Clinical Nutrition 42 (2023) 1875–1888

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Original article

Hair and cord blood element levels and their relationship with air pollution, dietary intake, gestational diabetes mellitus, and infant neurodevelopment

Yin-Yin Xia [a, b, c, 1], Jamie V. de Seymour [d, 1], Xiao-Jia Yang [b, 1], Lin-Wei Zhou [a, 1], Yue Liu [a, b, c], Yang Yang [a, c], Kathryn L. Beck [d], Cathryn A. Conlon [d], Toby Mansell [e, f], Boris Novakovic [e, f], Richard Saffery [e, f], Ting-Li Han [c, g, h, **], Hua Zhang [a, c, *], Philip N. Baker [i]

[a] Department of Obstetrics and Gynaecology, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China
[b] Department of Occupational and Environmental Hygiene, School of Public Health, Research Center for Medicine and Social Development, Innovation Center for Social Risk Governance in Health, Chongqing Medical University, Chongqing, China
[c] Mass Spectrometry Center of Maternal Fetal Medicine, Chongqing Medical University, Chongqing, China
[d] School of Sport, Exercise and Nutrition, College of Health, Massey University, Auckland, New Zealand
[e] Molecular Immunity, Murdoch Children's Research Institute, Melbourne, VIC, Australia
[f] Department of Paediatrics, University of Melbourne, Melbourne, VIC, Australia
[g] Department of Obstetrics and Gynaecology, The Second Affiliated Hospital of Chongqing Medical University, Chongqing, China
[h] Institute of Life Sciences, Chongqing Medical University, Chongqing, China
[i] College of Life Sciences, University of Leicester, Leicester, United Kingdom

A R T I C L E I N F O

Article history:
Received 9 April 2023
Accepted 10 August 2023

Keywords:
Hair elements
Inductively coupled plasma-mass spectrometry
Gestational diabetes mellitus
Infant neurodevelopment
Air pollutant exposures
Maternal diet

S U M M A R Y

Background & aims: Exposure to a range of elements, air pollution, and specific dietary components in pregnancy has variously been associated with gestational diabetes mellitus (GDM) risk or infant neurodevelopmental problems. We measured a range of pregnancy exposures in maternal hair and/or infant cord serum and tested their relationship to GDM and infant neurodevelopment.
Methods: A total of 843 pregnant women (GDM = 224, Non-GDM = 619) were selected from the Complex Lipids in Mothers and Babies cohort study. Forty-eight elements in hair and cord serum were quantified using inductively coupled plasma-mass spectrometry analysis. Binary logistic regression was used to estimate the associations between hair element concentrations and GDM risk, while multiple linear regression was performed to analyze the relationship between hair/cord serum elements and air pollutants, diet exposures, and Bayley Scales of infant neurodevelopment at 12 months of age.
Results: After adjusting for maternal age, BMI, and primiparity, we observed that fourteen elements in maternal hair were associated with a significantly increased risk of GDM, particularly Ta (OR = 9.49, 95% CI: 6.71, 13.42), Re (OR = 5.21, 95% CI: 3.84, 7.07), and Se (OR = 5.37, 95% CI: 3.48, 8.28). In the adjusted linear regression model, three elements (Rb, Er, and Tm) in maternal hair and infant cord serum were negatively associated with Mental Development Index scores. For dietary exposures, elements were positively associated with noodles (Nb), sweetened beverages (Rb), poultry (Cs), oils and condiments

Abbreviations: BMI, Body mass index; BSID, Bayley scales of infant development; CI, Confidence interval; CLIMB, Complex lipids in mothers and babies; FDR, False discovery rate; FFQ, Food frequency questionnaire; GDM, Gestational diabetes mellitus; ICP-MS, Inductively coupled plasma mass spectrometry; LUR, Land use regression; MDI, Mental development index; OGTT, Oral glucose tolerance test; OR, Odds ratio; PDI, Psychomotor development index; VIF, variance inflation factor; PM, Particulate matter; Li, Lithium; Be, Beryllium; B, Boron; Na, Sodium; Mg, Magnesium; Al, Aluminum; Si, Silicon; P, Phosphorus; S, Sulfur; K, Potassium; Ca, Calcium; Sc, Scandium; Ti, Thallium; V, Vanadium; Cr, Chromium; Mn, Manganese; Fe, Iron; Co, Cobalt; Ni, Nickel; Cu, Copper; Zn, Zinc; Ga, Gallium; Ge, Germanium; As, Arsenic; Se, Selenium; Rb, Rubidium; Sr, Strontium; Y, Yttrium; Zr, Zirconium; Nb, Niobium; Mo, Molybdenum; Ag, Silver; Cd, Cadmium; Cs, Cesium; Ba, Barium; La, Lanthanum; Ce, Cerium; Pr, Praseodymium; Nd, Neodymium; Sm, Samarium; Eu, Europium; Gd, Gadolinium; Tb, Terbium; Dy, Dysprosium; Ho, Holmium; Er, Erbium; Tm, Thulium; Yb, Ytterbium; Lu, Lutetium; Hf, Hafnium; Ta, Tantalum; W, Wolfram; Re, Rhenium; Hg, Hydrargyrum; Pb, Lead; Th, Thorium; U, Uranium.

* Corresponding author. Department of Obstetrics and Gynaecology, The First Affiliated Hospital of Chongqing Medical University, Chongqing, 400016, China.
** Corresponding author. Department of Obstetrics and Gynaecology, The Second Affiliated Hospital of Chongqing Medical University, Chongqing, 400016, China.
E-mail addresses: tinglihan@cqmu.edu.cn (T.-L. Han), zh2844@gmail.com (H. Zhang).
[1] These authors share first authorship.

https://doi.org/10.1016/j.clnu.2023.08.009

(Ca), and other seafood (Gd). In addition, air pollutants PM2.5 (LUR) and PM10 were negatively associated with Ta and Re in maternal hair.

Conclusions: Our findings highlight the potential influence of maternal element exposure on GDM risk and infant neurodevelopment. We identified links between levels of these elements in both maternal hair and infant cord serum related to air pollutants and dietary factors.

1. Introduction

Exposomics is a field of research investigating cumulative chemical and non-chemical exposures throughout an individual's life [1]. Exposures to environmental pollutants, diet, and other lifestyle factors can be involved in the development and progression of diseases. Such exposure may also influence pregnancy outcomes and lead to long-term adverse consequences for maternal and infant health.

Gestational diabetes mellitus (GDM) is the most prevalent metabolic disorder during pregnancy, affecting 12.8–16.7% of all pregnancies in mainland China [2]. Epidemiological evidence suggests that exposure to GDM in utero not only increases the incidence of diabetes and metabolic disorders in later life [3], but also elevates the risk of impaired neurodevelopment in the offspring [4]. Children born to mothers diagnosed with GDM exhibited higher inattention scores, poor social competence, lower working memory, inadequate motor skills, and spatial impairment [5–8].

