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Association of maternal multi-metal exposure and dyslipidemia: a study of air pollution on pregnancy outcomes

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Abstract

Background Exposure to air pollutants, including heavy metals, is a major environmental concern of public health and these environmental toxicants have been associated with pregnancy complications.

Objectives An air pollution on pregnancy outcome (APPO) study was performed to investigate the adverse effects of fine particulate matter ($PM_{2.5}$) exposure on pregnancy outcomes. This study examined the association between maternal urinary metal mixtures and pregnancy complications, including dyslipidemia and preterm birth (PTB).

Methods The concentrations of 16 metals were measured in 60 urine samples collected during the second trimester pregnancy. Logistic regression and Bayesian kernel machine regression (BKMR) models were used to analyze the single and overall effects of metal exposure on pregnancy complications, respectively.

Results Logistic regression analysis showed a significant difference in urinary Ni and Zn concentrations between those exposed to high and low concentrations of fine particulate matter with an aerodynamic diameter of less than 2.5 μm ($PM_{2.5}$) and those not exposed. Four metals (Ni, Sc, Mo, and Cs) were positively associated with total cholesterol (TC) levels, but not with triglyceride (TG) levels and PTB. The BKMR model showed that the overall mixture of 16 metals was positively correlated with high TC and TG levels during the third trimester of pregnancy, and the individual effects of Mo and Pb were the most significant. However, we were only able to identify a trend between maternal exposure to metal mixtures and PTB.

Conclusions BKMR analyses showed a positive association between exposure to multi-metal mixtures and higher maternal TC and TG levels, a factor that contributes to PTB. Therefore, this also suggests that multi-metal exposure during pregnancy may be a potential risk factor for PTB.

Keywords Heavy metals, Overall effect, Triglyceride, Total cholesterol, Pregnancy outcomes

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Introduction

Several studies have revealed a positive association between maternal particulate matter (PM) exposure and adverse pregnancy and birth outcomes, including preterm birth (PTB), small for gestational age, low birth weight at term, and gestational diabetes mellitus (GDM) [1–4]. Our air pollution on pregnancy outcome (APPO) study is a hospital-based prospective cohort study conducted in South Korea among 1,200 pregnant women to determine the correlations between exposure to PM less than 2.5 μm in aerodynamic diameter ($PM_{2.5}$) or less than 10 μm in aerodynamic diameter (PM_{10}) and pregnancy complications [5]. Recent epidemiological studies have shown that PM contains heavy metals, and these PM-bound metals may be risk factors for maternal pregnancy complications, such as thyroid dysfunction [6, 7]. Heavy metals are well-known health risk for pregnant women. Preterm birth (PTB), defined as delivery before 37 weeks of gestation, has been linked to several trace metals such as Mn, Pb, Cd, Zn, and Hg. PTB is considered a major health issue in many countries because it leads to neural development loss and mortality in premature infants [7–10]. Many studies have determined the relationship between single toxic metal exposure and preterm delivery, but the adverse effects of multiple pollutant exposure on pregnancy complications have rarely been addressed [11–13].

Physiological alteration during pregnancy is an important consideration, as they are thought to be associated with abnormal changes in medical indications such as blood pressure and lipids, hemoglobin, and glucose levels [14–17]. Of these, maternal lipid levels are positively associated with preterm delivery and GDM [15, 18, 19]. High triglyceride (TG) levels in early or late pregnancy can increase the risk of cardiovascular disorders and cause PTB [20]. Hypercholesterolemia during pregnancy also increases the risk of PTB by causing an unnecessary buildup of immune cells to remove excess cholesterol [15]. Moreover, maternal metal exposures can significantly elevate blood lipid levels, and this association between metals and dyslipidemia may contribute to adverse pregnancy outcomes or maternal/neonatal health problems during pregnancy [21, 22].

In this study, we aimed to analyze the correlations between environmental pollution and pregnancy complications using the APPO study. First, we measured the concentrations of 16 metals in urine samples from pregnancy women with high and low PM exposure. Second, we used logistic regression and Bayesian kernel machine regression (BKMR) statistical models to identify associations between metal exposure during pregnancy and atypical changes in lipid profiles, such as blood TG and total cholesterol (TC) levels. BKMR is a flexible model that shows the non-linear relationship between numerous exposures and specific outcomes using a machine learning tool. A trend of association between maternal multi-metal exposure during pregnancy and PTB was then examined using BKMR analysis.

