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Metal Exposure in Chinese Pregnant Women from Dalian and Association with Clinical Indicators

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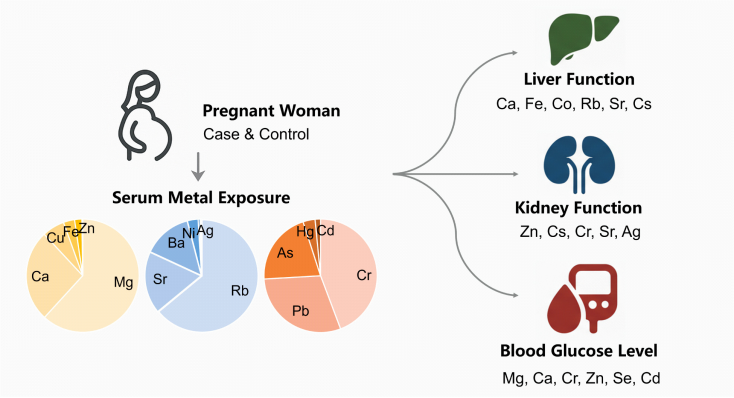
Highlights

- Mg and Ca account for 88.28% of the total content of eight essential metals
- Elevated prenatal exposure to Hg and Ag linked to elevated health risks
- Ca, Fe, Co, Rb, Sr, and Cs were associated with liver function parameters
- Mg, Ca, Cr, Zn, Se, and Cd were associated with blood glucose regulation
- Cr, Zn, Sr, and Ag concentrations were related to uric acid levels

Abstract: Maternal serum metal levels can significantly affect pregnancy outcomes and fetal health. This study investigated the associations between serum heavy metal concentrations and hematological parameters in 209 pregnant women in Dalian. Mg and Ca were the predominant metals, with concentrations of 18,493 μg/L and 8060 μg/L, respectively, comprising 88.28% of the total concentration of eight essential metals. Notably, toxic metals such as Cr and Pb show levels comparable to possibly essential trace metals like Co and Mn, highlighting the necessity of enhanced surveillance to mitigate health hazards. Analysis of serum metal concentrations and composition profiles in serum of pregnant woman between case and control groups using multiple linear regression, revealed that elevated prenatal exposure to Hg and Ag was associated with significantly increased health risks. Levels of Ca, Fe, Co, Rb, Sr, and Cs correlated with liver function markers, while Zn and Cs correlated with kidney function indicators. Cr, Zn, Sr, and Ag concentrations were associated with uric acid levels. After adjusting for multiple metals and potential confounders, statistical associations were found between specific metals (e.g., Mg, Ca, Cr, Zn, Se, Cd) and blood glucose levels, indicating a potential link to glucose metabolism. These findings may inform targeted interventions for gestational diabetes and liver function management in pregnant women. Further research is required to elucidate these relationships and their implications for pregnancy outcomes.



1. Introduction

Heavy metals pose significant threats to human health due to their pervasive environmental contamination and recognized toxicity. Over 25% of the global disease burden is linked to environmental exposure to toxic metals [1]. Critically, As, Cd, Cr, Hg, and Pb are classified as Group I carcinogens by the International Agency for Research on Cancer (IARC) [2]. Concurrently, Hg and Pb are identified as environmental endocrine-disrupting chemicals (EDCs) [3]. These EDCs interfere with normal endocrine function upon entering the human body by mimicking hormones or disrupting the activity of endogenous hormones, which may contributing to thyroid disorders, infertility, diabetes, obesity, and various homeostatic imbalances [4]. Emerging epidemiological evidence highlights the disproportionate vulnerability of certain populations—such as pregnant women, children, and the elderly—to the harmful effects of environmental pollutants [5]. Critically, studies such as the US National Health and Nutrition Examination Survey (NHANES) have demonstrated the transplacental transfer of metals between pregnant women and their developing fetuses [6]. The risk is compounded by the potential for localized high-concentration pollution in specific regions, driven by extensive production and application of certain metal compounds. Consequently, quantifying exposure levels to these metals within susceptible populations in specific areas, particularly pregnant women, is crucial for accurate health risk assessment.

During sensitive prenatal periods, changes in maternal blood metal concentrations and the ensuing oxidative imbalances have been shown to contribute to adverse pregnancy outcomes and may even result in irreversible health effects on the fetus. For instance, excessive gestational exposure to toxic metals, such as As, Cd, Cr, Hg, and Pb is corrected with an increased risk of gestational diabetes mellitus and impaired glucose homeostasis [7], cardiovascular disease and hypertension [8], fetal intrauterine growth restriction [9], and elevated risk of preterm birth [10]. Consequently, it is recommended that pregnant women with blood Pb levels ≥ 5 μg·dL^{-1} should receive counseling to prevent further exposure [11]. On the other hand, essential elements, including Co, Cu, Fe, Mg, Mn, Se, and Zn, play vital roles in regulating maternal and fetal metabolism, mitigating oxidative stress, supporting placental development, and facilitating fetal organ growth [12]. Deficiencies or imbalances in these essential metals have been linked to adverse perinatal outcomes such as fetal growth restriction, preterm birth, stillbirth [13], immune dysfunction [14], and complications such as hyperglycemia and hyperlipidemia [15]. Importantly, there is significant metabolic interaction between metals. For example, deficiencies in essential metals may enhance the absorption of non-essential metals [16]. Given their critical roles in maternal/fetal health, the concentrations of maternal serum metals are key physiological indicators necessitating careful monitoring during pregnancy.

Early identification of metal imbalances enables timely intervention against exposure-related pathologies [17], requiring advanced analytical methods to characterize interactions in metal mixtures. Despite extensive research on metal exposure in occupational and general populations, studies on multi-metal exposure in pregnant women—a highly vulnerable group—remain scarce. Previous studies have examined maternal metal exposure and health outcomes, but most have focused on inland populations (e.g., Shanxi, Henan) [18–22] where dietary patterns and environmental sources differ significantly from coastal regions like Dalian. Limited research exists on how coastal environmental factors, including seafood consumption and industrial pollution, influence metal exposure during pregnancy. Therefore, this study established a rapid pretreatment method for the determination of multiple metals in human serum, by using inductively coupled plasma-mass spectrometry (ICP-MS). And then investigate the exposure levels and distribution characteristics of multiple metals in serum samples from pregnant women in Dalian, a coastal city in China. This study is novel in its comprehensive analysis of 22 metals and their simultaneous associations with liver, kidney, metabolic, and cardiovascular indicators in pregnant women, offering a broader understanding of the interplay between metal exposure and maternal health. The objectives of this study are to (1) quantify the internal exposure burden of both toxic and essential metals in this vulnerable population, and (2) explore potential correlations between metal exposure and associated health risks. This work provides essential baseline data for understanding metal exposure risks among pregnant women and will help inform public health strategies for reducing these risks.