Recent epidemiological studies have reported associations between air pollution exposure with the development of GDM and infant neurodevelopment [9–11]. Air pollution is a ubiquitous exposure and is emitted from many sources, such as industrial facilities, cars, and airplanes. The primary forms of measured are pollution include particulate matter (PM10: <10 μm in diameter; PM2.5: <2.5 μm) [12]. Using vital birth statistics records in Florida, USA, Hu et al. observed an association between exposure to PM2.5 with an increased risk of GDM [13]. Moreover, studies have indicated that air pollution exposure is associated with an impairment of the central nervous system as early as in utero and through the first year of life [10,14,15]. Grace et al. found that prenatal exposure to PM10 was associated with poorer neurodevelopment at two years of age, particularly in language, cognition, and adaptive behavior [15]. Therefore, evidence suggests that air pollution exposure during pregnancy is a potential risk factor for GDM development and impairments in offspring neurodevelopment.

Maternal diet is another widely accepted factor contributing to GDM manifestation and infant neurodevelopment. Several cohort studies have shown that a maternal diet rich in fruits, vegetables, legumes, and whole grains significantly decreased the risk of GDM, whereas a diet characterized by high intakes of red meat and processed meats was associated with an elevated risk of GDM [16–18]. Other studies have also reported that maternal nutrient deficiencies significantly elevated the offspring's risk for impaired neurodevelopment [19,20]. Numerous studies from both human and rodent models have reported that maternal high-fat diets aberrantly influence the neurodevelopment of their offspring [21–25]. Recently, our published work observed that higher scores on a dietary pattern characterized by high intakes of pasta, sweetened beverages, oils and condiments, were associated with lower infant Psychomotor Development Index (PDI) scores on the Bayley scales of Infant development at 12 months of age [26]. Studies have also found that prenatal exposure to mercury (Hg) during pregnancy, which can accumulate in fish and seafood, was associated with impaired infant neurodevelopment [27–29]. Thus, maternal diet and air pollution exposure are two modifiable external exposures that may be involved in the development of GDM and impaired infant neurodevelopment.

Exposure to certain elements is associated with the development of GDM and impaired infant neurodevelopment [30,31]. Findings from clinical studies have highlighted associations between Hg, cadmium (Cd), sodium (Na), and arsenic (As) levels in maternal blood, urine, umbilical cord blood, and meconium with an increased risk of GDM [32–35]. For example, Rezaei et al. found that higher levels of As, Cd, and Hg in maternal serum were associated with an increased risk of GDM [36]. Another study reported that maternal urinary thallium (Tl) levels were higher in women who developed GDM [37]. Importantly, many elements can cross the placental barrier to the fetus [38]. Gestation is a crucial period for fetal brain development. Some elements may adversely impact fetal neurodevelopment as they have a high affinity for competing transporters used by essential elements [39]. Prenatal exposures to Hg, Cd, and Pb have also been shown to disrupt the development of the fetal nervous system, which can have long-term consequences on the child's cognitive and motor abilities, and behaviors [40–42].

Several studies have utilized hair as a robust biological specimen to reflect the long-term exposure of elements in pregnancy and linked these findings to the development of GDM and infant neurodevelopment. Previous studies have reported that high levels of Hg and Sn in maternal hair were associated with an increased risk of GDM [43,44], whereas others found maternal Hg exposure associated with offspring neurodevelopment [45–47]. Moreover, several studies have reported that elevated umbilical cord blood Hg, lead (Pb), and manganese (Mn) concentrations were associated with gross motor development delay and cognitive deficits during infancy [48–50]. Although elemental studies concerning GDM and infant neurocognition have progressed, they are still limited. Blood and urine were commonly explored to measure trace element exposure but results are generally inconsistent, possibly due to the transient nature of the biological specimens analyzed [51,52]. Hair, on the other hand, grows at a relatively constant rate (10–12 mm per month) during pregnancy, making it a robust biological specimen to reflect longer-term exposure [53,54].

However, no study to date has combined data on exposure to air pollutants, diet, and elements during pregnancy to evaluate their association with GDM risk and infant neurodevelopment. Therefore, this study aimed to combine exposomics and elementomics to investigate: (1) possible associations of maternal hair elements with the risk of GDM and infant neurodevelopment at one year of age; (2) possible associations of infant cord blood elements and infant neurodevelopment at one year of age; (3) whether the changes in maternal hair elements related to GDM and neurodevelopment are related to external exposures such as air pollutants and maternal diet.

2. Methods

2.1. Study population

Participants in this study were from The Complex Lipids in Mothers and Babies (CLIMB) study, established in Chongqing, China, during 2015–2017 (Chinese Clinical Trial Register number: ChiCTR-IOR-16007700). Detailed information about the CLIMB study has been published previously [55]. Women were first enrolled in the CLIMB study at the First Affiliated Hospital of Chongqing Medical University and Chongqing Health Centre for Women and Children during their clinic visit between 11 and 14 gestational weeks (according to ultrasound-confirmed dating). A total of 1500 women in early pregnancy participated in the CLIMB study. The CLIMB inclusion criteria were: (1) Agreed to participate in the study; (2) Aged from 20 to 40 years; (3) Had a singleton pregnancy; (4) No previous history of diabetes. For this study, we excluded 608 women without hair samples (n = 272), sufficient hair (weight<3.5 mg) (n = 296), dietary questionnaires (n = 21) or air pollution exposure data (n = 19). A total of 49 mothers who were lost to follow-up were also excluded. The current study thus included 843 mothers (224 women with GDM diagnosed according to the International Association of Diabetes and Pregnancy Study Group (IADPSG) Guidelines and 619 women without GDM) with available early pregnancy hair samples who had completed dietary questionnaires and had available air pollution exposure data (Fig. 1). From these 843 pregnancies, 116 umbilical cord blood samples were collected. Neurocognitive development data was available for 694 infants (Bayley Scales of Infant Development [Psychomotor Development Index (PDI) and Mental Development Index (MDI)] available at 12 months). Written informed consent was obtained from all study participants for any data and sample collection and use. All study protocols were reviewed and approved by the Ethics Committee of Chongqing Medical University (No.2014034). In this study, all procedures performed were in full agreement with the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice E6 (ICH-GCP).

2.2. Chemicals and reagents

Analytical and internal standards were purchased from Agilent Technologies. ICP-MS-grade nitric acid (65%) and acetone were obtained from ANPEL Laboratory Technologies (Shanghai, China). Ultrapure deionized water (18 mΩ) was obtained from a water purification system (Aoside, China). A calibration standard solution was prepared by diluting 10 μg/mL of mixed-element standard solutions (Multi-element Calibration Standard 2 A: Ag, Al, As, Ba, Be, Ca, Cd, Co, Cr, Cs, Cu, Fe, Ga, K, Li, Mg, Mn, Na, Ni, Pb, Rb, Se, Sr, Tl, U, V, Zn; Multi-element Calibration Standard 4: B, Ge, Mo, Nb, P, Re, S, Si, Ta, Ti, W, Zr; Multi-element Calibration Standard 1: Ce, Dy, Er, Eu, Gd, Ho, La, Lu, Nd, Pr, Sc, Sm, Tb, Th, Tm, Y, Yb; Agilent; USA) or a single-element standard solution (Multi-element Calibration Standard 2 A-HG: Hg; Agilent; USA). Two sets of standard solutions for calibration curves were prepared by diluting in 5% HNO_3. The first standard solution contained all the purchased elements (except Hg, ≤2500 μg/L), and the second contained only Hg (≤2.5 μg/L). A bulk standard containing all quantified elements was prepared and aliquoted this into 20 identical sets as quality control samples. An instrumental internal standard solution was also prepared by diluting 100 μg/mL of standard solution (ICP-MS Internal Standard Mix: Bi, Ge, In, Li, Lu, Rh, Sc, Tb; Agilent; USA) in 5% HNO_3 (ICP-MS Internal Standard Mix: 5% HNO_3 = 1: 200).

