, and Apgar score. The subsample of this study included 125 mother-newborn pairs who had complete data (DRC, genotype, and cord blood metal concentrations). This study was approved by the Bioethics Committee of the IMSS and by the Bioethics Committee for Research in Human Subjects of CINVESTAV.

2.2. DNA extraction

Umbilical cord blood samples were collected at the time of delivery in EDTA tubes and stored at −80 °C until analyses. Umbilical cord blood was used to evaluate prenatal metal exposure, as it is a source of fetal/newborn cells (Il'yasova et al., 2015). DNA extraction was performed using a QIAamp DNA Mini Kit (Qiagen, Hilden, Germany) following the manufacturer's procedure. Prior to extraction, the samples were thawed according to the procedure of Yamagata et al. (2021) for better efficiency. The purity and concentration of DNA were determined using a spectrophotometer, and DNA integrity was assessed in agarose gels.

2.3. Genotyping SNVs

SNV genotyping was performed using the following TaqMan™ probes for allelic discrimination: rs1052133 (*OGG1*) ID C__3095552_1_, rs1136410 (*PARP1*) ID C__1515368_1_, and a probe for rs6721961 (*NFE2L2*) (Table S1) (#Catalog 4331349, Applied Biosystems, Waltham, USA) and the TaqMan™ Universal PCR Master Mix (Applied Biosystems, Waltham, USA). A final DNA concentration of 50 ng was used, and the PCR was run on a QuantStudio 7 Flex Real-Time PCR system (Applied Biosystem, Foster City, CA, USA). The conditions were as follows: one cycle of 2 min at 50 °C, one cycle of 10 min at 95 °C (activation), 40 cycles of 15 s at 95 °C (denaturation), and one cycle of 1 min at 60 °C (annealing/extension). At least 70% of the samples were evaluated in duplicate to confirm their genotypes as a quality control; the duplicate concordance rate was >99%. Hardy-Weinberg equilibrium was determined by using Arlequin version 3.0 software (Excoffier et al., 2007).

2.4. DNA repair capacity using the challenge-comet assay

Slides were prepared with two aliquots of 10 μL of cord blood containing 1×10^5 cells that were incubated with 890 μl of RPMI 1640 medium supplemented with 10% fetal bovine serum (Sigma Aldrich, Carlsbad, USA) and 1% penicillin–streptomycin (Gibco, Carlsbad, USA). Subsequently, 1 mM H_2O_2 was added to both aliquots and then incubated for 10 min at room temperature; this concentration was chosen from a H_2O_2 curve. After incubation, one aliquot was subjected to the alkaline comet assay using low and normal melting point agarose (Fisher Scientific, Suwanee, USA) (Chuang and Hu, 2004; Singh et al., 1988).

The second aliquot was incubated in RPMI 1640 medium supplemented for 60 min at 37 °C and 5% CO_2 to enable the repair process. Then, the blood was placed on a slide to perform the alkaline comet assay. DNA migration was determined in 100 randomly selected cells from each sample (50 cells per slide) and expressed as tail length (TL) using Comet Assay IV software. To calculate the DRC, the following formula was used (Xu et al., 2020): $DRC = [(TL\ 0\ min - TL\ 60\ min/TL\ 0\ min) \times 100\%]$, where DRC is the DNA repair capacity (%), TL 0 min is the TL immediately after the challenge with H_2O_2, and TL 60 min is the TL after enabling repair.

2.5. Quantification of essential and potentially toxic elements by ICP–MS

Aliquots of 1 mL of cord blood (previously tempered and homogenized at room temperature) were diluted 1:10 with 18.2 megohm deionized water, 30% H_2O_2 (Merck, Darmstadt, Germany), and 65% nitric acid (Merck, Darmstadt, Germany) for microwave digestion (Milestone, Sorisole, Italy). This pretreatment was performed in the cord blood samples, blood reference standards from the Quebec National Institute of Public Health (INSPQ), and multielement calibration standards 2, 3, 4, and 5 (PerkinElmer, Waltham, USA). Quantification was performed on an ICP–MS NexION 300D (PerkinElmer, Waltham, USA). Once the equipment was optimized following the manufacturer's recommended procedure, the calibration graph (0–100 ppb) was prepared with the multielement calibration standards, followed by the quantification of six INSPQ blood reference standards. Twenty-four elements could be quantified: Co, Cu, iodine (I), molybdenum (Mo), Se, Zn, antimony (Sb), As, barium (Ba), beryllium (Be), bismuth (Bi), Cd, cesium (Cs), Pb, Mn, Hg, platinum (Pt), silver (Ag), strontium (Sr), tellurium (Te), thallium (Tl), tin (Sn), titanium (Ti), and uranium (U) **(Table S2).** The percentages of recovery and coefficients of variation were calculated, with values of 80–120% and no more than 10%, respectively. Subsequently, quantification of the samples was performed (in duplicate), and the concentrations are reported in ppb (ng/mL). The method was validated and performed in the Metal Laboratory of the Research Laboratory and Toxicology Service (LISTO) located in the Department of Toxicology of Cinvestav, which is accredited (INV-007-013(19)) by the Mexican Accreditation Entity (ema A.C.).