2. Materials and Methods

2.1. Chemicals

Nitric acid (HNO_3, ≥65%) was purchased from CNW Technologies GmbH (Dusseldorf, Germany), and the Triton X-100 (purity > 99%) was obtained from Merck Company (Rahway, NJ, USA). A custom multi-metal standard stock solution, a Hg standard stock solution, and a mixed internal standard (ISTD) solution were sourced from Agilent Technologies, Inc. (Santa Clara, CA, USA). Ultrapure water (resistivity ≥ 18.2 MΩ·cm) was generated using a Milli-Q® water purification system (Millipore D 24 UV, MilliporeSigma, Burlington, MA, USA). A vortex mixer (XW-80A, Shanghai Jingke Industrial Co., Ltd., Shanghai, China) was used for thorough mixing of samples and reagents. Quantification of metal concentrations was

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performed using an 8900 Triple Quadrupole ICP-MS (Agilent Technologies Co., Ltd., USA).

2.2. Sample Collection

The study adhered to The International Code of Medical Ethics of the World Medical Association for experiments involving human participants. Serum samples were collected from pregnant women attending routine examinations at the Department of Obstetrics and Gynecology, The Second Affiliated Hospital of Dalian Medical University, between August 2021 and June 2022. Whole blood was collected via venipuncture using serum tubes (Sanli Medical Instrument Co., Ltd., Changsha, China) with a clot activator and gel separator. Samples were centrifuged at 3500 rpm for 10 min at 4 °C within two hours of collection. The isolated serum was then aliquoted into clean cryovials and stored at −80 °C until analysis.

2.3. Sample Preparation and ICP-MS Analysis

For analysis, 200 μL of thawed serum were transferred to a clean tube, followed by the addition of 3.8 mL of a freshly prepared extraction solution (1% HNO_3, 0.01% Triton X-100). The mixture was vortexed vigorously for 5 min using the vortex mixer to ensure complete homogenization and extraction. Afterward, 4 mL of the mixture was centrifuged at 4500 g·min^{-1} for 5 min to precipitate particulates and proteins. The resulting supernatant was carefully decanted and filtered through a 0.22 μm filter before ICP-MS analysis, which was typically conducted within 24 h. Detected metals including Magnesium (Mg), Calcium (Ca), Vanadium (V), Chromium (Cr), Manganese (Mn), Iron (Fe), Cobalt (Co), Nickel (Ni), Copper (Cu), Zinc (Zn), Gallium (Ga), Arsenic (As), Selenium (Se), Rubidium (Rb), Strontium (Sr), Argentum (Ag), Cadmium (Cd), Cesium (Cs), Barium (Ba), Hydrargyrum (Hg), Lead (Pb) and Uranium (U).

To minimize matrix effects, all calibration standards were prepared using a matrix-matching approach in the extraction solution [23]. The multi-metal standard stock solution (10 ppm, excluding Hg) was serially diluted (10-fold dilution factor per step) using the extraction solution to prepare calibration standards at concentrations of 0.1, 0.5, 1, 5, 10, 20, and 50 μg·L^{-1}. For Hg, the standard stock solution (10 ppm) was serially diluted with a solution containing 1% (*v*/*v*) HNO_3 and 2% (*v*/*v*) HCl in ultrapure water, producing calibration standards at concentrations of 0.1, 0.2, 0.5, 1, and 2 μg·L^{-1}. The mixed internal standard stock solution (10 ppm) was serially diluted using a diluent containing 1% (*v*/*v*) HNO_3 and 20% (*v*/*v*) isopropanol in ultrapure water with a final concentration of 500 μg·L^{-1}. The detailed parameters of the instrumental analysis method are described in the Supplementary Material Table S1.

2.4. Quality Assurance and Quality Control

To validate the extraction method, spiking recovery experiments were performed on serum samples by adding metal standards at concentrations of 1 μg·L^{-1} and 5 μg·L^{-1}. Recovery rates for each metal ranged from 72.87% to 117.62% at 1 μg·L^{-1} and 76.19% to 124.05% at 5 μg·L^{-1}, demonstrating the reliability of the extraction procedure (Tables S2 and S3). To minimize contamination risks, all sample pretreatment procedures were conducted using plastic materials exclusively. Additionally, procedural blanks were processed concurrently with each sample batch to monitor potential contamination from reagents and laboratory equipment throughout the analytical workflow. Detection was carried out only after the ICP-MS instrument had been successfully tuned. Internal standards (^{6}Li, Sc, Ge, Rh, In, Tb, Lu, Bi) were used for calibration to minimize "drifting effects" during prolonged analysis. Recovery rates for internal standards ranged from 82% to 117%. A seven-point calibration curve (0.1 to 50 μg·L^{-1}) was established, with correlation coefficient exceeding 0.999 for each element. Each sample was analyzed in triplicate, and the average of the three measurements was used. The relative deviation between parallel measurements for all samples was less than 5%. To ensure accuracy, calibration was performed for every batch of 50 samples. Method detection limits (MDLs) for each metal are presented in Table S4. Method blanks were tested after every 10 samples, and all results were below MDLs.

2.5. Statistical Analysis

Data analysis was conducted using SPSS version 26.0 (SPSS Inc., Chicago, IL, USA). To ensure the statistical significance of the data, concentrations of metals below the MDLs were substituted with a value equal to the MDL divided by the square root of two [24]. The normality of the data was tested using the Kolmogorov-Smirnov test, and non-parametric testing (Mann-Whitney U test) was used for between-group comparisons (case vs. control). Data were expressed as medians and interquartile ranges (IQRs). Given the typical skewed distribution of metal concentrations, values were log-transformed to approximate normality prior to regression analysis. A multiple linear regression model was applied to evaluate the relationships between metal concentrations and clinical indicators, adjusting for age, BMI, and parity. Adjusted R^2 values reflected the percentage of variance in clinical indicators explained by the metal concentrations. *p*-value < 0.05 was considered statistically significant. The variance inflation factor (VIF) was examined for each metal to assess multicollinearity; all VIF values were below 5, indicating that multicollinearity was not a major concern. The results are presented as standardized (β) coefficients.

3. Results and Discussion

3.1. General Characteristics

General characteristics of the 209 pregnant women were shown in Table 1. Participants were categorized into two groups based on their health status, including control group (n = 28) and case group (n = 181). The control group consisted of healthy pregnant women with no underlying diseases, while The case group included pregnant women diagnosed with clinical conditions such as hypertensive disorders (based on systolic ≥ 140 mmHg or diastolic ≥ 90 mmHg), gestational diabetes (defined as fasting glucose ≥ 5.1 mmol/L or 2-h glucose ≥ 8.5 mmol/L during OGTT), PCOS (confirmed by Rotterdam criteria), and uterine fibroids (confirmed by ultrasound). The maternal age ranged from 19 to 43 years, with 20.57% of participants classified as of advanced maternal age (≥35 years). The body mass index (BMI), calculated as weight in kilograms divided by height in meters squared ($kg \cdot m^{-2}$), was used as an important parameter to determine the degree of obesity and basic health status of the human body, and the World Health Organization (WHO) documents that the healthy BMI range is between 18.5–24.9 $kg \cdot m^{-2}$ for adults [25]. In this study, BMI for each woman was taken from the medical record, strikingly, 68.42% of the women in this cohort were overweight (BMI ≥ 25.0 $kg \cdot m^{-2}$), and only 30.62% had an acceptable BMI. None of the participating women in this study reported smoking or drinking alcohol during their pregnancy. Approximately 98.09% (205 out of 209) of the participants reported supplementing their diet with folic acid, vitamins, and/or various other dietary nutrients during pregnancy.