Materials and methods

Study participants

This study was one of the primary analyses planned for APPO study cohort, which enrolled 1,200 pregnant women at seven university hospitals in South Korea from January 2021 and December 2023 to investigate the correlation between PM exposure and pregnancy outcomes. Details of the inclusion criteria have been described previously [5]. Urine Samples collected during the second trimester of pregnancy were used in this study. Participants who withdrew consent or lacked information due to failure to follow up were excluded.

All study participants provided written informed consent for their data to be used for research purpose. The study was conducted in accordance with the Declaration of Helsinki and adhered to all relevant guidelines and regulations for research involving human participants. Ethical approval was obtained from the institutional review boards of the participating hospitals [Ewha Womans University Mokdong Hospital (EUMC 2021–04-032), Yonsei University Severance Hospital (4–2021-0414), Kangwon National University Hospital (KNUH-B-2021–04-012–008), Keimyung University Dongsan Medical Center (2021–04-073), Korea University Guro Hospital (2021GR0233), Ewha Womans University Seoul Hospital (2021–04-022), and Ulsan University Hospital (2022–04-020)].

Data collection

Because $PM_{2.5}$ at 15 $\mu g/m^3$ was known to be the World Health Organization (WHO) reference concentration, the APPO study cohort was divided into two groups: those with the low $PM_{2.5}$ exposure ($PM_{2.5} < 15$ $\mu g/m^3$) and high $PM_{2.5}$ exposure (> 15 $\mu g/m^3$) groups on average during pregnancy [5]. 30 samples with the lowest and 30 samples with the highest exposure to $PM_{2.5}$ from the total sample population were used in this study (Figure S1). A questionnaire survey collected basic demographic data, including maternal age, pre-pregnancy body mass index (BMI), education, socioeconomic status, and household income. Information of second trimester blood tests and pregnancy complications, such as PTB and GDM, were obtained from electronic medical records. The individual exposure $PM_{2.5}$ concentrations of the pregnant women were calculated using a time-activity based model that collects indoor and outdoor $PM_{2.5}$ concentrations and considers the daily location and time duration

of pregnant women [23, 24]. The equation is presented below.

$$C_{ind} = \{(C_{household\ indoor} \times T_{household\ indoor}) + (T_{indoor\ not\ at\ home} \times C_{indoor\ not\ at\ home}) + (T_{outdoor} \times C_{outdoor})\} \div 24$$

where C_{ind}: individual $PM_{2.5}$ exposure

$C_{household\ indoor}$: indoor household $PM_{2.5}$ concentration

$T_{household\ indoor}$: time spent indoors at home

$C_{indoor\ not\ at\ home}$: indoor $PM_{2.5}$ concentration (not within a household)

$T_{indoor\ not\ at\ home}$: time spent indoors (but not at home)

$C_{outdoor}$: outdoor $PM_{2.5}$ concentration based on address

$T_{outdoor}$: time spent outdoors

Indoor $PM_{2.5}$ concentrations were measured with an AirGuard K (Kweather, Co., Korea) device which determine the household air quality with a light scattering laser sensor and record data every minute and transmits the information online. The outdoor $PM_{2.5}$ concentration data were obtained from Air Korea (https://www.airkorea.or.kr/web), a service of the South Korean Ministry of Environment that monitors urban air based on the subject's residence.

Measurement of urine metals

To monitor metal pollutant exposure in pregnant women, we used urine samples from participants ($n=60$) exposed to low and high concentrations of $PM_{2.5}$ during the second trimester of pregnancy. Urine samples (5 ml) were stored at −80 °C and then transported to the institution (Smartive Corporation Institute for Life & Environment Technology, Hanam, Korea) for metal analysis.

Nineteen metals (Sb, Ba, Cd, Ce, Cs, Cr, Cu, Eu, Au, Pb, Mn, Hg, Mo, Ni, Sc, Ti, V, Yb, and Zn) were selected for determination based on two criteria: $PM_{2.5}$ bound metal composition [25] and detectable metals in urine samples. For the sample preparation, 300 µL of urine and 1 ml of 1% HNO_3 were added into 15 ml polypropylene tubes for overnight nitrification, followed by treatment with an internal standard solution for 1 h. Urinary metals were identified using an inductively coupled plasma mass spectrometer (ICP-MS) (NexION 2000B, PerkinElmer, Buckinghamshire, UK), where 100 µL of urine was mixed with an internal standard solution for detection and Hg was measured using a dynamic mechanical analyzer (DMA) (DMA-80 evo, Milestone, Sorisole, Italy). Detailed information on the limit of detection (LOD) for all urine metals and the ICP-MS and DMA analytical conditions is provided in Tables S1 and S2. Urinary creatinine concentrations were determined using a Beckman Coulter AU creatinine analyzer (AU5800, Beckman Coulter Inc., CA, USA). The concentration of each metal was adjusted using creatinine, and these values were used for further statistical analyses.