2.3. Hair and cord blood collection and inductively coupled plasma-mass spectrometry analysis

Maternal hair strands were collected at the first clinic visit (11–14 weeks of gestation) and were taken from the occipital area, 0.5 cm away from the scalp. The hair samples were stored in aluminum foil in a self-sealing bag at −20 °C. Hair segments were cut based on the method published by Delplancke et al. [56]. The samples from the scalp-end of the hair (0–3.6 cm) were collected and analyzed to represent early pregnancy. Trained nurses collected cord blood samples from the participants' umbilical cords into serum separator vacutainer tubes containing separator gel at delivery time. The tubes were centrifugated twice using the following procedure: 3000 rpm at 4 °C for 10 min, and 4000 rpm at 4 °C for another 10 min. The supernatant was transferred into cryotubes (Micronic, Lelystad, Netherlands), and then stored at −80 °C until analysis.

The hair segments were washed once with 18 mΩ deionized water for 10 min and then two times with acetone for 10 min prior

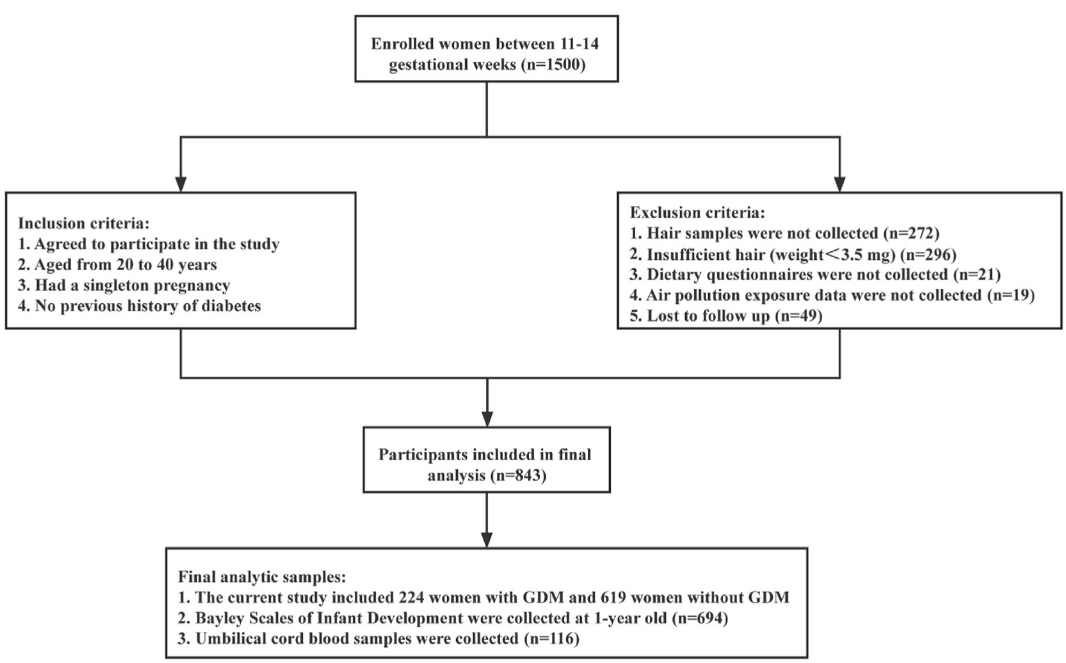

Fig. 1. Flowchart of study participants.

to drying in a draught oven (Heratherm Oven, Thermo Scientific). After washing, the hair sample was weighed (4 mg ± 0.5 mg), placed into 15 mL polytetrafluoroethylene digestion tubes, and added 200 μL of concentrated nitric acid (65%). For the cord serum samples, a 100 μL aliquot of each sample was mixed with 200 μL of concentrated nitric acid (65%) in 15 mL polytetrafluoroethylene digestion tubes. Then, tubes were capped, and the samples were microwave digested for 30 min. After the samples had dissolved, they were made up to a volume of 3 mL with 18 mΩ deionized water and were transferred to 15 mL centrifuge tubes.

Forty-eight elements were analyzed in the digested hair and cord serum samples (Fig. S1) by inductively coupled plasma-mass spectrometry (ICP-MS, Agilent 8900, USA) using helium mode. The system generates a high-force vacuum environment (6.79×10^{-4} Pa); radio-frequency (RF) power: 1550 w, RF matching: 1.80 V, sampling depth: 10 mm, nebulizer gas flow: 1.05 L/min, peristaltic pump speed: 0.1 rps, atomization chamber temperature: 2 °C. All digested hair samples, cord serum samples, and calibration standards were injected using a SPS 4 autosampler (Agilent Technologies). The instrumental internal standard solution was jointly analyzed with injected samples by a peristaltic pump to monitor the precision of the ICP-MS.

2.4. Data collection for air pollutants, maternal dietary patterns, and infant neurodevelopment assessment

Air pollution exposure data were collected from 21 air quality monitoring stations in the main urban area of Chongqing. The data were gained from the reports published by the Chongqing Ecological Protection Bureau between 2015 and 2017. The indicators of air quality included particulate matter less than 2.5 μm in diameter (PM2.5) and less than 10 μm in diameter (PM10). In this study, we selected air pollution exposure data from the first trimester for analysis, and have used two methods, namely proximal and land use models, to estimate the amount of maternal exposure during pregnancy. With regards to the proximal model, the exposures were calculated as daily concentrations averaged over each trimester [57]. Meanwhile, we also used land use regression (LUR) models to estimate the PM2.5 exposure of our study population [58]. Furthermore, participants did not change their addresses during the study period.

At the end of the first trimester of pregnancy, participants completed a 96-item food frequency questionnaire (FFQ), which reflected maternal dietary intake over the three months prior. This FFQ was an adaptation based on the FFQ used in the S-PRESTO study to suit pregnant women in Chongqing [59]. The 96 items were condensed into 28 food groups based on food groupings previously published in studies of pregnant Chinese women [60,61]. These food groups were used in a principal components analysis to derive dietary patterns consumed in the cohort [26]: two main dietary patterns were derived – a pattern high in fish, poultry, and vegetable intake (FPV-based dietary pattern) and a pattern high in pasta, sweetened beverages, oils and condiments (PSO-based dietary pattern). Using the regression method, all study participants received a score for each dietary pattern.

Of 843 singleton live births, 694 infants underwent neurodevelopment assessment between 11.5 and 12.5 months of age using the Chinese version of the Bayley Scales of Infant Development (BSID), which resulted in scores on two main indices: psychomotor development index (PDI) and mental development index (MDI) [62]. The PDI component comprised 81 items that assessed fine and gross motor skills. The MDI component included 163 items that assessed cognitive functioning, language development, and personal and social development. The raw scores were transformed into standardized scores using the norms for the Chinese population [62]. The standardized index scores were categorized into the following subgroups (0–69: poor, 70–79: borderline, 80–89: low average, 90–109: average, 110–119: high average, 120–129: excellent, ≥130: very excellent) [63].