The element blood concentrations were analyzed according to the guide for the analysis of data with nondetected values (EPA, 2000); samples that presented values below the limit of detection (LOD) were replaced by the LOD divided by the square root of two (Hornung and Reed, 1990).

2.6. Statistical analysis

The distribution of the data for each variable was verified. The sociodemographic and clinical characteristics of the participants are presented as the arithmetic mean and standard deviation (SD) or frequency and percentage. The concentrations of the essential and potentially toxic elements presented nonnormal distributions; therefore, they were natural log-transformed and are presented as geometric means and interquartile ranges (IQRs). Pearson's correlations between essential element concentrations and between essential and potentially toxic element concentrations in cord blood were performed with the R corrplot package (Wei and Simko, 2021). DRC data are presented as the median and IQR. The allelic (ancestral and derived) and genotypic frequencies were estimated for the three SNVs, and their influence on DRC was evaluated under codominant, dominant, and recessive models.

To identify possible mixtures or patterns of metal exposure, a principal component analysis (PCA) with orthogonal rotation was performed. Metals that presented a concentration above the LOD in at least 70% of the samples (Cu, I, Se, Zn, As, Ba, Cs, Sr, Mn, Sb, Pb, and Ti) were included in the analysis. The number of patterns was determined from a graphical evaluation and considering an eigenvalue ≥1. The characterization and naming of patterns was based on metals with a loading factor over 0.30 or under −0.30.

Weighted quantile sum (WQS) regression was used to identify the contribution of each element in the mixture, as well as the relationship between the WQS index of the mixture and the outcome variable (Carrico et al., 2015). The dataset was divided into 40% for training and 60% for validation, and 1000 bootstrap samples were used for parameter estimation. The element concentrations were converted into quartiles, and we constructed our model in negative (null or bad DRC) and positive (good DRC) directions.

The associations of metal/metalloid mixtures (identified by PCA) and SNVs with DRC were estimated using independent linear regression models adjusted for maternal age, prepregnancy BMI, vitamin intake during pregnancy, passive smoking, gestational age, newborn sex, and basal DNA damage. The final model was also adjusted by the two other exposure patterns. To evaluate the potential modifying effect of the *PARP1* rs1136410 variant, the final linear models for each metal mixture identified by PCA were stratified by *PARP1* rs1136410 alleles (ancestral *vs.* derived), and stratified WQS regression was also performed. The diagnosis of each lineal model of PCA mixtures included a graphic evaluation of residual normality, linearity, and homoscedasticity. Statistical analyses were performed with STATA version 15.1 (StataCorp LLC.) and R version 4.2.2 (R Core Team, 2021); WQS regression was performed with the *gWQS* package (Renzetti et al., 2022). Statistical significance was considered at $p < 0.05$.

3. Results

3.1. Sociodemographic and clinical characteristics of the participants

The main sociodemographic and clinical characteristics of the 125 mother-newborn pairs are presented in Table 1. The mean age of the mothers at delivery was 26.5 ± 4.6 years; most of them (76.2%) had more than a high school education. The mean hemoglobin concentration was 13.1 ± 0.87 g/dL at the last prenatal control, and 45.8% of the

Table 1
Sociodemographic and clinical characteristics of the participants.

Characteristics	Arithmetic mean ± SD or n (%)
Mothers	
Age (years)	26.5 ± 4.6
Education:	
< Middle School	31 (23.8)
≥ High School	99 (76.2)
Parity:	
1	39 (29.8)
2	51 (38.9)
≥ 3	41 (31.3)
Pre-pregnancy BMI:	
Underweight	5 (3.8)
Normal weight	60 (45.8)
Overweight and obesity	66 (50.4)
Hemoglobin (g/dl)	13.1 ± 0.87
Working during pregnancy:	
Yes	73 (55.7)
No	58 (44.3)
Passive smoking:	
Yes	26 (19.8)
No	105 (80.2)
Newborns	
Gestational age (weeks)	39 ± 1.4
Delivery:	
Natural	103 (78.6)
Cesarean	28 (21.4)
Sex:	
Girls	70 (53.4)
Boys	61 (46.6)
Size (cm)	49.5 ± 1.9
Weight (g)	3219 ± 366
Apgar score	8 ± 0.5

BMI: Body mass index; **SD:** Standard deviation.

mothers had a normal prepregnancy BMI (18.5–24.9 kg/m^2), while 50.4% had overweight or obesity (>25 kg/m^2). A total of 19.8% of the mothers reported having been exposed to secondhand tobacco smoke (passive smoking), and only three mothers reported alcohol consumption (data not shown). The newborns had a mean gestational age of 39 ± 1.4 weeks; 53.4% were girls, and 46.6% were boys. Most newborns (78.6%) were born by natural delivery with a mean birth weight of 3219 ± 366 g and a mean Apgar score of 8 ± 0.5. The newborns appeared to be healthy, with no malformations or diagnosis of intrauterine growth restriction.