Statistical analysis

Urinary metal concentrations below the LOD were corrected to LOD/$\sqrt{2}$. Metals (Ce, Eu, Yb) with more than 50% of the values below the LOD were excluded from the analysis (Table S1). Therefore, 16 of the 19 metals were used in this study and creatinine-adjusted metal concentrations were logarithmically transformed because of the skewed distribution of urinary metal concentrations. The basic socio-demographic characteristics and blood lipid levels of study participants were represented as a number (%) or mean ± standard deviation (SD) (Table 1).

Single metal analysis model

A logistic regression model was used to determine the correlation between single urinary metal concentrations and TC, TG, and pregnancy outcomes, such as PTB and GDM. Crude (unadjusted) and single-metal models were represented by calculating the odds ratios, 95% confidence intervals (CIs), and p-values. Linear regression analyses were used to examine the relationship between urinary metals and blood lipid levels during pregnancy and regression coefficients and p-values were calculated. The single model was adjusted for the following covariates: maternal pre-pregnancy BMI, age, education, income, and exposure to $PM_{2.5}$ (by concentration) during the second trimester.

Multi-mixture metal analysis model

The BKMR analysis was performed to assess the overall effects of exposures to multiple metals on pregnancy complications [26]. The analysis using the BKMR model can provide a flexible approach that uses Gaussian kernel functions to determine multiple environmental exposure–response functions and allows for nonlinear and non-additive effects. The model equation is as follows:

$$Y_i = h\left(Hg_i,\ V_i,\ Cr_i,\ Mn_i,\ Ni_i,\ Cu_i,\ Zn_i,\ Sc_i,\ Ti_i,\ Mo_i,\ Cd_i,\ Sb_i,\ Cs_i,\ Ba_i,\ Au_i,\ Pb_i\right) + \beta x_i$$

$$i = 1, \cdots, n$$

where Y is the outcome as a continuous variable, h is a function of predictor variables Hg_i, V_i, Cr_i, Mn_i, Ni_i, Cu_i, Zn_i, Sc_i, Ti_i, Mo_i, Cd_i, Sb_i, Cs_i, Ba_i, Au_i, and Pb_i and

Table 1 Basic characteristics of study participants

Characteristics	*N* (%) Total (*N* = 60)		*N* (%), mean ± SD		*P*-value
			Low $PM_{2.5}$ (*n* = 30)	High $PM_{2.5}$ (*n* = 30)	
Age (years)					
< 35 years	25 (41.7)		30.1 ± 2.9	29.9 ± 3.2	0.44
≥ 35 years	35 (58.3)		38.7 ± 2.9	38.9 ± 1.5	
Pre-BMI (kg/m^2)					
< 23.0	17 (28.3)		21.2 ± 1.2	20.2 ± 1.8	0.29
≥ 23.0	43 (71.7)		26.1 ± 2.9	26.3 ± 3.8	
Education level					
< High school	5 (8.3)		2 (6.9)	0	0.14
≥ High school	55 (91.7)		27 (93.1)	30 (100)	
Income per month					
< 4 million won	22 (43.1)		9 (37.5)	13 (48.1)	0.73
4–6 million won	13 (25.5)		7 (29.2)	6 (22.2)	
> 6 million won	16 (31.4)		8 (33.3)	8 (29.6)	
Lipid levels (mother at 3rd trimester)					
Total cholesterol (mg/dL)	< 200	7(13)	3 (5.6)	4 (7.4)	0.13
	≥ 200	47(87)	24 (44.4)	23 (42.6)	
Triglyceride (mg/dL)	< 175	2(4.1)	1 (2)	1 (2)	0.89
	≥ 175	47(95.9)	25 (51.0)	22 (44.89)	

$PM_{2.5}$ (particulate matter with aerodynamic diameter < 2.5 μm), BMI (body mass index)

represents an exposure–response relationship, and the coefficient β is the effect assumed of the x covariate for the individual i. Covariates used included maternal age, BMI, education, income, and exposure to $PM_{2.5}$ during the second trimester. The BKMR model is primarily based on a nonlinear profit model that uses kernel machine regression rather than logistic regression by incorporating multiple exposure variables to represent the association between multiple exposures and the response function. The cumulative and independent effects of multiple urinary heavy metals on pregnancy complications were analyzed using a Markov chain Monte Carlo algorithm sampler with 10,000 iterations to evaluate the association between multimetal exposure and binary pregnancy outcomes, such as PTB and GDM.