2.5. Clinical outcomes and covariates

Maternal clinical information was collected at enrollment using a structured questionnaire, including maternal age, body mass index (BMI), smoking status, alcohol consumption, primiparity, previous miscarriage, marital status, ethnicity, household income, occupation, and total years of schooling (Table 1). Infant gestational age at delivery, birthweight, and Apgar score for 1 min were collected at birth (Table S1). Plasma glucose was measured during a 75-g oral glucose tolerance test (OGTT) conducted between 22 and 28 weeks gestation. The diagnosis of GDM was performed according to the IADPSG guidelines. Participants were diagnosed with GDM if they met one or more of the following criteria: fasting plasma glucose (FG) ≥5.1 mmol/L, 75-g 1 h OGTT ≥10.0 mmol/L, 75-g 2 h OGTT ≥8.5 mmol/L.

2.6. Statistical analysis

The data distribution was evaluated by inspecting P–P plots and Shapiro–Wilk W test results. All element concentrations were naturally log-transformed before statistical analysis as they had skewed distributions. Baseline characteristics of participants with and without GDM were compared using the Mann–Whitney U test for continuous variables. χ^2 Test or Fisher's exact test was used for categorical variables. Binary logistic regression analyses with adjustment for confounders (age, BMI, and primiparity) were performed to compare the differences in elements between women with GDM and controls. Multivariate linear regression with adjustment for confounders (GDM, age, BMI, infant gestational age at delivery, birthweight, and Apgar score for 1 min) was used to analyze associations of maternal hair elements and cord serum elements with infant neurodevelopment scores. Multivariate linear regression with adjustment for confounders (age and BMI) was performed to analyze the relationship between air pollutants, food groups, dietary pattern scores, and hair or cord serum elements. In addition, Pearson's correlation was used to study the association between significant elements and air pollutants. False discovery rates (FDR) were calculated based on the Benjamini-Hochberg process using the q-value R package [64] for accounting for multiple comparisons. P-values <0.05 and q-values (FDR) < 0.05 were considered statistically significant. All statistical analyses were performed using SPSS software (version 23.0). The periodic table of elements, percentage plot of standardized score areas for PDI and MDI, and linear association bar chart were illustrated using Microsoft Excel (version 2019). Forest plots, fold change, boxplots, linear association matrix graphs, and Pearson's correlation shadow graph were constructed using the ggplot 2 R package [65].

3. Results

3.1. Study participant characteristics

The demographic and clinical characteristics of the 843 participants are described in Table 1. Compared with the Non-GDM group, the women with GDM were older and had a higher BMI ($p < 0.05$). Additionally, primiparity was lower in the GDM group ($p < 0.05$). No significant differences were observed between the GDM and Non-GDM groups for smoking, alcohol consumption, history of previous miscarriage, marital status, ethnicity, income group, occupation, and educational attainment ($p > 0.05$).

Table 1
Demographic and clinical characteristics of study participants.

	GDM (n = 224)	Non-GDM (n = 619)	*P* value
Age (years)	29 (27, 32)	28 (26, 30)	0.004**
BMI (kg/m²)	22.0 (20.0, 24.1)	20.9 (19.3, 22.7)	< 0.001***
75-g OGTT (mmol/l)			
Fasting blood glucose (mmol/l)	5.1 (4.7, 5.3)	4.6 (4.4, 4.8)	< 0.001***
75-g 1 h OGTT (mmol/l)	9.6 (8.6, 10.4)	7.2 (6.4, 8.3)	< 0.001***
75-g 2 h OGTT (mmol/l)	8.5 (7.4, 9.2)	6.7 (6.0, 7.3)	< 0.001***
Smoking and/or drinking, n (%)			0.58
YES	0 (0)	4 (0.6)	
NO	224 (100)	615 (99.4)	
Primiparity, n (%)			0.007**
YES	160 (71.4)	496 (80.1)	
NO	64 (28.6)	123 (19.9)	
Miscarriages, n (%)			0.41
YES	100 (44.6)	296 (47.8)	
NO	124 (55.4)	323 (52.2)	
Marriage, n (%)			0.89
YES	221 (98.7)	608 (98.2)	
NO	3 (1.3)	11 (1.8)	
Han nationality, n (%)			0.88
YES	220 (98.2)	605 (97.7)	
NO	4 (1.8)	14 (2.3)	
Income groups, n (%)			0.83
<2000 ¥ /month	48 (21.4)	119 (19.2)	
<4000 ¥ /month	83 (37.1)	232 (37.5)	
<7000 ¥ /month	69 (30.8)	190 (30.7)	
<10,000 ¥ /month	24 (10.7)	78 (12.6)	
Occupation, n (%)			0.34
Full time work	50 (22.3)	129 (20.8)	
Part time work	119 (53.1)	306 (49.4)	
Student	55 (24.6)	184 (29.7)	
Educational years	16 (15, 16)	16 (15, 16)	0.40
Bayley Scales of Infant Development	**GDM (n = 182)**	**Non-GDM (n = 512)**	
Psychomotor Development Index	86 (77, 98)	86 (77, 95)	0.72
Mental Development Index	94 (83, 105)	97 (84, 107)	0.20

The values are represented as the median with IQR (interquartile range) or n (%).
P values are for statistical comparison between the two groups (Mann–Whitney U test, Chi-square test, or Fisher's exact test).
P values is significant at $p < 0.05$; ***$p < 0.001$, **$p < 0.01$.
BMI–body mass index; GDM-gestational diabetes mellitus; OGTT-oral glucose tolerance test.

Moreover, scores on the infant neurodevelopment indices were not significantly different between the two groups ($p > 0.05$). However, there was a higher proportion of low MDI standardized scores (<70) in the GDM group (Fig. 5C). Subsequent logistic regression models included maternal age, BMI, and primiparity as confounders.

3.2. Hair elementomics profiling

Out of the total 57 elements measured, forty-eight were quantitatively detected, including four alkali metals, four alkaline earth metals, thirteen lanthanoids, two actinoids, eighteen transition metals, four post-transition metals, one metalloid, and two non-metal elements (Fig. S1).

3.3. Hair elements associated with GDM development

Eighteen elements were found to be associated with GDM ($p < 0.05$): Ta, Re, Ag, Cs, Tl, Eu, Se, Nb, Th, Na, K, Rb, Gd, Sm, and Al were found in higher concentrations in the hair of women with GDM compared to the Non-GDM group, while Ni, As, and Er, were found in lower concentrations in the hair of GDM cases compared to the Non-GDM group (Table 2). Fourteen elements remained statistically significant after excluding the collinearity (Table S2) and adjusting for multiple comparisons ($q < 0.05$) (Fig. 2A). The most significant of these findings were Ta, Re, and Se, where each one-unit increase in the ln-transformed hair element levels was associated with an 849% [Ta: OR (95% CI) = 9.49 (6.71, 13.42)], 421% [Re: OR (95% CI) = 5.21 (3.84, 7.07)], and 437% [Se: OR (95% CI) = 5.37 (3.48, 8.28)] increase in the odds of developing GDM (Table 2). The odds ratios of all significant elements are displayed in Table 2. In addition, all 14 of the elements showed a positive fold change between the two groups (GDM element concentration/ Non-GDM element concentration), indicating that they are increased in the GDM group (Fig. 2B). The concentrations of the 14 elements in the GDM and non-GDM groups are displayed in Fig. 2C.