3.2. Concentrations of essential and potentially toxic elements in umbilical cord blood

Twenty-four elements were quantified, of which six were essential elements and 18 were PTMs (Table S2); 12 elements (Cu, I, Se, Zn, As, Ba, Cs, Mn, Sb, Sr, Pb, and Ti) presented concentrations above the LOD in at least 72% of the samples (Table 2). The average and range concentrations of essential elements were as follows: Zn (1761 ng/mL; 1484–2224), Cu (454.39 ng/mL; 356.42–617.95), I (162.48 ng/mL; 54.63–241.48), and Se (160 ng/mL; 121.69–218.36). Regarding the potentially toxic elements, the highest concentrations observed in the participants were for Mn (30.43 ng/mL; 22.64–40.62), Sr (16.74 ng/mL; 12.42–24.14), Ti (9.17 ng/mL; 7.80–14.56), and Pb (4.08 ng/mL; 2.36–16.67). The essential elements showed normal concentrations, except for Mn, since participants presented concentrations above the reference value (4–15 ng/mL; ATSDR, 2012); therefore, Mn was classified as a PTM.

A correlation analysis between essential and potentially toxic elements was performed (Fig. S1). Significant positive correlations were observed between essential metals, such as Cu and Se ($r = 0.90$), Cu and Zn ($r = 0.80$), and Se and Zn ($r = 0.70$), and between essential metals and PTMs, such as Cu and As ($r = 0.64$), Se and As ($r = 0.75$), Cu and Cs ($r = 0.65$), Se and Cs ($r = 0.72$), Cs and Zn ($r = 0.65$), and Se and Mn ($r = 0.62$). Finally, significant positive correlations were shown between PTMs, such as As and Cs ($r = 0.59$), As and Sb ($r = 0.36$), and Cs and Sb ($r = 0.30$). In addition, negative correlations were observed between essential elements and PTMs, such as Ba and I ($r = -0.24$), Ba and Mn ($r = -0.34$), Ba and Se ($r = -0.25$), Sr and Cu ($r = -0.23$), Sr and I ($r = -0.20$), and Sr and Se ($r = -0.26$).

Table 2
Essential and potentially toxic elements with concentration above the limit of detection in umbilical cord blood.

Elements[a]	% Samples > LOD	Geometric mean ng/mL	IQR (P25 – P75) ng/mL
Essential			
Copper (Cu)	100	454.39	356.42–617.95
Iodine (I)	100	162.48	54.63–241.48
Selenium (Se)	100	160.58	121.69–218.36
Zinc (Zn)	100	1761	1484–2224
Potentially toxic			
Antimony (Sb)	100	2.11	1.69–2.57
Arsenic (As)	72	1.83	0.03–15.51
Barium (Ba)	86.4	2.37	1.76–9.61
Cesium (Cs)	100	2.13	1.77–2.62
Lead (Pb)	84.8	4.08	2.36–16.67
Manganese (Mn)	100	30.43	22.64–40.62
Strontium (Sr)	98.4	16.74	12.42–24.14
Titanium (Ti)	97.6	9.17	7.80–14.56

LOD: Limit of detection; **IQR**: Interquartile range.
[a] Elements with at least 70% of samples above the LOD are shown.

3.3. Association between DNA repair capacity and prenatal exposure to mixtures of essential and potentially toxic elements

Regarding DRC, negative values (damage not repaired) and positive values (damage repaired) were observed in the newborns, with a median (IQR) of 1.2% (−7.1, 10.0) (Fig. S2); 46% of the participants showed null DRC (values lower than 0).

Three different mixtures of metals were identified by PCA (**Table S3**). The first mixture, called "As, Cs, and essential elements", was characterized by increasing concentrations of As, Cs, Cu, Se, and Zn. The second mixture, called "mixed elements", was characterized by increasing concentrations of Zn, Ba, and Ti and a decreasing concentration of I. Finally, the third mixture, called "potentially toxic metals", was characterized by increasing concentrations of Sr, Mn, Pb, and Ti. For mixture 1 (As, Cs, and essential elements), the concentration of As ranged from 0.03 ng/mL to 15.51 ng/mL based on the IQR, representing an approximately 517-fold increase. Whereas, the concentrations of Cs and the other essential elements (Cu, Se, and Zn) only increased by approximately 1.4- to 1.8-fold (**Table 2**).

Only mixture 1 (As, Cs, and essential elements) was significantly associated with the average DRC [−1.35 (−2.72; 0.03); $p = 0.05$] after adjusting for confounders and other identified mixtures (Table 3). No significant associations were observed for the other two mixtures. Similar results were observed in the WQS regression model. An increase in the WQS index of the mixture was associated with a significant reduction in DRC [−7.23 (95%CI-14.05; −0.39), $p = 0.04$] after adjusting for confounders (Table 3; Fig. 1). As was the principal contributor (37.8%) and Ba (15.5%), Mn (13.9%), and Sb (9.6%) contributed to a lesser extent (Fig. 1). According to PCA, Ba, Mn, and Sb were included in other patterns.