Table 1. General characteristics of 209 pregnant woman.

Characteristics	No. (n = 209)	%
BMI ($kg \cdot m^{-2}$)		
Underweight (<18.5)	2	0.96
Acceptable weight (18.5–24.9)	64	30.62
Overweight (≥25)	143	68.42
Age of pregnant		
≤30 years	79	37.80
30–34 years	87	41.63
≥35 years	43	20.57
Parity		
Nulliparous	102	48.80
Multiparous	107	51.20

3.2. Concentrations of Metals in Serum Samples

The concentrations and descriptive statistics for each metal in the maternal serum are presented in Table S5. According to previous study, the 22 metals are categorized into three groups based on their known roles in the human body [26]: toxic metals (including Cr, As, Cd, Hg, and Pb), essential metals (including Mg, Ca, Fe, Cu, Zn, Mn, Co, and Se), and possibly essential trace metals (including V, Ni, Ga, Rb, Sr, Ag, Cs, Ba, and U). Interestingly, the detection rates of Ga and U were relatively low, at 53.36% and 45.74%, respectively, while the detection rates for all other metals were exceeded 78%. Ga and U were excluded from the statistical analysis. As shown in Figure 1, a distinct gradient was observed in maternal serum concentrations of essential metals, ordered as follows: Mg > Ca > Cu > Fe > Zn > Se > Mn > Co. For possibly essential trace metals, the gradient is as follows: Rb > Sr > Ba > Ni > Ag > V > Cs, and for toxic metals: Cr > Pb > As > Hg > Cd. The mechanisms of metal accumulation in the human body are complex and influenced by a combination of external environmental factors and internal metabolic processes. Consequently, serum metal concentrations exhibit considerable variability, as reflected in the data by the notably wide concentration ranges observed—particularly for essential metals. This variation may stem from multiple factors, including maternal supplement use and household environmental exposures. Potential contributors to elevated metal levels include secondhand smoke, occupational hazards, and contamination from dietary sources, drinking water, or air pollution.

Currently, reference values for serum metal concentrations in pregnant women remain limited, with established normal ranges available only for a select few elements, including Fe, Mg, and Zn. In this study, the concentrations of these metals in serum of pregnant women were compared to those from healthy populations and previous reports. The comparison with previous studies were listed in Tables 2 and 3. For example, the concentration of Mg in the serum of healthy individuals ranged from 18.2 to 23.1 $mg \cdot L^{-1}$, which is consistent with the Mg concentration reported in this study (18.49 $mg \cdot L^{-1}$). Similarly, the serum concentration of Fe (895.11 $\mu g \cdot L^{-1}$) falls within the reported normal range of 720–1430 $\mu g \cdot L^{-1}$ [18], while lower than levels found in pregnant women from other regions in China (e.g., Hangzhou [27]: 1810 $\mu g \cdot L^{-1}$), Guizhou [19] (1049.44 $\mu g \cdot L^{-1}$), Jilin [20] (1494 $\mu g \cdot L^{-1}$), and Shanxi [21,22] (1719 $\mu g \cdot L^{-1}$ and 1330 $\mu g \cdot L^{-1}$) in China. The variation in Fe levels among pregnant women may be attributed to differences in dietary Fe intake, as Fe supplementation is routinely recommended during pregnancy. The empirical lower limit for Zn is 0.7 $mg \cdot L^{-1}$, with a normal Zn concentration of approximately 1 $mg \cdot L^{-1}$ [28]. Zn levels (605.68 $\mu g \cdot L^{-1}$) in our study were comparable to those reported in most regions of China.

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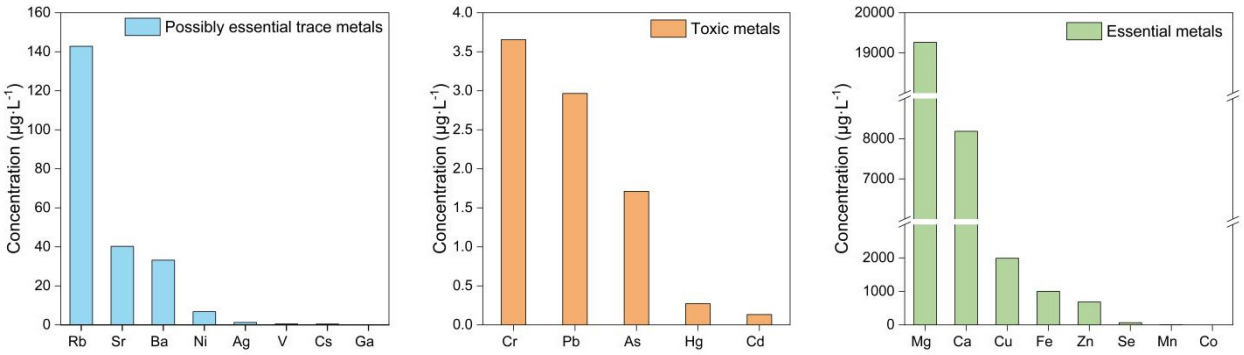

Figure 1. Concentrations (μg·L⁻¹) of metals in pregnant woman's serum samples from Dalian city.

Table 2. Concentrations (μg·L⁻¹) of essential metals in pregnant woman's serum samples from China different regions.

Reference	Region	Sample Size (n)	Essential Metals (μg·L⁻¹)							
			Mg	Ca	Mn	Fe	Co	Cu	Zn	Se
This study	Dalian	209	18,493.37	8060.96	3.95	895.11	0.30	1956.43	605.68	62.32
Zhuang et al. [27]	Hangzhou	149	14,860	63,250	—	1810	—	2420	650	—
Jia et al. [29]	Zhangjiakou	20	21,620	—	16.59	—	—	1470	880	302.87
Wang et al. [19]	Guizhou	1000	20,416.2	96,587.98	—	1049.44	—	1481.26	787.15	—
Liu et al. [20]	Jilin		—	101,000	—	1494	—	1826	1324	—
Zhou et al. [30]	Foshan	8169	34,027	56,910.76	45.05	—	—	1309.05	7390.5	—
Ma et al. [31]	Wuhan	292	—	—	—	—	0.19	1807.49	—	88.03
Xu et al. [21]	Shanxi	148	—	—	1.47	1719	0.79	1538	729	142
Tian et al. [22]	Shanxi	477	—	—	2.09	1330	1.20	1720	644	—

Table 3. Concentrations (μg·L⁻¹) of toxic metals in pregnant woman's serum from China different regions.