3.4. Maternal hair and cord serum elements associated with infant neurodevelopment scores at 12 months

We divided the standardized MDI and PDI scores into seven categories. The percentage of infants with scores in each category is displayed in Fig. 3A and C. As shown in Fig. 3B and D, maternal hair elements were predominantly negatively associated with infant MDI scores. In a model adjusted for confounders, five maternal hair elements were found to have a significant negative association with infant MDI scores at 12 months of age ($q < 0.05$): Na ($\beta = -0.12$; $p = 0.005$, $q = 0.040$), K ($\beta = -0.10$; $p = 0.017$, $q = 0.040$), Rb ($\beta = -0.11$; $p = 0.012$, $q = 0.040$), Er ($\beta = -0.16$; $p = 0.017$, $q = 0.040$), and Tm ($\beta = -0.18$; $p = 0.017$, $q = 0.040$) (Fig. 3B). Furthermore, three infant cord serum elements were also found to be negatively associated with MDI scores in an adjusted model: Rb ($\beta = -0.22$; $p = 0.024$, $q = 0.037$), Er ($\beta = -0.34$; $p = 0.002$, $q = 0.005$), and Tm ($\beta = -0.40$; $p = 0.0001$, $q = 0.001$) (Fig. 3D). The standardized regression coefficients of the linear regression models of infant neurodevelopment with maternal hair elements and infant cord serum elements are displayed in Fig. S2. Moreover, we analyzed the associations between maternal hair elements and

Table 2
Comparison of first trimester hair element concentrations (μg/L) between pregnant women with and without GDM.

Elements	GDM (n = 224)	Non-GDM (n = 619)	OR (95%CI)	*p* value	q value
Na	72.869 (50.805, 180.494)	67.786 (32.510, 132.147)	1.22 (1.06, 1.40)	<0.01**	0.01*
Mg	51.798 (41.551, 71.508)	50.498 (34.874, 63.062)	1.14 (0.92, 1.41)	0.23	0.31
Al	19.461 (13.508, 29.703)	12.802 (11.520, 26.156)	1.47 (1.11, 1.96)	0.01*	0.02*
P	159.401 (145.821, 188.621)	211.967 (180.146, 229.704)	1.21 (0.82, 1.76)	0.34	0.41
K	162.122 (73.742, 220.279)	59.454 (10.937, 113.125)	1.18 (1.04, 1.35)	0.01*	0.03*
Ca	91.689 (63.942, 113.075)	96.211 (77.995, 116.491)	0.88 (0.66, 1.17)	0.39	0.43
Ti	2.415 (1.992, 4.091)	2.112 (0.965, 3.851)	1.04 (0.87, 1.23)	0.70	0.63
V	0.016 (0.012, 0.028)	0.027 (0.014, 0.043)	0.89 (0.75, 1.06)	0.18	0.27
Cr	0.589 (0.325, 0.690)	1.852 (0.469, 8.665)	1.02 (0.85, 1.21)	0.86	0.69
Mn	0.288 (0.232, 0.406)	0.399 (0.308, 0.475)	0.87 (0.73, 1.03)	0.10	0.18
Fe	15.715 (13.615, 25.462)	16.574 (15.240, 88.090)	0.89 (0.70, 1.14)	0.36	0.42
Co	0.008 (0.006, 0.014)	0.015 (0.013, 0.024)	1.07 (0.93, 1.23)	0.37	0.42
Ni	0.348 (0.209, 0.901)	0.430 (0.160, 1.269)	1.20 (1.02, 1.40)	0.03*	0.06
Cu	14.878 (13.000, 16.436)	15.234 (11.930, 25.226)	0.99 (0.71, 1.38)	0.96	0.72
Zn	285.914 (245.006, 359.654)	268.800 (237.356, 382.751)	0.96 (0.68, 1.36)	0.83	0.68
Ga	0.011 (0.005, 0.015)	0.006 (0.005, 0.013)	0.96 (0.85, 1.08)	0.47	0.47
As	0.073 (0.054, 0.107)	0.075 (0.067, 0.088)	1.28 (1.01, 1.64)	0.04*	0.09
Se	0.290 (0.235, 0.336)	0.275 (0.233, 0.307)	5.37 (3.48, 8.28)	<0.001***	<0.001***
Rb	0.064 (0.045, 0.173)	0.056 (0.049, 0.099)	1.28 (1.09, 1.49)	<0.01**	0.01*
Sr	2.145 (1.323, 2.988)	2.316 (1.532, 3.008)	1.01 (0.82, 1.25)	0.93	0.71
Y	0.003 (0.002, 0.006)	0.006 (0.002, 0.013)	1.02 (0.89, 1.16)	0.83	0.68
Zr	0.025 (0.017, 0.033)	0.023 (0.016, 0.027)	0.94 (0.78, 1.14)	0.54	0.52
Nb	0.006 (0.005, 0.010)	0.005 (0.002, 0.005)	1.90 (1.57, 2.31)	<0.001***	<0.001***
Mo	0.031 (0.021, 0.048)	0.034 (0.003, 0.051)	1.13 (0.93, 1.38)	0.21	0.30
Ag	0.086 (0.045, 0.141)	0.035 (0.014, 0.482)	1.88 (1.63, 2.16)	<0.001***	<0.001***
Cd	0.022 (0.014, 0.062)	0.014 (0.013, 0.015)	1.02 (0.89, 1.18)	0.76	0.65
Cs	0.007 (0.003, 0.012)	0.005 (0.001, 0.007)	1.65 (1.32, 2.05)	<0.001***	<0.001***
Ba	1.375 (0.981, 1.707)	1.167 (0.669, 1.223)	1.04 (0.85, 1.26)	0.72	0.64
La	0.005 (0.004, 0.012)	0.006 (0.006, 0.012)	1.11 (0.94, 1.31)	0.23	0.31
Ce	0.011 (0.008, 0.026)	0.011 (0.011, 0.013)	0.99 (0.84, 1.17)	0.91	0.71
Pr	0.002 (0.001, 0.004)	0.002 (0.001, 0.005)	1.12 (0.96, 1.31)	0.16	0.24
Nd	0.004 (0.002, 0.007)	0.008 (0.004, 0.009)	1.06 (0.91, 1.23)	0.46	0.47
Sm	0.002 (0.001, 0.005)	0.002 (0.001, 0.003)	1.13 (1.01, 1.26)	0.04*	0.08
Eu	0.001 (0.001, 0.002)	0.001 (0.0006, 0.001)	1.29 (1.12, 1.49)	<0.001***	<0.001***
Gd	0.002 (0.001, 0.002)	0.002 (0.0004, 0.006)	1.28 (1.09, 1.49)	<0.01**	0.01*
Tb	0.777 (0.417, 0.903)	0.314 (0.047, 0.469)	0.87 (0.74, 1.02)	0.09	0.16
Dy	0.002 (0.002, 0.002)	0.002 (0.001, 0.006)	1.08 (0.95, 1.22)	0.26	0.33
Ho	0.001 (0.001, 0.002)	0.001 (0.001, 0.002)	1.13 (0.99, 1.30)	0.07	0.13
Er	0.001 (0.001, 0.002)	0.002 (0.001, 0.003)	1.20 (1.01, 1.42)	0.04*	0.08
Tm	0.001 (0.001, 0.002)	0.001 (0.001, 0.001)	1.12 (0.97, 1.30)	0.13	0.21
Yb	0.001 (0.001, 0.003)	0.003 (0.002, 0.004)	0.96 (0.81, 1.13)	0.60	0.55
Ta	0.033 (0.023, 0.062)	0.017 (0.015, 0.018)	9.49 (6.71, 13.42)	<0.001***	<0.001***
Re	0.004 (0.003, 0.006)	0.002 (0.002, 0.004)	5.21 (3.84, 7.07)	<0.001***	<0.001***
Hg	0.700 (0.521, 1.006)	0.686 (0.221, 0.702)	1.09 (0.92, 1.29)	0.34	0.41
Tl	0.005 (0.004, 0.006)	0.004 (0.003, 0.005)	1.73 (1.39, 2.16)	<0.001***	<0.001***
Pb	0.307 (0.214, 0.839)	0.469 (0.352, 0.704)	0.94 (0.80, 1.11)	0.45	0.47
Th	0.001 (0.001, 0.002)	0.001 (0.0003, 0.001)	1.33 (1.13, 1.57)	<0.01**	<0.01**
U	0.078 (0.051, 0.086)	0.098 (0.031, 0.126)	1.05 (0.87, 1.27)	0.60	0.55