3.4. Association between the OGG1 rs1052133, PARP1 rs1136410, and NFE2L2 rs6721961 variants and DNA repair capacity

The genotypic and allelic frequencies of the participants are presented in Table 4. For the *OGG1* rs1052133 variant, 37.7% of the participants were wild-type homozygous (CC), 46.1% were heterozygous (CG), and 16.1% were mutant homozygous (GG), with a frequency of the derived allele (G) of 39.2%. For the *PARP1* rs1136410 variant, 30.8% of the participants were wild-type homozygous (AA), 45.4% were heterozygous (AG), and 23.8% were mutant homozygous (GG), with a frequency of the derived allele (G) of 46.5%. For the *NFE2L2* rs6721961 variant, 63.1% of the participants were wild-type homozygous (CC), 32.3% were heterozygous (CA), and 4.6% were mutant homozygous (AA), with a frequency of the derived allele (A) of 20.8%. The three SNVs were in Hardy-Weinberg equilibrium ($p > 0.05$).

The association analyses revealed that none of the three SNVs was significantly associated with DRC (Table 5, Tables S4 and S5). However, for the *PARP1* rs1136410 variant (Table 5), we observed marginal reductions in DRC in the recessive ($p = 0.10$) and allelic models ($p = 0.13$); therefore, this variant was considered for further analyses.

3.5. The PARP1 rs1136410 variant modulates the effect of prenatal exposure to a mixture of essential and potentially toxic elements on DNA repair capacity

Stratified analysis by *PARP1* rs1136410 alleles was performed to evaluate the modulating role of this variant on DRC (Table 6). The inverse association between mixture 1 (containing As, Cs, and essential elements) and DRC was significant among newborns carrying of the derived allele (G) [−2.41 (−3.91; −0.92) *vs.* −0.36 (−1.63; 0.90)]. The WQS regression model showed a significant effect only in the negative direction [−14.63 (95%CI -22.45; −6.81), $p < 0.01$], with Cs (25.2%), Ba (21.1%), and As (17.2%) as the principal contributors (Fig. 2); As and Cs belonged to mixture 1, while Ba was part of mixture 2. This suggests a modulating role of the *PARP1* rs1136410 variant. No significant

Table 3
DNA repair capacity according to prenatal exposure to mixtures of essential and potentially toxic elements.

Mixtures	Model 1 β (95% CI)	*p* value	Model 2 β (95% CI)	*p* value	Model 3 β (95% CI)	*p* value	Model 4 β (95% CI)	*p* value
PCA[a]								
As, Cs, and essential elements	−1.02 (−2.34; 0.31)	0.13	**−1.75 (-3.06; -0.43)**	**0.01**	**−1.64 (-2.96; -0.33)**	**0.01**	**−1.35 (-2.72; 0.03)**	**0.05**
Mixed	**2.49 (0.29; 4.70)**	**0.03**	2.10 (−0.1; 4.26)	0.06	2.06 (−0.1; 4.19)	0.06	1.29 (−0.92; 3.50)	0.25
Potentially toxic	0.21 (−2.28; 2.70)	0.87	1.26 (−1.22; 3.74)	0.32	1.98 (−0.49; 4.44)	0.11	1.81 (−0.60; 4.22)	0.14
WQS regression								
Positive direction	0.08 (−8.41; 8.49)	0.98	2.81 (−4.81; 10.43)	0.47	0.96 (−7.81; 9.13)	0.83		
Negative direction	**−6.55 (-13.13; 0.03)**	**0.05**	**−7.53 (-13.51; -1.55)**	**0.02**	**−7.23 (-14.05; -0.39)**	**0.04**		

Mixtures characterization: **As, Cs, and essential elements:** As, Cs, Cu, Se, and Zn. **Mixed:** I, Zn, Ba, and Ti. **Potentially toxic:** Sr, Mn, Pb, and Ti.
Model 1: unadjusted. **Model 2:** adjusted for basal tail length parameter.
Model 3: adjusted for model 2 and mother's age, vitamin intake during pregnancy, passive smoking, prepregnancy BMI, gestational age, and newborn's sex. **Model 4:** adjusted for model 3 and prenatal exposure to mixtures of essential and potentially toxic elements.
CI: confidence interval; **PCA**: principal component analysis; **WQS:** weighted quantile sum.
[a] The associations were estimated using independent linear.