All statistical analyses were performed using SPSS version 18 and R version 4.3.1 (packages "bkmr" and "ggplot2"); $p < 0.05$ (two-tailed) and 95% CIs indicated statistically significant differences.

Results

Characteristics of the study population

Table 1 shows the general characteristics of the 60 study participants, with a mean maternal age of 34.5 ± 5.2 years. The majority of participants had a pre-pregnancy BMI of 23.0 or higher (71.7% vs. 28.3%), had completed high school or higher education (91.7% vs. 8.3%), and there were no smokers in the study. No significant differences in baseline characteristics such as age, BMI and education were observed between the low and high $PM_{2.5}$ concentration groups (Table 1).

$PM_{2.5}$ exposure and urinary metal concentration

The samples were divided into two groups indicating a low and a high exposure to PM, based on the level of $PM_{2.5}$ exposure during the second trimester of pregnancy. The high-exposure PM group showed significantly higher concentrations of $PM_{2.5}$ and PM_{10} compared to the low-exposure PM group. When evaluating the association between $PM_{2.5}$ exposure and 16 heavy metals measured during the second trimester of pregnancy, most showed no significant difference between groups, with only Ni and Zn exhibiting significant differences between the low and high-exposure groups (Table S3).

Elevated blood lipids during pregnancy: associations with urinary metal concentrations and pregnancy complications

In this study, blood lipid concentrations, particularly TC (≥ 200, 87% vs. 13%) and TG (≥ 175, 95.9% vs. 4.1%) levels, were significantly increased in the third trimester of pregnancy (Table 1). Multiple linear regression analysis,

Table 2 Association of single urinary metal concentrations with blood lipid levels

Urinary metal (Ln-μg/g creatine)	3rd Total cholesterol				3rd Triglyceride			
	Unadjusted model		Adjusted model [a]		Unadjusted model		Adjusted model [a]	
	B (SE)	*p-value*	*B* (SE)	*p-value*	*B* (SE)	*p-value*	*B* (SE	*p-value*
Hg	8.04 (9.73)	0.41	4.86 (10.69)	0.65	18.59 (33.12)	0.58	18.59 (33.12)	0.58
V	14.16 (7.89)	0.08	9.73 (8.63)	0.27	-39.02 (29.03)	0.19	-39.02 (29.03)	0.19
Cr	16.42 (9.04)	0.08	13.06 (10.14)	0.21	34.97 (32)	0.28	34.97 (32)	0.28
Mn	10.6 (8.41)	0.21	6.37 (9.62)	0.51	15.43 (27.31)	0.58	15.42 (27.31)	0.57
Ni	26.46 (9.18)	**0.01***	23.02 (10.76)	**0.04***	4.96 (32.6)	0.88	4.96 (32.6)	0.88
Cu	30.09 (13.72)	**0.03***	28.31 (14.77)	0.06	13.27 (45.28)	0.77	13.27 (45.27)	0.77
Zn	16.38 (11.93)	0.18	18.64 (13.59)	0.18	43.62 (38.81)	0.27	43.62 (38.81)	0.27
Sc	26.07 (12.09)	**0.04***	33.05 (13.15)	**0.02***	18.76 (41.71)	0.66	18.76 (41.71)	0.65
Ti	27.91 (13.86)	0.05*	28.24 (16.12)	0.09	5.71 (46.7)	0.90	5.71 (46.7)	0.90
Mo	21.11 (8.44)	**0.02***	25.78 (9.23)	**0.01***	13.87 (28.54)	0.63	13.87 (28.54)	0.63
Cd	6.43 (6.32)	0.31	6.94 (7.29)	0.35	11.92 (20.43)	0.56	11.92 (20.43)	0.56
Sb	12.25 (8.79)	0.17	11.89 (9.58)	0.22	-12.75 (28.95)	0.66	-12.75 (28.94)	0.66
Cs	31.77 (14.3)	**0.03***	34.25 (15.45)	**0.03***	-18.5 (48.1)	0.70	-18.5 (48.1)	0.70
Ba	5.96 (7.36)	0.42	7.27 (9.01)	0.42	28.33 (24.45)	0.25	28.33 (24.45)	0.25
Au	1.1 (4.8)	0.82	5.48 (6.03)	0.37	-10.18 (16.65)	0.54	-10.18 (16.64)	0.54
Pb	13.76 (8.64)	0.12	11.39 (9.8)	0.25	12.07 (32.77)	0.71	-3.48 (36.49)	0.92

[a] Adjusted for normalized Age, BMI, income, educational level, PM 2.5 concentration

* *P*-value indicates below 0.05

Table 3 Association of single urinary metal concentrations with adverse pregnancy outcomes