Data are presented as medians (25th percentile, 75th percentile); the data have been ln-transformed for binary logistic regression.
Binary logistic regression analyses were adjusted for maternal age, BMI, and primiparity.
p values and q values are significant at p, q < 0.05; ***p, q < 0.001, **p, q < 0.01, *p, q < 0.05.
GDM-gestational diabetes mellitus; OR-odds ratio; CI-confidence intervals.

infant cord serum elements using a linear regression model. Twenty-one elements in maternal hair were correlated with twenty-seven elements in infant cord serum, while most were negative linear associations (Fig. S3).

3.5. Associations between maternal hair and cord serum elements of significance and maternal diet

Of the fourteen maternal hair elements significantly associated with GDM, four were also significantly associated with maternal food group consumption (Fig. S4). A negative linear relationship was observed between processed meats and the element Se [β (95% CI) = −0.10 (−0.15, −0.04)] in the adjusted model. Positive linear associations were found between noodle consumption and the element Nb [β (95% CI) = 0.12 (0.03, 0.20)]; sweet beverages and the element Rb [β (95% CI) = 0.06 (0.02, 0.10)]; and poultry and element Cs [β (95% CI) = 0.15 (0.04, 0.26)], in the adjusted model (Table S3).

Of the nine cord serum elements significantly associated with infant neurodevelopment (Fig. 3D), two were positively associated with maternal food group consumption in the adjusted model: oils and condiments and element Ca [β (95% CI) = 0.11 (0.03, 0.18)], and other seafood and element Gd [β (95% CI) = 0.14 (0.04, 0.25)] (Table S4). In addition, a negative association was found between the element Th and the PSO-based dietary pattern, which was reported by de Seymour et al. (2022) to be associated with infants' PDI scores at 12 months of age [adjusted model: β (95% CI) = −0.54 (−0.99, −0.08)] (Table S5).

3.6. Associations between maternal hair and cord serum elements of significance and environmental pollutant exposure

Associations between measured PM and the estimated levels of PM and the significant maternal hair elements are illustrated in Figs. 4 and 5. Ta and Re of the fourteen hair elements significantly

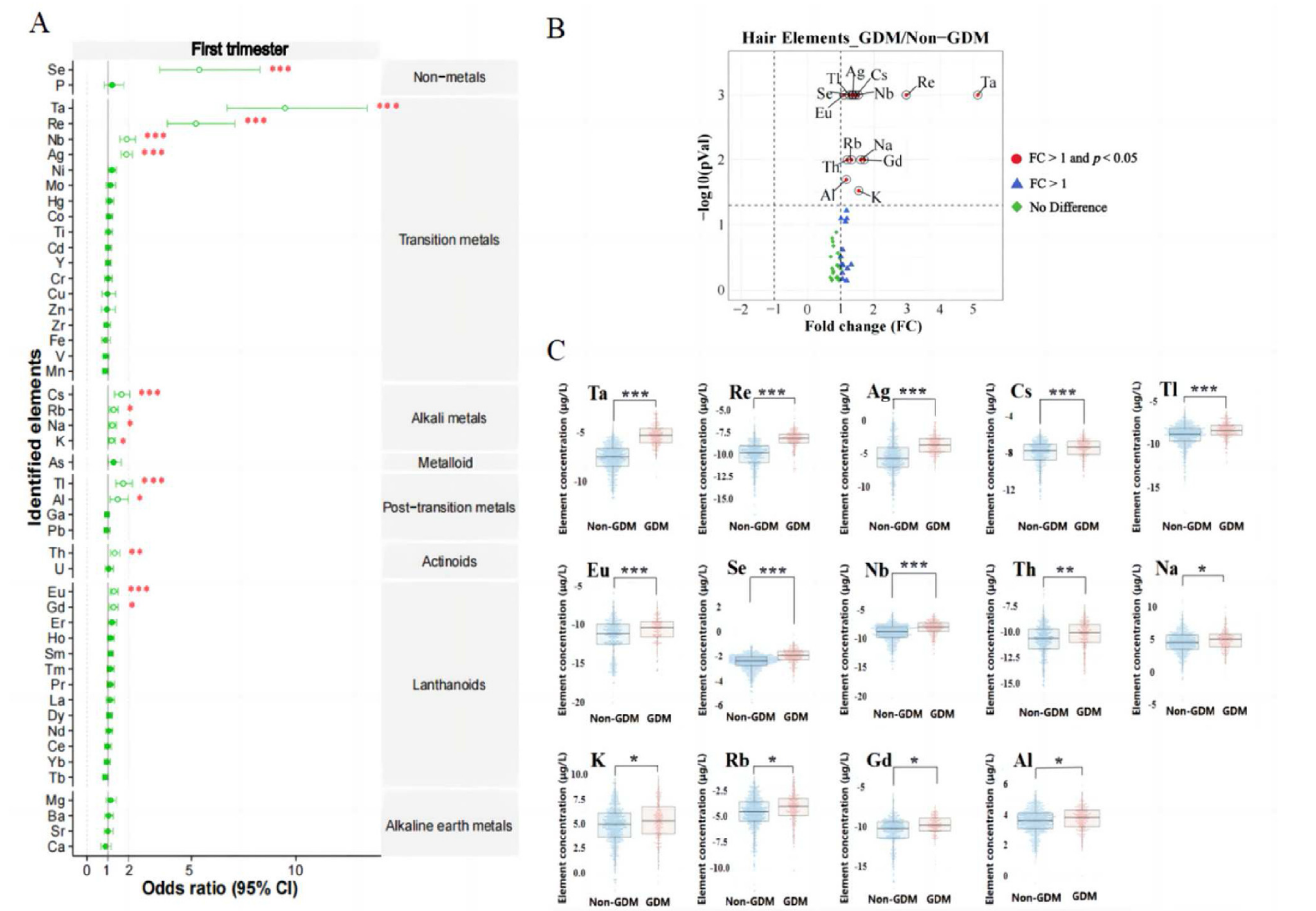

Fig. 2. First trimester hair element exposure and the development of gestational diabetes mellitus. (A) The odds ratios between first trimester hair element concentrations and GDM. A hollow circle represents significant differences. (B) The volcano plot of fold changes to describe quantity changes of hair element concentration between GDM and Non-GDM groups. Fold change = GDM group/Non-GDM group. (C) The concentrations of significant elements in participants with and without GDM. The blue dot and red dot represent the concentrations of each hair sample. ***q < 0.001, **q < 0.01, *q < 0.05. GDM: gestational diabetes mellitus. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