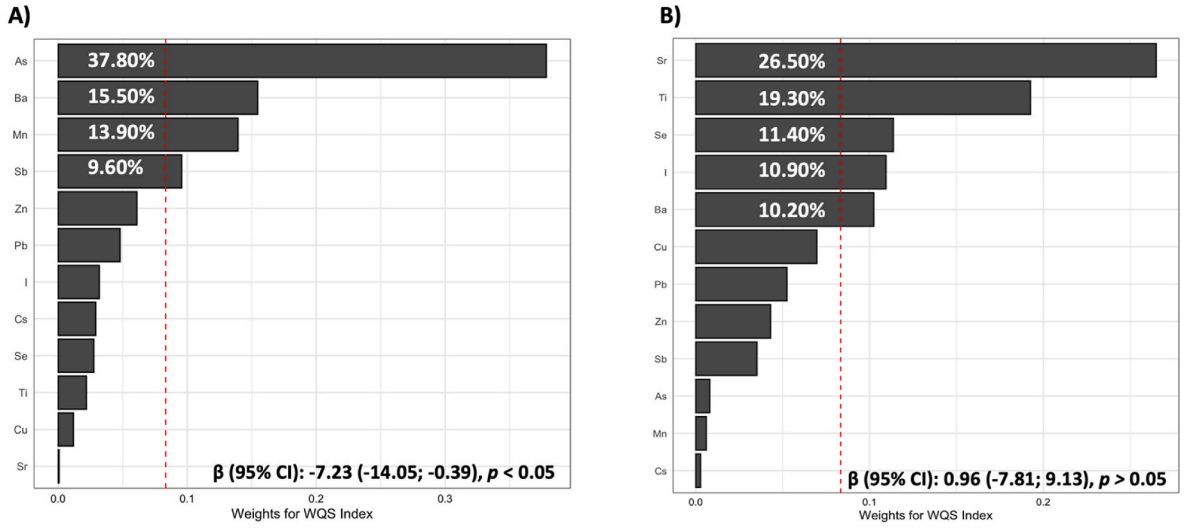

Fig. 1. WQS regression model weights of each element contributing to the overall effect on DNA repair capacity. A) negative and **B)** positive direction. The WQS regression coefficients are at the bottom of figures; both models were adjusted by basal tail length, mother's age, vitamin intake during pregnancy, passive smoking, prepregnancy body mass index, gestational age, and newborn's sex. The bars correspond to the weight of each element contributing to the effect on DRC (percentage). The dashed red line represents the cutoff τ to discriminate which element has a significant weight greater than zero. **CI:** confidence interval; **WQS:** weighted quantile sum.

Table 4
Genotypic and allelic frequencies of the variants studied in the participants.

SNVs[a]	Genotype/Allele	(n, %)
***OGG1;* rs1052133**	CC	49 (37.7)
	CG	60 (46.1)
	GG	21 (16.1)
	C (ancestral)	158 (60.8)
	G (derived)	102 (39.2)
***PARP1;* rs1136410**	AA	40 (30.8)
	AG	59 (45.4)
	GG	31 (23.8)
	A (ancestral)	139 (53.5)
	G (derived)	121 (46.5)
***NFE2L2*; rs6721961**	CC	82 (63.1)
	CA	42 (32.3)
	AA	6 (4.6)
	C (ancestral)	206 (79.2)
	A (derived)	54 (20.8)

[a] They are in Hardy-Weinberg equilibrium according to the Chi-square test; $p > 0.05$.

differences were observed concerning newborns carrying the ancestral allele (A).

4. Discussion

In this study, we evaluated prenatal exposure to mixtures of essential and potentially toxic metals/metalloids and their effect on DRC in newborns from the MAMC. By PCA, we identified three patterns of exposure to metals/metalloids, and individually or combined prenatal exposure to As was inversely associated with DRC. Interestingly, newborns carrying the derived allele (G) of the *PARP1* rs1136410 variant were more susceptible to the effects of exposure to a mixture of metals, particularly As, Cs, and Ba.

We were interested in evaluating metals/metalloids as mixtures, as they represent actual exposures. Our group recently reported a systematic review of the adverse effects of prenatal exposure to PTMs on offspring (Paz-Sabillón et al., 2022). We found that most of the studies focused on individual elements, and few evaluated element mixtures, which represents a more real exposure. There are several statistical approaches in the literature to evaluate the toxicity of mixtures of contaminants; among them are PCA and WQS methods, which were used in the present study. Both methods have advantages; PCA reduces

Table 5
Association between *PARP1* rs1136410 variant and the DNA repair capacity.

PARP1; rs1136410	n	Model 1	*p* value	Model 2	*p* value	Model 3	*p* value
		β (95% CI)		β (95% CI)		β (95% CI)	
Codominant							
AA	40	–		–		–	
AG	59	0.61 (−5.92; 7.15)	0.85	0.09 (−6.22; 6–39)	0.98	−0.72 (−6.95; 5.51)	0.82
GG	31	−2.82 (−10.45; 4.81)	0.47	−4.95 (−12.42; 2.52)	0.19	−5.55 (−12.81; 1.71)	0.13
p trend			0.50		0.22		0.15
Dominant							
AA	40	–		–		–	
AG + GG	90	−0.57 (−6.63; 5.49)	0.85	−1.58 (−7.49; 4.32)	0.60	−2.41 (−8.19; 3.37)	0.41
Recessive							
AA + AG	99	–		–		–	
GG	31	−3.19 (−9.73; 3.35)	0.34	−5.00 (−11.40; 1.39	0.12	−5.13 (−11.39; 1.13)	0.10
Alleles							
A (ancestral)	139	–		–		–	
G (derived)	121	−1.41 (−5.33; 2.52)	0.48	−2.48 (−6.30; 1.34)	0.20	−2.86 (−6.54; 0.82)	0.13

The associations were estimated using an independent linear regression model.
Model 1: unadjusted. **Model 2:** adjusted for basal tail length parameter.
Model 3: adjusted for model 2 and mother's age, vitamin intake during pregnancy, passive smoking, prepregnancy BMI, gestational age, and newborn's sex.
CI: confidence interval.