Urinary metal (Ln-μg/g creatine)	PTB				GDM			
	Crude model[a]		Single model[b]		Crude model[a]		Single model[b]	
	OR (95%CI)	*p-value*	OR (95%CI)	*p-value*	OR (95%CI)	*p-value*	OR (95%CI)	*p-value*
Hg	0.90 (0.29–2.82)	0.86	0.95 (0.28–3.22)	0.93	0.62 (0.23–1.66)	0.34	0.36 (0.09–1.45)	0.15
V	1.22 (0.49–3.08)	0.67	1.55 (0.46–5.22)	0.48	0.59 (0.29–1.21)	0.15	0.48 (0.16–1.41)	0.18
Cr	1.25 (0.48–3.22)	0.65	1.09 (0.34–3.42)	0.89	0.67 (0.32–1.38)	0.28	0.66 (0.25–1.74)	0.40
Mn	0.83 (0.28–2.42)	0.73	0.81 (0.2–3.32)	0.76	0.42 (0.15–1.17)	0.10	0.17 (0.03–1.15)	0.07
Ni	0.98 (0.49–1.98)	0.95	1.21 (0.47–3.12)	0.69	0.68 (0.38–1.2)	0.18	0.67 (0.27–1.62)	0.37
Cu	1.02 (0.19–5.39)	0.98	0.62 (0.04–9.37)	0.73	0.84 (0.19–3.76)	0.82	0.48 (0.08–2.88)	0.42
Zn	1.02 (0.19–5.39)	0.98	1.25 (0.21–7.55)	0.81	2.34 (0.67–8.2)	0.18	1.19 (0.26–5.44)	0.82
Sc	1.52 (0.4–5.8)	0.54	2.26 (0.5–10.16)	0.29	0.42 (0.1–1.7)	0.22	0.22 (0.03–1.83)	0.16
Ti	1.07 (0.21–5.31)	0.94	1.08 (0.14–8.44)	0.94	0.38 (0.09–1.56)	0.18	0.07 (0.00–1.55)	0.09
Mo	1.27 (0.49–3.33)	0.62	1.58 (0.48–5.23)	0.45	0.56 (0.21–1.48)	0.24	0.27 (0.05–1.36)	0.11
Cd	0.53 (0.26–1.12)	0.10	0.41 (0.09–1.81)	0.24	0.94 (0.51–1.72)	0.83	0.73 (0.35–1.5)	0.39
Sb	1.16 (0.42–3.19)	0.77	1.34 (0.35–5.11)	0.67	0.53 (0.21–1.32)	0.17	0.39 (0.11–1.39)	0.15
Cs	1.63 (0.37–7.09)	0.52	1.59 (0.25–9.95)	0.62	0.17 (0.02–1.67)	0.13	0.15 (0.00–6.86)	0.33
Ba	1.08 (0.45–2.57)	0.87	1.01 (0.39–2.58)	0.98	1.35 (0.65–2.81)	0.42	1.19 (0.43–3.28)	0.74
Au	0.86 (0.49–1.54)	0.62	0.75 (0.29–1.91)	0.55	1.22 (0.76–1.94)	0.42	1.39 (0.64–3.03)	0.40
Pb	2.04 (0.58–7.17)	0.27	1.56 (0.45–5.47)	0.48	0.81 (0.39–1.66)	0.56	0.72 (0.27–1.94)	0.52

[a] Crude model was represented by crude odds ratio (OR) with 95% confidence interval (CI)

[b] Single model was adjusted for normalized Age, BMI, income, educational level, PM 2.5 concentration

adjusted for potential covariates, identified Ni, Sc, Mo, and Cs as significantly associated with increased TC levels in the third trimester. However, maternal urinary metal concentrations did not correlate with increased blood TG levels (Table 2). Additionally, multivariable logistic regression analysis revealed no significant differences in urinary metal concentrations between the preterm birth (PTB) and gestational diabetes mellitus (GDM) groups (Table 3).