Reference	Study Region	Sample Size (n)	Toxic Metals (μg·L⁻¹)				
			As	Cd	Hg	Pb	Cr
This study	Dalian	209	0.98	0.07	0.21	1.39	2.57
Liang et al. [32]	Ma'an Shan	3416	1.77	66.20	0.36	0.86	2.88
Ma et al. [31]	Wuhan	292	—	—	0.28	7.80	—
Xu et al. [21]	Shanxi	148	15.2	0.73	0.26	0.49	0.27
Tian et al. [22]	Shanxi	477	—	0.78	0.23	0.87	1.01
Zhao et al. [33]	Shanghai	220	2.682	1.398	2.035	42.361	—

Among the toxic metals, As concentration in Dalian maternal serum (0.98 μg·L⁻¹) was lower than that reported in Ma'an Shan [32] (1.77 μg·L⁻¹), Shanghai [33] (2.682 μg·L⁻¹), and Shanxi [21] (15.2 μg·L⁻¹). Conversely, Cr (2.57 μg·L⁻¹) and Pb (1.39 μg·L⁻¹) concentrations in this study exceeded those from Shanxi [21,22] (0.27–1.01 μg·L⁻¹ and 0.49–0.87 μg·L⁻¹, respectively). However, the observed Pb level (1.39 μg·L⁻¹) remained substantially below the CDC's health-based reference value of 50 μg·L⁻¹ [11]. The uptake of Pb into the body is impacted by the frequency and amount of the material being ingested, as well as the bioaccessibility of the Pb, or how readily it will be absorbed if ingested [34,35]. Human activity has dispersed Pb in the environment, resulting in extensive and persistent contamination of soil [36] and dust [37]. The elevated levels in Dalian was high might be attributable to local industrial activities, traffic-related pollution, or regional environmental background. Notably, the concentration of Cd (0.07 μg·L⁻¹) in this study were markedly lower than values in Ma'an Shan [32] (66.20 μg·L⁻¹), Shanxi [21,22] (0.73–0.78 μg·L⁻¹), and Shanghai [33] (1.398 μg·L⁻¹). Critically, not all toxic metals in maternal serum exhibit low concentrations (such as Cr and Pb), and some even reach levels comparable to essential metals (such as Co and Mn). Many elements remain understudied in the Chinese population, resulting in a significant paucity of comparable reference data.

Mg and Ca are the most abundant essential metals in serum, as shown in Figure 2a, Mg and Ca together account for 88.28% of the total concentration of eight essential metals. Long-term Mg deficiency, in particular, has been linked to gestational diabetes due to its effect on insulin synthesis and secretion, potentially leading to pancreatic β-cell dysfunction and affect the binding of insulin to its receptors [38]. Severe Ca deficiency can lead to adverse effects such as leg cramps, preeclampsia, and fetal growth restriction [39]. For possible essential trace metals (Figure 2b), Rb, Sr, and Ba are the predominant metals in serum, collectively representing approximately 95.95% of the total concentration. However, Ni unexpectedly

constitute 3.08% of this category, with Ag, V, and Cs accounting for 0.97%. For toxic metals (Figure 2c), Cr, Pb, and As are the most abundant metals in serum, the three elements together account for 94.63% of the total concentration. These findings underscore the necessity for strengthened biomonitoring programs to reduce prenatal exposure risks to environmental contaminants.

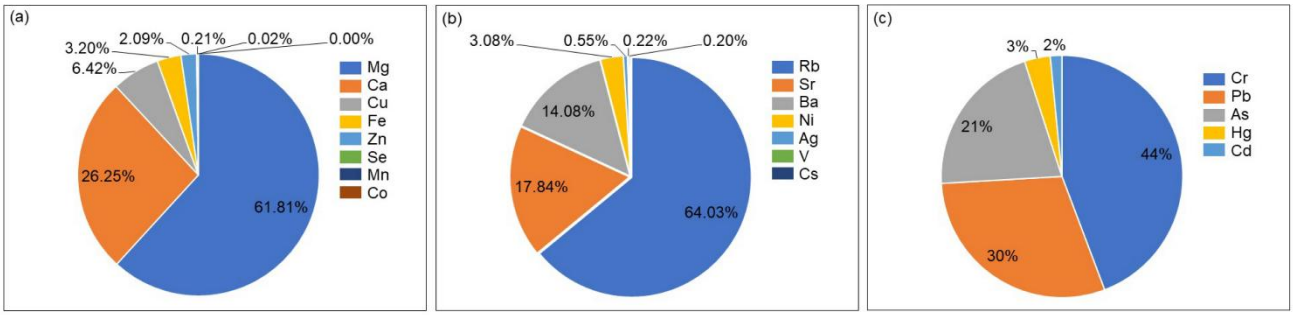

Figure 2. Concentration distribution and composition of metals in serum samples of pregnant women. (**a**) essential metals; (**b**) possible essential trace metals; (**c**) toxic metals.

3.3. Association Between Maternal Metal Exposure and Health Risks

In this study, the 209 pregnant women were divided into two groups: the healthy group (n = 28) and the disease group (n = 181). The concentration and compositional profiles of metals in serum of pregnant woman between case and control groups were shown in Figure 3 and Table S6. For essential metals (Figure 3a), serum concentrations showed no statistically significant differences ($p > 0.05$) between case and control groups, suggesting comparable maternal levels of these micronutrients. Figure 3b displays concentrations of possibly essential trace metals, revealing a statistically significant elevation in Ag levels among cases compared to controls ($p < 0.01$). This disparity may reflect differential environmental exposures or disease-associated metabolic alterations. Regarding toxic metals (Figure 3c), Hg levels are significantly elevated in the case group versus controls (* $p < 0.05$), indicating health risks associated with high Hg exposure. No statistically significant differences were observed for other toxic metals in case and control groups. Overall, these findings highlight the need for targeted monitoring of Ag and Hg, given their significantly elevated levels in the case group. Further research should investigate exposure sources and clinical implications of these metal elevations, particularly regarding maternal-fetal health outcomes.