associated with GDM were also significantly associated with the air pollutant measures (Fig. 4A). In the adjusted model, Re was negatively associated with PM10 ($\beta = -0.11$, $p = 0.004$, q = 0.048). The element Ta showed a negative association with PM2.5 (LUR) ($\beta = -0.11$, $p = 0.0004$, q = 0.002). Ta had a negative correlation with PM2.5 (LUR) in the Non-GDM group (r = −0.166, q = 0.0006) (Fig. 4B). Two (K and Rb) of the five maternal hair elements associated with MDI were also significantly associated with some of the air pollutants (Fig. 5A). Both K and Rb were positively associated with the estimated PM2.5 (K: $\beta = 0.11$, $p = 0.001$, q = 0.007; Rb: $\beta = 0.14$, $p = 0.0003$, q = 0.003) in the adjusted model. The correlation analysis found that K was positively correlated with PM2.5 (LUR) (r = 0.210, q = 0.013) and Rb also was positively correlated with PM2.5 (LUR) (r = 0.196, q = 0.013) in the GDM group (Fig. 5B). Nevertheless, only two infant neurodevelopment-related elements (As and Gd) in cord serum were associated with air pollutants when the statistical significance was set at $p < 0.1$ (Fig. S5).

4. Discussion

This study extensively investigated early pregnancy maternal hair and umbilical cord serum element concentrations and their association with GDM and infant neurodevelopment. Our analyses demonstrated that fourteen maternal hair elements were significantly associated with an increased risk of GDM, particularly tantalum (Ta), rhenium (Re), and selenium (Se). Furthermore, GDM-related hair elements were negatively associated with air pollutant exposure (PM2.5 (LUR) and PM10 related to Ta and Re, respectively) and positively associated with maternal diet (Nb, Rb, and Cs related to noodles, sweet beverages, and poultry, respectively). Three elements (Rb, Er, and Tm) were negatively associated with maternal hair and cord serum infant MDI scores. Interestingly, the infant neurodevelopment-related element Rb and K were positively associated with air pollutants PM2.5 based on the LUR model. Our results indicate that air pollutant exposure and maternal diet may impact on several elements that are related to GDM and infant neurodevelopment.

4.1. Maternal hair elements and GDM

Exposure to certain elements has been shown to induce oxidative stress and inflammation, both associated with adverse pregnancy outcomes [66–68]. These etiologies are often regarded as the pathogenic mechanisms of insulin resistance, leading to the development of GDM (66). Our study showed that fourteen maternal hair elements (Ta, Re, Se, Tl, Eu, Gd, Na, Al, K, Ag, Nb, Rb, Cs, Th) were associated with an increased risk of GDM (Fig. 2A). A birth cohort study in China hypothesized that the observed association between high thallium (Tl)

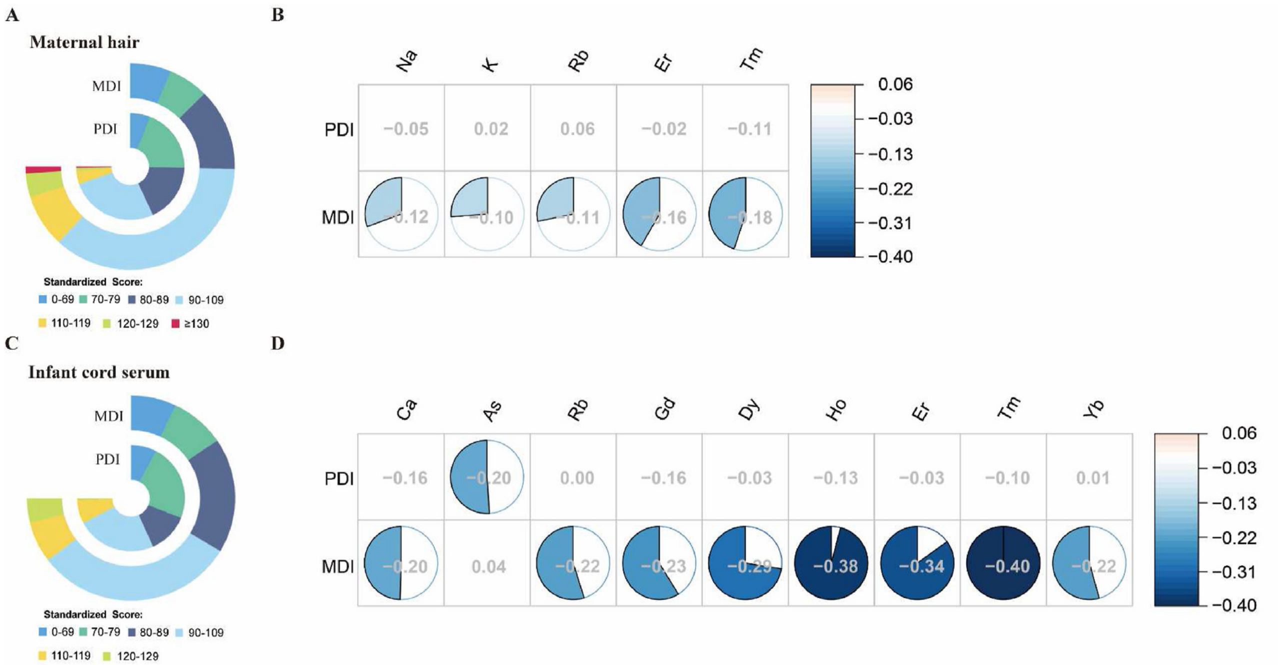

Fig. 3. Linear regression analyses of infant neurodevelopment with elements. The distribution of standardized scores across the two developmental domains of the Bayley Scales of Infant Development in maternal hair (A) and cord serum samples (C). Standardized regression coefficients of the linear regression models of infant neurodevelopment with first trimester maternal hair elements (B) and infant cord serum elements (D). The models were adjusted for GDM, maternal age, BMI, infant gestational age at delivery, birthweight, and Apgar score at 1 min. Blue indicates negative linear associations. Only the significant associations ($p < 0.05$ and $q < 0.05$) between elemental concentration and infant neurodevelopment were displayed as pie charts. MDI: mental development index, PDI: psychomotor development index. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