Multi-metal exposure and dyslipidemia based on BKMR model

The BKMR model was used to determine the overall effect of a mixture of 16 metals (based on urinary concentrations) on blood TC and TG concentrations. All 16 metals were assessed as important elements with posterior inclusion probabilities (PIPs) > 0.5 (Table S4), resulting in a positive combined effect of urinary heavy metal exposure in the second trimester on TC levels in the third trimester (Fig. 1A). Several metals (Mo, Sb, Cs, and Au) show positive correlations with TC, as indicated by the blue lines trending upward toward the right (Fig. 1B). Figure 2A showed the overall risk summary plot, indicating that exposure to TG has a non-linear effect with significant impacts appearing only above a certain threshold (approximately the 0.5 quantile), and higher levels of TG exposure producing stronger positive effects on the outcome variable. The

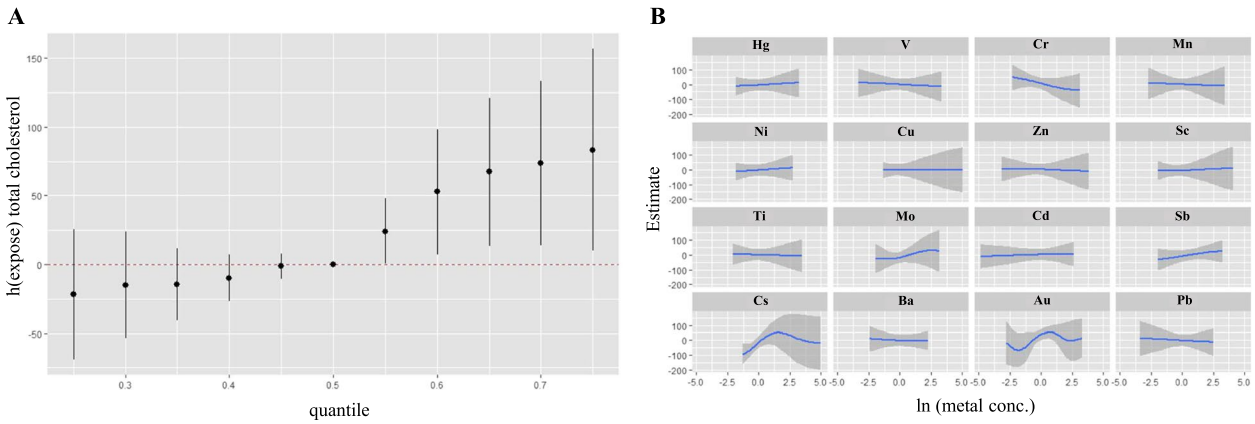


Fig. 1 Correlation of multi-metal concentrations in urine with total cholesterol levels using BKMR model (**A**) The plot represents the estimated joint effects of a latent of triglyceride increase from the median between the 25th and 75th percentiles with 95% confidence intervals (CI). **B** Plots (blue line) show the univariate exposure–response functions with 95% CI (gray region) for exposure to each metal on total cholesterol when other metals were fixed at the median concentration. The model was adjusted for normalized age, body mass index (BMI), income, education level, and particulate matter < 2.5 μm diameter ($PM_{2.5}$) concentration

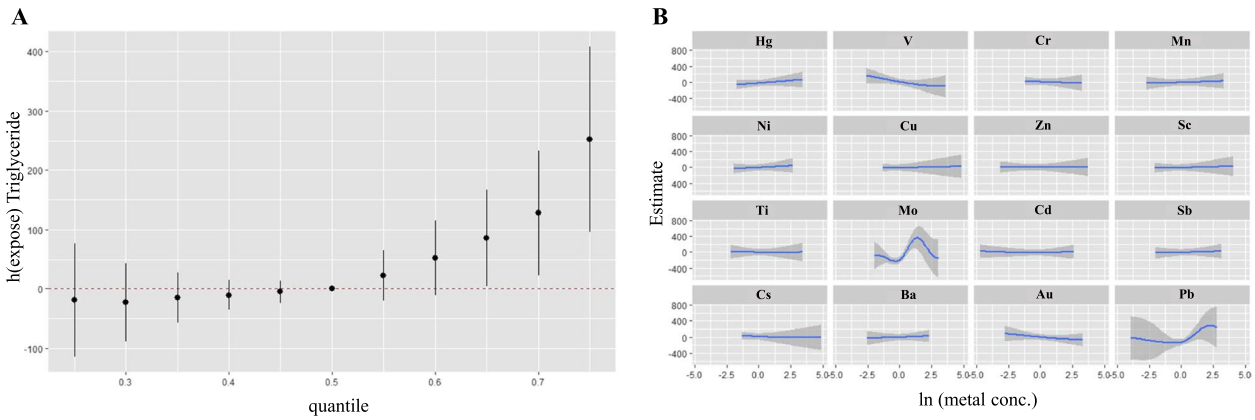


Fig. 2 Correlation of multi-metal concentrations in urine with triglyceride levels using BKMR model (**A**) The plot represents the estimated joint effects of a latent of triglyceride increase from the median between the 25th and 75th percentiles with 95% confidence intervals (CI). **B** Plots (blue line) show the univariate exposure–response functions with 95% CI (gray region) for exposure to each metal on triglycerides when other metals were fixed at the median concentration. The model was adjusted for normalized age, BMI, income, education level, and $PM_{2.5}$ concentration

strong non-linear relationships exhibited by Mo and Pb, suggesting significant effects above certain concentration thresholds, while most other metals show more reliable estimates within the ln (metal conc.) range of -2.5 to 2.5 (Fig. 2B).