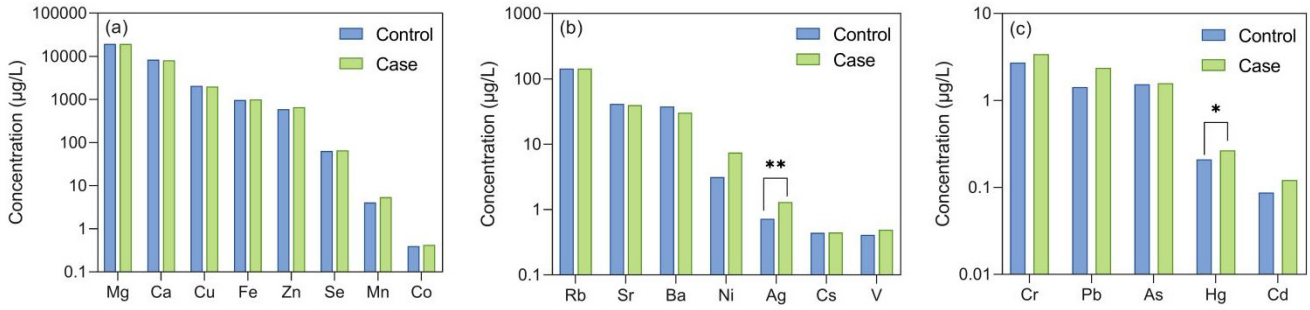

Figure 3. Concentration distribution and composition of metals in serum samples of pregnant women in Case and Control. (**a**) essential metals; (**b**) possible essential trace metals; (**c**) toxic metals. Asterisks above the bars indicate a statistically significant difference between the case and control groups (* $p < 0.05$, ** $p < 0.01$).

3.3.1. Effect of Metal Exposure on Liver Function

The liver plays a critical role in the absorption, metabolism, and storage of various metals, making its proper function essential for maintaining the homeostasis of essential and trace metals [40]. Clinically, the function of the liver is often assessed using eight common biomarkers [41,42]. Table 4 represents the strength of the relation between liver function markers and metal mixtures, among the eight liver function indicators, only serum albumin (Alb) was found to correlate with metal concentrations. Multiple linear regression models, adjusted for age, BMI, and parity, revealed a significant overall association ($R^2 = 0.248$, $F = 2.510$, $p < 0.00001$). Several metals showed statistically significant associations with Alb levels: a 1 μg/L increase in Ca was associated with a 0.0008 increase in Alb ($\beta = 0.0008$, $p < 0.05$), while a 1 μg/L increase in Fe was associated with a decrease in Alb of 0.0018 units ($\beta = -0.0018$, $p < 0.05$). A

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1 μg/L increase in Co was associated with a 1.1760 unit increase in Alb (β = 1.1760, $p < 0.01$). Conversely, a 1 μg/L increase in Sr was associated with a reduction in Alb of 0.1214 units (β = −0.1214, $p < 0.001$), and a 1 μg/L increase in Cs was associated with a 10.430 unit increase in Alb (β = 10.430, $p < 0.01$).

Table 4. Associations between mixed metals and Alb levels in serum samples from the pregnant woman.

	β	*p*	95%CI	VIF
Mg	-1.018×10^{-5}	0.8956	(−0.0002, 0.0001)	1.855
Ca	0.0008	0.0494	(2.13×10^{-6}, 0.0016)	3.740
V	0.5559	0.6418	(−1.7990, 2.9100)	4.530
Cr	−0.0334	0.8221	(−0.3265, 0.2597)	2.950
Mn	0.0355	0.6178	(−0.1046, 0.1755)	4.702
Fe	−0.0018	0.0165	(−0.0033, −0.0003)	1.423
Co	1.1760	0.0048	(0.3632, 1.9900)	1.060
Ni	0.0094	0.3405	(−0.0100, 0.0288)	1.206
Cu	−0.0018	0.0829	(−0.0039, 0.0002)	2.000
Zn	−0.0007	0.5897	(−0.0035, 0.0020)	2.888
As	0.1336	0.4777	(−0.2369, 0.5040)	1.302
Se	0.0392	0.0793	(−0.0046, 0.0831)	2.164
Rb	−0.0390	0.0553	(−0.0789, −0.0009)	3.306
Sr	−0.1214	0.0007	(−0.1909, −0.0520)	2.681
Ag	−0.6842	0.1138	(−1.5340, 0.1654)	1.185
Cd	0.0552	0.9726	(−3.1080, 3.2180)	1.287
Cs	10.4300	0.0029	(3.6270, 17.2400)	2.592
Ba	−0.0042	0.8033	(−0.0372, 0.0289)	1.501
Hg	−4.2090	0.1103	(−9.3830, 0.9661)	1.445
Pb	−0.0106	0.9473	(−0.3272, 0.3059)	2.064
Parity	0.5754	0.1388	(−0.1883, 1.3390)	1.224
BMI	0.0774	0.3399	(−0.0822, 0.2370)	1.327
Age	0.0045	0.9616	(−0.1781,0.1870)	1.261

The role of serum Alb as a binding protein for various metal ions is well-documented. Alb's molecular structure, with its multiple binding sites facilitated by suitable donor groups, allows it to interact with metals of diverse geometrical shapes and coordination properties [43]. This binding capability can affect the bioavailability, transport, and toxicity of metal ions, potentially explaining the significant correlations observed in our study. For instance, Payne et al. noted a strong positive correlation between serum Ca levels and Alb (r = 0.867), highlighting the physiological interdependence between Ca homeostasis and albumin [44]. Similarly, Wang et al. reported a positive correlation between serum Ca and Alb levels in pregnant women with gestational hypertension (r = 0.3513, $p < 0.001$), suggesting that disruptions in Ca metabolism during pregnancy may affect Alb levels and liver function [45]. Amirtharaj et al. showed that the binding ability of serum Alb with Co was slightly reduced in patients with fatty liver disease compared to controls [46]. The negative correlation between Fe and Alb indicate that elevated or misregulated Fe homeostasis could impact Alb synthesis or stability, thus reflecting compromised liver function. While existing studies on the relationship between Sr and Alb are sparse, the observed negative correlation in our study is intriguing. One study reported a link between decreased serum Alb levels and urinary Sr concentrations [47]. These findings provide theoretical support for the observed relationships in this study, suggesting that certain metals may influence liver function through their interactions with Alb. This association underscores the importance of considering metal exposure as a potential factor in liver health assessments.

3.3.2. Effect of Metal Exposure on Renal Function Parameters

The identification of modifiable risk factors associated with the progression of chronic kidney disease (CKD) is crucial [48]. The relationship between metal mixtures and renal function parameters, specifically serum creatinine, uric acid, and urea levels. Our findings indicated significant correlations of metal concentrations with creatinine and uric acid, while no significant relationship was observed with urea levels. The results are summarized in Tables 5 and 6, which were from multiple linear regression models adjusted for age, BMI, and parity. For serum creatinine, the model fit statistics were $R^2 = 0.2482$ and F = 2.693, $p < 0.001$. Several factors were significantly associated with creatinine levels: a 1 μg/L increase in Cr was associated with a decrease of 0.4817 units in creatinine (β = −0.4817, $p < 0.05$), while a 1 μg/L increase in Zn was associated with an increase of 0.0092 units (β = 0.0092, $p < 0.0001$). Similarly, a 1 μg/L increase in Cs was associated with an increase of 11.5300 units (β = 11.5300, $p < 0.05$). Additionally, each one-year increase in age was associated with an increase of 0.3114 units in creatinine (β = 0.3114, $p < 0.05$). Elevated serum creatinine is a marker of impaired kidney function and reflects a decline in glomerular filtration rate (GFR). Alarcon et al. conducted a 6-month longitudinal study of 48 patients with chronic kidney failure undergoing hemodialysis, finding a significant positive correlation between Zn and serum creatinine [49]. This suggests Zn's potential role in CKD pathophysiology, possibly through oxidative stress pathways, given its known regulation of antioxidant enzymes [50]. In the analysis of uric acid, which is both a marker and a modifiable risk factor for CKD [51], the model fit statistics are $R^2 = 0.2797$ and F = 2.650, $p < 0.001$. Four metals showed significant associations: a 1 μg/L increase in Cr was associated with a decrease of 5.6460 units in uric acid (β = -5.6460, $p < 0.05$), whereas a 1 μg/L increase in Zn was associated with an increase of 0.0755 units (β = 0.0755, $p < 0.01$). A 1 μg/L increase in Sr was associated with an increase of 1.9850 units (β = 1.9850, $p < 0.01$), and a 1 μg/L increase in Ag was associated with a decrease of 16.1000 units (β = −16.1000, $p < 0.05$). Collectively, these findings underscore the complex interactions between metal exposure and renal function parameters. It is evident that metal exposure could be an important yet modifiable risk factor for CKD.