Table 6
DNA repair capacity according to the prenatal exposure to mixtures of essential and potentially toxic elements stratified by *PARP1* rs1136410 alleles.

Mixtures	Model 1				Model 2			
	Allele A (n = 135)		Allele G (n = 113)		Allele A (n = 135)		Allele G (n = 113)	
	β (95% CI)	*p* value	β (95% CI)	*p* value	β (95% CI)	*p* value	β (95% CI)	*p* value
PCA[a]								
As, Cs, and essential elements	−0.82 (−2.04; 0.39)	0.18	**−2.52 (-3.94; -1.10)**	**< 0.01**	−0.36 (−1.63; 0.90)	0.57	**−2.41 (-3.91; -0.92)**	**< 0.01**
Mixed	**2.24 (0.42; 4.06)**	**0.02**	1.68 (−0.80; 4.16)	0.18	1.89 (−0.04; 3.83)	0.06	0.46 (−2.02; 2.95)	0.71
Potentially toxic	**2.21 (0.08; 4.34)**	**0.04**	1.47 (−1.30; 4.24)	0.30	1.99 (−0.12; 4.10)	0.06	1.30 (−1.34; 3.94)	0.33
WQS regression								
Positive direction	0.91 (−5.12; 6.94)	0.77	−9.64 (−20.16; 0.88)	0.08				
Negative direction	−3.57 (−8.18; 1.04)	0.13	**−14.63 (-22.45; -6.81)**	**< 0.01**				

Mixtures characterization: **As, Cs, and essential elements:** As, Cs, Cu, Se, and Zn. **Mixed:** I, Zn, Ba, and Ti. **Potentially toxic:** Sr, Mn, Pb, and Ti.
Model 1: adjusted for basal tail length parameter, mother's age, vitamin intake during pregnancy, passive smoking, prepregnancy BMI, gestational age, and newborn's sex.
Model 2: adjusted for model 1 and prenatal exposure to mixtures of essential and potentially toxic elements.
CI: confidence interval; **PCA**: principal component analysis; **WQS:** weighted quantile sum.
[a] The associations were estimated using an independent linear regression model.

the number of variables with a minimum loss of information, where a single variable can explain a large part of the results and can identify the common way of exposure. WQS regression has the advantage of incorporating several contaminants into a single index, thus avoiding any problem of overfitting and collinearity and estimating the contribution of each element in negative or positive directions (Yu et al., 2022).

DRC is defined as the ability of a cell to repair DNA damage (Nagel et al., 2014), and is used as a biomarker of genomic instability and premature aging (Collins and Azqueta, 2012; Maynard et al., 2015). Efficient DNA repair is essential to maintain genome stability to prevent different types of cancer (Jalal et al., 2011). Different assays are used to determine DRC, including the challenge-comet assay, which induces damage with an oxidative agent that is repaired by the BER pathway (Collins and Azqueta, 2012).

The adverse effect on DRC observed in newborns exposed mainly to As may be attributed to the wide range of As concentrations (517-fold) compared to those of the essential elements (1.4- to 1.8-fold) present in the pattern. We hypothesized that the adverse effect caused by As was not antagonized by the essential elements in these newborns; this result was confirmed by WQS regression. In accordance with our results, the International Agency for Research on Cancer (IARC) classifies As and its compounds within Groups 1, 2A, and 3 (IARC, 2012). Alteration of the BER repair pathway is one of the proposed mechanisms of As carcinogenesis, as several proteins involved in this pathway, including PARP1, are targeted by this metalloid. As inhibits PARP1 by interacting with the zinc finger domains of the protein, resulting in the inability to bind DNA (Kutuzov et al., 2021; Muenyi et al., 2015) and consequently affecting DRC.

To our knowledge, this is the first study reporting the effect of metal mixture exposure, particularly the high negative contribution of As exposure on DRC in susceptible populations, such as newborns. Few studies have studied DRC in children. Méndez-Gómez et al. (2008) showed that DRC was negatively associated with As urine concentrations in schoolchildren from an area with a Pb refinery and natural As contamination in drinking water. Decreased DRC was also reported in children living in a mining area with high levels of As and Pb (Jasso-Pineda et al., 2012). In addition, *in vitro* exposure to heavy metals (As, Cd, and Ni) significantly altered the choice of DNA repair pathway for double-strand breaks, contributing to genetic damage (Morales et al., 2016).