Multi-metal exposure and PTB based on BKMR model

A BKMR model with component-wise variable selection and hierarchical variable selection was implemented for the latent continuous binary outcome of PTB and GDM to identify the important elements of all multi-metal exposures and to estimate the potential non-linear correlation between urinary multi-metals and adverse pregnancy outcomes. With respect to PTB outcomes, we preliminarily selected 12 important metals by component-wise variable selection (PIP > 0.5; Fig. 3A) and then further analyzed the 12 metals determined by hierarchical variable selection for those at high risk of PTB [Hg and Cs: conditional posterior inclusion probability (condPIP) > 0.5] (Table S4). However, the cumulative exposure–response functions showed that the joint effects of the 16 urinary multi-metals exposures on PTB were not significant. Compared with when all metals were at their median values, a positive trend was observed when all metal exposures were in the lower quantiles, but no overall effect on PTB was observed when all metal exposures were at the higher quantiles (Fig. 3B).

Discussion

This study used logistic regression analysis and BKMR models to identify associations between maternal exposure to 16 metals during pregnancy (based on urine concentrations) and higher lipid concentrations. Logistic regression analysis showed that maternal metal exposure, particularly concentrations of Ni, Sc, Mo, and Cs, were associated with increased levels of TC in the maternal blood. Maternal Ni exposure can impair the activities of lipid metabolites, such as the anti-migratory ability of lyso-phosphatidylcholine in blood vessels, which may cause PTB [21, 27, 28]. However, no heavy metals were associated with PTB. Therefore, we applied the BKMR method to assess the health effects of multi metal exposure during pregnancy. The BKMR model revealed that the entire 16-metal mixture may contribute to increased maternal TC and TG concentrations during pregnancy, and a trend toward PTB was also identified.

The individual effects of heavy metals and other environmental pollutants and chemicals are typically evaluated using traditional logistic regression models to assess health effects. However, because people are exposed to multiple environmental contaminants simultaneously, it is a more reasonable approach to analyze the cumulative effects of multiple metal exposures with the BKMR model than with a single contaminant analysis model. The BKMR model used in this study revealed a positive combined effect of 16-metal mixture on high blood TC and TG levels in pregnant women that could not be obtained with a logistic regression model. While the study did not provide clear evidence that multiple metal mixtures act as a risk factor for PTB, the BKMR model did reveal an association between multiple metal exposures during pregnancy and maternal hyperlipidemic profile, a well-known risk factor for PTB.

While BKMR has many advantages, such as the ability to handle high-dimensional data and accommodate non-linear relationships, it also has limitations in our study context. With only 60 observations and few PTB and GDM cases (7 and 11, respectively), using 16 metal

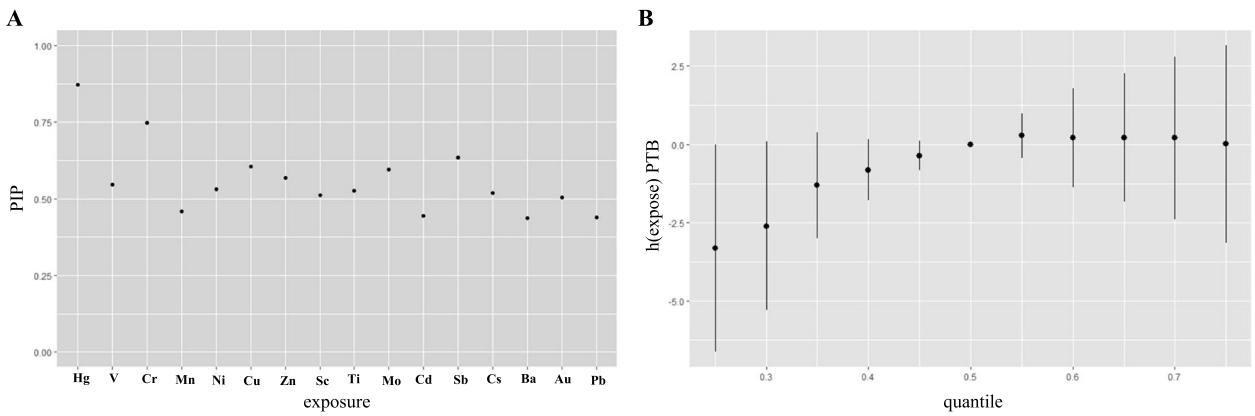


Fig. 3 Overall effects of multi-metal exposures in urine and PTB using BKMR model (**A**) PIP > 0.5 indicate the importance of each exposure metal. **B** The plot represents the estimated joint effects in a latent probability of preterm birth from the median between the 25th and 75th percentiles with 95% CI. The model was adjusted for normalized age, body mass index (BMI), income, education level, and particulate matter < 2.5 μm diameter ($PM_{2.5}$) concentration