Table 5. Associations between mixed metals and creatinine levels in serum samples from the pregnant woman.

	β	*p*	95%CI	VIF
Mg	−0.0002	0.1932	(−0.0004, 0.0001)	2.0505
Ca	−0.0005	0.4288	(−0.0018, 0.0008)	3.9597
V	−0.3233	0.8692	(−4.1950, 3.5490)	4.6231
Cr	−0.4817	0.0422	(−0.9463, −0.0171)	3.0404
Mn	−0.0913	0.4452	(−0.3269, 0.1443)	4.8482
Fe	0.0002	0.8704	(−0.0022, 0.0026)	1.4534
Co	−0.7048	0.2837	(−1.9990, 0.5893)	1.0670
Ni	−0.0065	0.6783	(−0.0374, 0.0244)	1.2138
Cu	0.0000	0.9845	(−0.0036, 0.0035)	2.0141
Zn	0.0092	<0.0001	(0.0048, 0.0135)	2.9083
As	0.0060	0.9843	(−0.5967, 0.6087)	1.2443
Se	−0.0371	0.3013	(−0.1077, 0.0336)	2.1157
Rb	0.0069	0.8397	(−0.0604, 0.0742)	3.3530
Sr	0.0885	0.1503	(−0.0324, 0.2095)	2.7694
Ag	0.2776	0.6961	(−1.1240, 1.6790)	1.1579
Cd	3.6460	0.1552	(−1.3960, 8.6870)	1.3114
Cs	11.5300	0.0491	(0.0473, 23.0000)	2.6792
Ba	−0.0416	0.1432	(−0.0974, 0.0142)	1.5247
Hg	−5.2330	0.2318	(−13.8400, 3.3770)	1.4424
Pb	0.2253	0.4902	(−0.4181, 0.8687)	2.1162
Parity	−1.1990	0.0640	(−2.4680, 0.0706)	1.2558
BMI	0.0986	0.4597	(−0.1643, 0.3615)	1.3754
Age	0.3114	0.0422	(0.0111, 0.6117)	1.2937

Table 6. Associations between mixed metals and UA levels in serum samples from the pregnant woman.

	β	*p*	95%CI	VIF
Mg	−0.0015	0.3140	(−0.0045, 0.0014)	2.0561
Ca	−0.0090	0.2304	(−0.0236, 0.0057)	3.9589
V	−29.7000	0.1696	(−72.2100, 12.8100)	4.6160
Cr	−5.6460	0.0310	(−10.7700, −0.5213)	3.0511
Mn	−0.2809	0.8309	(−2.8750, 2.3130)	4.8524
Fe	0.0065	0.6300	(−0.0200, 0.0330)	1.4461
Co	−0.8336	0.9082	(−15.090, 13.420)	1.0670
Ni	0.1844	0.2860	(−0.1558, 0.5246)	1.2156
Cu	0.0293	0.1457	(−0.0103, 0.0688)	2.0535
Zn	0.0755	0.0025	(0.0269, 0.1241)	2.9368
As	1.3070	0.7044	(−5.4840, 8.0980)	1.2430
Se	−0.7374	0.0628	(−1.5150, 0.0398)	2.1289
Rb	0.3675	0.3265	(−0.3701, 1.1050)	3.3827
Sr	1.9850	0.0034	(0.6686, 3.3010)	2.7051
Ag	−16.1000	0.0419	(−31.600, −0.6010)	1.1606
Cd	44.2600	0.1173	(−11.260, 99.770)	1.3113
Cs	39.5900	0.5383	(−87.200, 166.40)	2.6989
Ba	−0.4116	0.1869	(−1.0250, 0.2017)	1.5165
Hg	−4.6830	0.9222	(−99.280, 89.910)	1.4456
Pb	1.1940	0.7398	(−5.8930, 8.2800)	2.1117
Parity	−13.2400	0.0640	(−27.260, 0.7792)	1.2539
BMI	1.2350	0.4023	(−1.6690, 4.1390)	1.3816
Age	−1.5040	0.3702	(−4.8080, 1.8010)	1.2952

3.3.3. Effect of Metal Exposure on Maternal Blood Pressure

Gestational hypertension is a common cardiovascular complication during pregnancy, which can lead to adverse pregnancy outcomes, including miscarriage, preterm birth, and even maternal and fetal mortality in severe cases [52]. This study analyzed the relationship between the concentrations of mixed metals and maternal blood pressure, with the results summarized in Tables 7 and 8. The multiple linear regression analysis for systolic blood pressure (SBP) revealed a significant model ($F = 2.739$, $R^2 = 0.2571$, $p < 0.0001$). Several factors were significantly associated with SBP: a 1 μg/L increase in Mg was associated with a 0.0006 unit increase in SBP (β = 0.0006, $p < 0.01$), while a 1 μg/L increase in Ca was associated with a 0.0030 unit decrease (β = −0.0030, $p < 0.01$). A 1 μg/L increase in Zn was associated with a 0.0106 unit increase (β = 0.0106, $p < 0.01$), and a 1 μg/L increase in As was associated with a 1.1300 unit increase (β = 1.1300, $p = 0.0283$). Similarly, a 1 μg/L increase in Ag was associated with a 2.3460 unit increase in SBP (β = 2.3460, $p < 0.05$). Additionally, each one-year increase in age was associated with a 0.6893 unit increase in SBP (β = 0.6893, $p < 0.01$). For diastolic blood