We evaluated the role of SNVs in the *PARP1*, *OGG1*, and *NFE2L2* genes in newborns exposed to metal/metalloid mixtures, as these SNVs are involved in the BER pathway or in the cellular response to oxidative stress, and only a marginal difference between the *PARP1* rs1136410 variant and DRC was observed. Carriers of the derived allele (G) who were exposed to As in pattern 1 were more susceptible to having a decreased DRC. The modulating effect of *PARP1* on DRC in newborns exposed to As was confirmed by WQS regression, and this effect was also

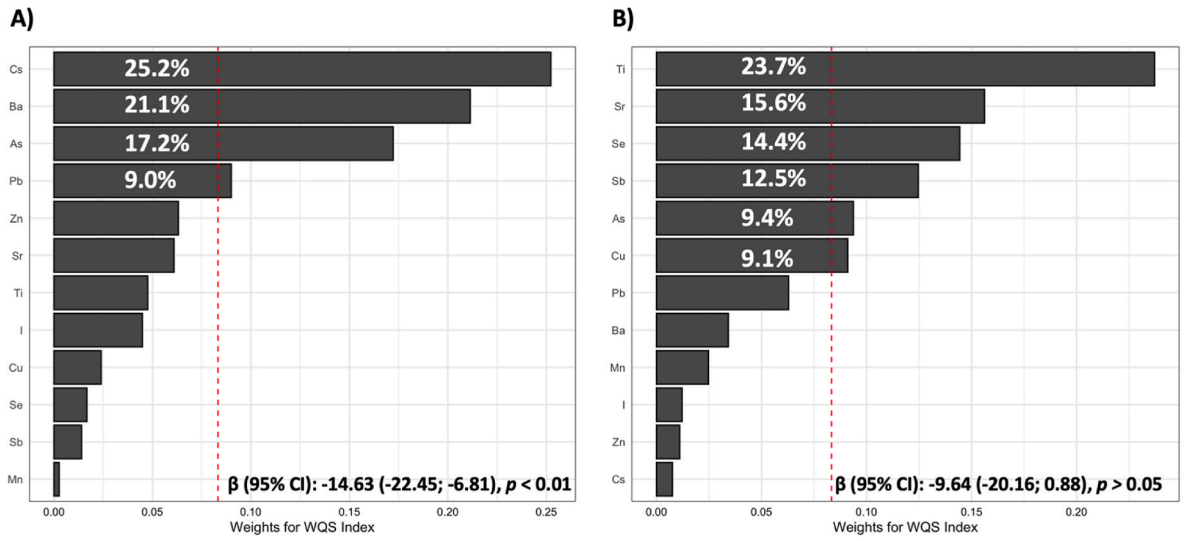

Fig. 2. WQS regression model weights of each element contributing to the overall effect on DNA repair capacity stratified by *PARP1* rs1136410 **(G) allele. A)** negative and **B)** positive direction. The WQS regression coefficients are at the bottom of figures; both models were adjusted by basal tail length, mother's age, vitamin intake during pregnancy, passive smoking, prepregnancy body mass index, gestational age, and newborn's sex. The bars correspond to the weight of each element contributing to the effect on DRC (percentage). The dashed red line represents the cutoff τ to discriminate which element has a significant weight greater than zero. **CI:** confidence interval; **WQS:** weighted quantile sum.

observed in newborns exposed to Ba and Cs. This suggests a modulating effect of the *PARP1* rs1136410 variant on DRC, highlighting that the interaction between environmental factors and genetics contributes to the development of disease or adverse effects (Virolainen et al., 2022). The *PARP1* gene encodes a protein with the same name that is involved in the DNA repair process (Chaudhuri and Nussenzweig, 2017). The nonsynonymous SNV rs1136410, located in exon 17 of *PARP1*, results in the substitution of an alanine for a valine in the catalytic domain of the protein (Val762Ala), which causes a lower affinity of PARP1 for its substrate NAD+ (Wang et al., 2007). This SNV has been reported to cause a 40% decrease in protein enzymatic activity (Wang et al., 2007). Additionally, it has been associated with a predisposition to several types of cancer, including gallbladder (Anjali et al., 2022), cervical (Roszak et al., 2013), esophageal (Zhou et al., 2021), breast (Alanazi et al., 2013), and bladder (Figueroa et al., 2007) cancer.

The average As concentration in the cord blood of newborns from the MAMC was 1.83 ng/mL, which is similar to those reported in the cord blood of newborns from Argentina (2.3 ng/mL; Herlin et al., 2019), China (1.71 ng/mL; Wang et al., 2022a), Croatia (1.95 ng/mL; Trdin et al., 2020), and Spain (1.36 ng/mL; Cabrera-Rodríguez et al., 2018). There is no established reference value for As in the cord blood of newborns; there is only an established reference value for adult populations, which is 1 ng/mL in unexposed individuals (ATSDR, 2007). This is of concern since the newborns in the present study had concentrations exceeding this value and were a susceptible population. The reported high concentrations in the newborns are in agreement with those previously reported in their mothers (Montes-Castro et al., 2019), since they presented a mean urine concentration of As of 22.94 μg/g of creatinine, which is above the reference value (8.3 μg/g of creatinine; Hays et al., 2010). In addition, positive correlations were observed between As and Pb concentrations in cord blood and maternal urine samples (Fig. S3). This suggests that maternal exposure also leads to exposure in newborns.