parameters plus confounders creates a risk of overfitting. This can make it difficult to distinguish real associations from noise in the data. Bayesian methods like BKMR can technically estimate models with more parameters than observations, but the results should be interpreted with caution. This study considered the balance between model flexibility and parsimony but acknowledges that this remains a methodological challenge [29]. Future studies with larger sample sizes or focused on a subset of the most biologically relevant metals may provide more robust findings. We believe the exploratory value of our approach outweighs these limitations, as it identifies potential non-linear relationships that merit further investigation.

There were a few limitations to this study. First, the study population of 60 pregnant women included 7 pregnant women with PTB and 11 pregnant women with GDM, which is a small number to analyze the effect of multiple metal exposures on pregnancy outcomes. This may have contributed to the uncertain results on the association between urinary metal mixture concentrations and PTB. Second, high-density lipoprotein (HDL), low-density lipoprotein (LDL), TC, and TG concentrations in the blood of pregnant women are important risk factors for PTB [30]. However, the study was unable to assess LDL and HDL levels of cholesterol in relation to metal exposure or pregnancy complications because more than 50% of the data were missing. Third, metals in urine are typically unstable and have short half-lives, which can lead to unreliable results because they are subject to high uncertainty and result in value that cannot be the cumulative exposure during pregnancy [31, 32]. Therefore, future studies should consider a larger population with repeated measurements of urinary metal concentrations. Furthermore, several studies have indicated that maternal diet is a potential factor that can affect metal concentrations in women of reproductive age [33–35]. Unmeasured confounders, such as dietary information, require further consideration, as maternal diet may have influenced maternal metal exposure in this study.

Conclusion

Our study showed the importance of applying BKMR analysis to assess pregnancy health effects of multi-pollutant exposure. A multi-pollutant model using the BKMR analysis provided the evidence of the correlation between metal mixtures and pregnancy health effects, such as dyslipidemia, which can cause PTB during pregnancy. This study may help to analyze the maternal health effects of multiple environmental pollution exposures. Future research is needed to investigate the exact mechanisms for the observed associations.

Abbreviations

APPO	Air pollution on pregnancy outcome
BKMR	Bayesian kernel machine regression
BMI	Body mass index
CI	Confidence interval
DMA	Dynamic mechanical analyzer
GDM	Gestational diabetes mellitus
HDL	High-density lipoprotein
ICP-MS	Inductively coupled plasma mass spectrometer
LDL	Low-density lipoprotein
LOD	Limits of detection
PIP	Posterior inclusion probabilities
PM_{10}	Particulate matter with an aerodynamic diameter < 10 μm
$PM_{2.5}$	Particulate matter with an aerodynamic diameter < 2.5 μm
PN	Particulate matter
PTB	Preterm birth
SD	Standard deviation
TC	Total cholesterol
TG	Triglyceride

Supplementary Information

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Supplementary Material 1. Figure 1. Study flow diagram showing the study plan.

Supplementary Material 2.

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Authors' contributions

YYG, YMH, and YAY designed the study concept and methodology; YYG, GL, SMK and RC performed the statistical analysis and visualization; YYG and SWP interpreted and analyzed the data; YYG wrote the manuscript; YJK supervised the study.

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Data availability

All the data from this study are included in the published article and supplementary information files.

Declarations

Ethics approval consent to participate

All study participants provided written informed consent. The present study was approved by the ethics committees of the institutional review boards of the participating hospitals [Ewha Womans University Mokdong Hospital (EUMC 2021–04-032), Yonsei University Severance Hospital (4–2021-0414), Kangwon National University Hospital (KNUH-B-2021–04-012–008), Keimyung University Dongsan Medical Center (2021–04-073), Korea University Guro Hospital (2021GR0233), Ewha Womans University Seoul Hospital (2021–04-022), and Ulsan University Hospital (2022–04-020)].
Written informed consent for participation was obtained.

Consent for publication
All data are de-identified and no individual data are included.

Competing interests
The authors declare no competing interests.

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