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pressure (DBP), the multiple linear regression analysis also showed a significant model ($F = 1.773$, $R^2 = 0.1830$, $p < 0.05$). A 1 μg/L increase in Mg was associated with a 0.0005 unit increase in DBP (β = 0.0005, $p < 0.01$), and a 1 μg/L increase in As was associated with a 1.1100 unit increase (β = 1.1100, $p < 0.01$). Each one-year increase in age was associated with a 0.4039 unit increase in DBP (β = 0.4039, $p < 0.05$). Mg plays a crucial role in regulating vascular tone and blood pressure by inhibiting the activity of adrenaline [53], potentially offering both physiological and pharmacological benefits for patients with primary hypertension [49]. This aligns with our findings, where elevated Mg levels were significantly correlated with both SBP and DBP, indicating that Mg dysregulation may contribute to hypertensive disorders during pregnancy. In contrast, the negative association between serum Ca levels and SBP is consistent with previous epidemiological studies. An epidemiological study of 9321 participants found a significant and independent correlation between serum Ca and both systolic and diastolic blood pressure [54]. Ca supplementation has been shown to significantly reduce SBP [55], suggesting a protective role of adequate Ca levels in maintaining normal blood pressure during pregnancy. This is noteworthy as adequate Ca intake is essential for preventing gestational hypertension, emphasizing the importance of nutritional monitoring for pregnant women. Zn plays a role in blood pressure regulation and the pathogenesis of hypertension is supported by clinical and laboratory data [56], demonstrating its involvement in endothelial function and oxidative stress response, both critical for vascular health. The significant positive association between serum Zn levels and SBP appears counterintuitive, given that Zn deficiency is typically observed in hypertensive patients [57]. However, compensatory physiological mechanisms might account for this discrepancy. Seyed et al. reported that Zn supplementation significantly reduced SBP in hypertensive patients, although it had no significant effect on DBP [58]. Therefore, Zn's role in hypertension and pregnancy warrants further investigation, particularly regarding the balance between deficiency and excess exposure.

Table 7. Associations between mixed metals and SBP levels in serum samples from the pregnant woman.

	β	*p*	95%CI	VIF
Mg	0.0006	0.0047	(0.0002, 0.0010)	1.7966
Ca	−0.0030	0.0093	(−0.0052, −0.0007)	3.6697
V	5.7730	0.0715	(−0.5091, 12.0600)	4.5097
Cr	−0.4389	0.2686	(−1.2190, 0.3415)	2.9494
Mn	−0.2028	0.2797	(−0.5719, 0.1663)	4.7008
Fe	0.0007	0.7346	(−0.0034, 0.0047)	1.4133
Co	1.1700	0.3031	(−1.0650, 3.4050)	1.0592
Ni	0.0196	0.4678	(−0.0335, 0.0727)	1.2059
Cu	0.0011	0.7113	(−0.0046, 0.0067)	2.0374
Zn	0.0106	0.0052	(0.0032, 0.0180)	2.8417
As	1.1300	0.0283	(0.1217, 2.1390)	1.3172
Se	−0.0836	0.1662	(−0.2023, 0.0351)	2.1960
Rb	0.0468	0.3881	(−0.0600, 0.1536)	3.3055
Sr	0.1152	0.2279	(−0.0727, 0.3032)	2.6129
Ag	2.3460	0.0455	(0.0470, 4.6450)	1.1926
Cd	3.0430	0.4889	(−5.6150, 11.7000)	1.3024
Cs	−8.8860	0.3270	(−26.7200, 8.9520)	2.4452
Ba	−0.0277	0.5442	(−0.1176, 0.0622)	1.4789
Hg	3.0940	0.6257	(−9.4000, 15.5900)	1.4614
Pb	−0.6766	0.1211	(−1.5340, 0.1806)	2.0636
Parity	−0.7154	0.4934	(−2.7720, 1.3410)	1.2288
BMI	0.1911	0.3829	(−0.2399, 0.6220)	1.2878
Age	0.6893	0.0062	(0.1983, 1.1800)	1.2493

Table 8. Associations between mixed metals and DBP levels in serum samples from the pregnant woman.

	β	*p*	95%CI	VIF
Mg	0.0005	0.0035	(0.0002, 0.0008)	1.7966
Ca	−0.0012	0.1657	(−0.0029, 0.0005)	3.6697
V	2.7760	0.2611	(−2.0820, 7.6330)	4.5097
Cr	−0.2398	0.4340	(−0.8432, 0.3636)	2.9494
Mn	−0.1297	0.3712	(−0.4151, 0.1557)	4.7008
Fe	−0.0019	0.2321	(−0.0050, 0.0012)	1.4133
Co	0.5398	0.5385	(−1.1890, 2.2680)	1.0592
Ni	0.0145	0.4869	(−0.0266, 0.0556)	1.2059
Cu	0.0011	0.6153	(−0.0033, 0.0055)	2.0374
Zn	0.0027	0.3532	(−0.0030, 0.0084)	2.8417
As	1.1100	0.0055	(0.3301, 1.8900)	1.3172

Table 8. *Cont.*

	β	*p*	95%CI	VIF
Se	−0.0273	0.5580	(−0.1190, 0.0645)	2.1960
Rb	0.0041	0.9220	(−0.0785, 0.0867)	3.3055
Sr	0.0080	0.9134	(−0.1373, 0.1534)	2.6129
Ag	0.9788	0.2787	(−0.7988, 2.7560)	1.1926
Cd	−1.3910	0.6824	(−8.0860, 5.3040)	1.3024
Cs	−0.5777	0.9342	(−14.3700, 13.2200)	2.4452
Ba	−0.0492	0.1646	(−0.1187, 0.0204)	1.4789
Hg	−2.4890	0.6118	(−12.1500, 7.1710)	1.4614
Pb	0.1206	0.7200	(−0.5422, 0.7834)	2.0636
Parity	−1.3310	0.1004	(−2.9210, 0.2592)	1.2288
BMI	0.1911	0.2594	(−0.1422, 0.5243)	1.2878
Age	0.4039	0.0372	(0.0242, 0.7836)	1.2493

3.3.4. Effect of Metal Exposure on Serum Glucose

Gestational diabetes mellitus (GDM) is one of the most common obstetric complications, affecting 14.8% of pregnant women in China [59]. Table 9 shows the relationship between metals and serum glucose using multivariate regression analysis ($F = 1.806$, $R^2 = 0.2011$, $p < 0.05$). Several metals were significantly associated with serum glucose: a 1 μg/L increase in Mg was associated with a 0.0001 unit increase in glucose (β = 0.0001, $p < 0.01$), whereas a 1 μg/L increase in Ca was associated with a 0.0002 unit decrease (β = −0.0002, $p < 0.05$). A 1 μg/L increase in Cr was associated with a 0.0844 unit increase (β = 0.0844, $p < 0.05$), and a 1 μg/L increase in Zn was associated with a 0.0008 unit decrease (β = −0.0008, $p < 0.05$). Similarly, a 1 μg/L increase in Se was associated with a 0.0177 unit increase in glucose (β = 0.0177, $p < 0.001$), and a 1 μg/L increase in Cd was associated with a 0.8174 unit decrease (β = −0.8174, $p < 0.05$). Mg plays a critical role in glucose transport across membranes and serves as a cofactor for enzymes involved in carbohydrate oxidation. It is also involved in carbohydrate metabolism, insulin secretion, and the activation of insulin receptor tyrosine kinases [60]. Previous studies have identified hypomagnesemia as being associated with diabetes [61]. Ca acts as a versatile intracellular messenger and is involved in regulating various biological processes throughout the human life cycle [62]. Some studies suggest that defects in the metabolism of divalent cations, including Ca, may be related to the development of diabetes and cardiovascular diseases [63]. The negative association between Ca and serum glucose in our study indicates that adequate Ca levels may contribute to better glucose regulation. Zn is essential for the synthesis, storage, and release of insulin [64], and lower serum Zn levels have been linked to an increased prevalence of type 2 diabetes and its complications [65]. Lin et al. reported that serum Se levels were positively correlated with fasting serum glucose and glycated hemoglobin levels [66]. Experimental studies have shown that exposure to Cd can lead to impaired glucose tolerance and diabetes [67], potentially due to the toxic effects of Cd on pancreatic β-cells, reducing insulin production. Cr has been found to enhance the sensitivity of insulin receptors in cell membranes, thereby improving insulin's ability to regulate blood glucose levels [68]. These findings highlight the significant role that metals play in the regulation of serum glucose levels. Further research is needed to explore the underlying mechanisms by which these metals affect glucose metabolism and insulin regulation.