Regarding Cs, only one study reported a concentration of 153 ng/mL in the umbilical cord blood of newborns from Argentina (Herlin et al., 2019), a value above that of 2.13 ng/mL observed in our study. A reference value of Cs is not available. It is important to mention that some studies have focused on analyzing radioactive Cs. There are no available studies reporting Ba concentrations in cord blood, and only a few have reported Ba concentrations in blood from adults. A population from China presented a mean Ba concentration of 50.65 ng/mL (Lv et al., 2021), while a clinical case reported a mean concentration of 7.15 ng/mL (Łukasik-Głębocka et al., 2014) from a control sample (unexposed). The concentrations of Ba in the present study were below those in the abovementioned studies; there is no proposed reference value for Ba in blood.

With respect to essential elements, the newborns in the present study presented a mean Cu concentration of 454.39 ng/mL, which is similar to that reported in newborns from the USA (426.0 ng/mL; Wells et al., 2011). However, it is below those reported in newborns from Belgium (564.0 ng/mL; Vriens et al., 2017) and Spain (655.08 ng/mL; Dahiri et al., 2023). The reference range of concentrations for Cu in cord blood proposed by McKeating et al. (2019) is 292.2–559.1 ng/mL; our participants' concentrations fell within this range. The mean concentration of Se in newborns was 160.58 ng/mL, which is lower than that reported in newborns from the USA (216.2 ng/mL; Cottrell et al., 2018). However, it is higher than those reported in newborns from China (129.04 and 121.22 ng/mL; Sun et al., 2014; Wang et al., 2022b) and Spain (117.66 ng/mL; Dahiri et al., 2023). The concentration of Se in our participants was adequate, as it exceeded 100 ng/mL, which is indicative of adequate Se intake (Hays et al., 2014). Finally, with respect to Zn concentrations, our participants presented an average concentration of 1761 ng/mL, which is below those observed in newborns from the USA (2181 ng/mL; (Cottrell et al., 2018), Japan (2002 ng/mL; Iwai-Shimada et al., 2019), and Spain (2220 ng/mL; Dahiri et al., 2023). However, it is above that reported in participants from Poland (1370 ng/mL; Kot et al., 2021) and similar to that reported in newborns from Argentina (1800 ng/mL; Herlin et al., 2019). McKeating et al. (2019) proposed a reference range for Zn in cord blood of 1033–1438 ng/mL; the concentrations observed in our participants were above this value. With this evidence, we can suggest that the newborns included in the present study presented normal concentrations of the evaluated essential elements except Mn.

As seems to be the toxic element contributing to the adverse effect on DRC in newborns in the present study. A potential source of As exposure in mothers from the MAMC may be through the diet, particularly rice. This metalloid is frequently observed in rice since fields are irrigated with water contaminated with As (Hojsak et al., 2015), and it has been quantified in Asian countries, such as China (Liu et al., 2023), India (Joardar et al., 2023), Nepal (Shao et al., 2023), and Vietnam (Le et al.,

2023). In 2017, Mexico imported 78.4% of its rice for human consumption from countries such as Thailand, Vietnam, and India (SAGARPA, 2017). However, further studies are needed to confirm the As concentrations in the rice consumed in the MAMC. Another dietary source of As could be seafood; however, this idea was rejected because fish consumption is very low in noncoastal areas from Mexico, such as the MAMC (PROFECO, 2019). Finally, we cannot rule out the source of As exposure from air pollution caused by industries located in the area and from more than 6 million vehicles circulating in the MAMC. Some PTMs, such as As, aluminum (Al), Mn, Ni, Sb, and Pb, are emitted into the atmosphere mostly by point sources of pollution and, to a minor degree, by natural and mobile sources (SEDEMA, 2021b).

One of the limitations of the present study is that As speciation in the blood was not performed to determine the As species, which are known to have different toxicity (ATSDR, 2007). Other limitations were that the original study design did not permit the establishment of a critical window of exposure and did not include a questionnaire focused on diet to evaluate its contribution.

In summary, our results suggest that the newborns from the MAMC included in the present study are susceptible to developing diseases in childhood or adulthood, as established by the DOHaD hypothesis. To our knowledge, this is the first study evaluating the association between prenatal exposure to essential and potentially toxic metal/metalloid mixtures and DRC in newborns, in addition to the modulating role of the *PARP1* rs1136410 variant on this association.

5. Conclusion

Prenatal exposure to a mixture of elements containing As, negatively impacted DRC in newborns, and the *PARP1* rs1136410 variant showed a modulating role in the association between exposure to PTMs and DRC. These findings need to be confirmed in populations with different exposure and genetic backgrounds. Additionally, longitudinal studies are required to prove the existence of critical exposure windows during pregnancy. Finally, the lack of reference values for PTMs in newborns is of concern, considering that they are more susceptible and vulnerable; therefore, more studies are needed to establish public health policies focused on prevention.

Credit author statement

Marvin Paz-Sabillón: data generation, statistical analyses, Visualization, Investigation, Writing – original draft. Nereida Montes-Castro: data generation, Investigation, Writing – review & editing. Emilio J. Córdova: technical supervision writing - review & editing. Luz M. Del Razo: Writing – review & editing. Luisa Torres-Sánchez: Conceptualization of statistical analysis, Writing – review & editing. Betzabet Quintanilla-Vega: supervision, Conceptualization, Writing – review & editing, Funding acquisition.

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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

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