Table 9. Associations between mixed metals and glucose levels in serum samples from the pregnant woman.

	β	*p*	95%CI	VIF
Mg	0.0001	0.0022	$(1.878 \times 10^{-5}, 0.0001)$	1.8284
Ca	−0.0002	0.0352	$(-0.0004, 1.378 \times 10^{-5})$	3.7231
V	−0.1077	0.6922	(−0.6442, 0.4287)	4.5614
Cr	0.0844	0.0177	(0.0149, 0.1539)	2.8250
Mn	0.0048	0.7674	(−0.0272, 0.0368)	4.7719
Fe	−0.0003	0.1348	(−0.0006, 0.0001)	1.4349
Co	0.0253	0.7850	(−0.1574, 0.2079)	1.0610
Ni	−0.0002	0.9407	(−0.0045, 0.0042)	1.2323
Cu	−0.0001	0.8213	(−0.0005, 0.0004)	2.0638
Zn	−0.0008	0.0158	(−0.0014, −0.0001)	2.7457
As	−0.0150	0.7240	(−0.0984, 0.0685)	1.3082
Se	0.0177	0.0005	(0.0078, 0.0276)	2.1213
Rb	−0.0028	0.5457	(−0.0119, 0.0063)	3.4252
Sr	0.0017	0.8370	(−0.0144, 0.0177)	2.6640

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Table 9. *Cont.*

	β	*p*	95%CI	VIF
Ag	−0.0174	0.6541	(−0.0937, 0.0590)	1.1961
Cd	−0.8174	0.0236	(−1.5240, −0.1109)	1.3269
Cs	−0.4225	0.5757	(−1.9100, 1.0650)	2.5536
Ba	−0.0038	0.3057	(−0.0111, 0.0035)	1.5443
Hg	−0.2155	0.6882	(−1.2740, 0.8426)	1.4265
Pb	0.0550	0.1373	(−0.0177, 0.1277)	1.9977
Parity	−0.0097	0.9143	(−0.1880, 0.1685)	1.2305
BMI	−0.0091	0.6249	(−0.0460, 0.0277)	1.3094
Age	0.0125	0.5506	(−0.0288, 0.0537)	1.2541

4. Conclusions

In this study, we analyzed the internal exposure levels of mixed metals in 209 serum samples from pregnant women in Dalian, China, using ICP-MS/MS. Mg and Ca were found to be the predominant metals in the serum of these pregnant women, with concentrations ranging from 18,493.37 μg·L^{-1} for Mg and 8060.96 μg·L^{-1} for Ca, respectively. Concentrations of essential metals in pregnant women were consistent with reference values from healthy populations. However, it is noteworthy that some metals, such as Co and Mn, were relatively higher compared to other regions in China. This underscores the need for strengthened monitoring of these metals to facilitate early intervention and prevent adverse health outcomes. Significant associations were observed for six metals (Ca, Fe, Co, Rb, Sr, and Cs) with liver function indicator of Alb levels. Zn and Cs were significantly associated with kidney function indicator of creatinine levels, while Cr, Zn, Sr, and Ag were significantly correlated with uric acid levels. We also found significant associations between Mg, Ca, Zn, and As with SBP, and between Mg and As with DBP. Furthermore, the multiple linear regression analysis revealed significant associations between Mg, Ca, Cr, Zn, Se, and Cd and glucose levels after adjusting for co-exposure to other metals and confounders.

This study is novel in its comprehensive analysis of 22 metals and their simultaneous associations with liver, kidney, metabolic, and cardiovascular indicators in pregnant women. However, it is important to note that the limited number of serum samples collected in this study resulted in weaker directional associations with disease risks. Future research should employ larger, multi-center design cohorts with comprehensive medication-free data to clarify mechanistic pathways linking metal concentrations to specific health indicators and advance understanding of maternal health risks. Based on these findings, we propose several actionable directions for future research. First, longitudinal studies that track metal concentrations serially across all trimesters of pregnancy are essential to establish temporal dynamics and better understand the critical windows of exposure for adverse outcomes. Second, intervention trials targeting modifiable exposure sources, such as reducing Hg intake from specific seafood species, could provide evidence-based strategies for risk mitigation and inform public health recommendations for pregnant women. Finally, further mechanistic research is needed to elucidate the biological pathways through which these metal mixtures influence maternal health, potentially incorporating omics technologies to discover novel biomarkers of effect and susceptibility.

Supplementary Materials

The additional data and information can be downloaded at: https://media.sciltp.com/articles/others/2510131708112480/GES-2508000088-SM-FC.pdf. Table S1: Operating parameters of ICP-MS; Table S2: Recovery rates of target metals in serum samples spiked after extraction (1 μg·L^{-1}); Table S3: Recovery rates of target metals in serum samples spiked after extraction (5 μg·L^{-1}); Table S4: Linear relationship of standard curves, method detection limits (MDLs); Table S5: Concentrations (μg·L^{-1}) of metals in pregnant woman's serum samples from Dalian city; Table S6 Concentration distribution and composition of metals in serum samples of pregnant women in Case and Control (μg·L^{-1}).

Author Contributions

N.G.: Conceptualization, Investigation, Visualization. Y.D.: Visualization, Writing-Original Draft. Y.G. and J.J.: Investigation. H.Z. and J.C.: Funding acquisition. D.Z.: Sampling for the study. All authors provided support and constructive criticism throughout the project. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement

This study received ethical approval from the Institutional Review Board of the Second Hospital of Dalian Medical University (The 251st Rapid Review, 2023).

Informed Consent Statement

Written informed consent has been obtained from the patient to publish this paper.

Data Availability Statement

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare no conflict of interest.

Use of AI and AI-Assisted Technologies

No AI tools were utilized for this paper.

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