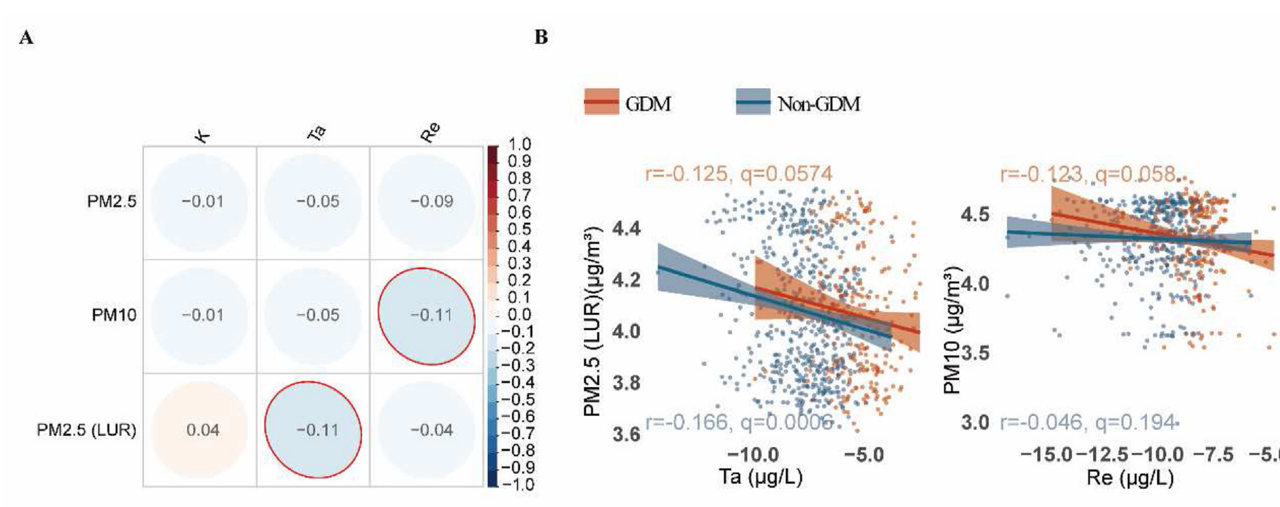

Fig. 4. Associations between air pollutants and the hair elements significantly associated with GDM. (A) Linear regression analyses of elements and air pollutants, adjusted for age and BMI. Numbers in the cells represent the standardized regression coefficients. Red and blue ellipses indicate positive and negative linear associations, respectively. The red ellipse outlines represent significant $q < 0.05$. LUR: land use regression model. (B) The correlation between the element concentration and the significant air pollutant level. The shadow around the trendline shows the 95% CI. GDM: gestational diabetes mellitus. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

exposure and GDM may be due to increased oxidative stress [37]. Exposure to Al has been associated with a higher risk of GDM and dysregulated lipid metabolism [69], which causes inflammation and insulin resistance [70]. Moreover, Markus et al. have indicated that excess Na intake plays a vital role in developing inflammatory reactions [71]. The roles of oxidative stress and inflammation are interconnected, and the upregulation of one leads to the elevation of the other [72]. Contrary to our result, where we found that Se was higher in the hair of women with GDM, Se is known to play a vital role in regulating oxidative stress and inflammatory response [73]. However, the Japan Environment and Children's study also reported that high Se in whole blood was a possible risk factor for GDM [32]. Hyo et al. suggested that the increased risk for GDM may result from insulin signaling disruption by high Se levels [74]. Some animal experiments have also observed that excessive selenoproteins (SP) impair insulin transduction which can lead to insulin resistance and glucose intolerance [75,76]. Given these findings, we hypothesize that elevated element levels observed in maternal hair in this study are

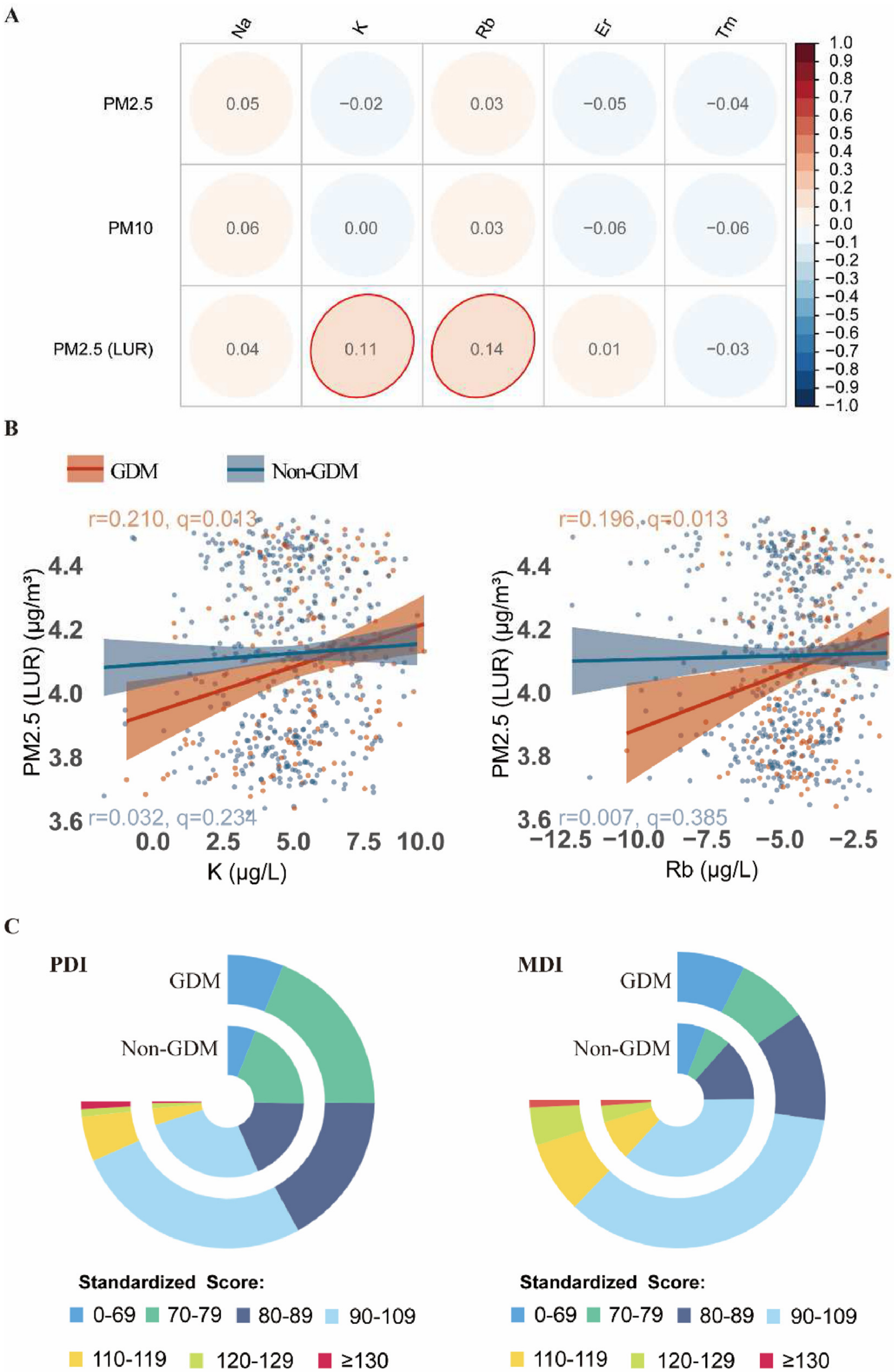

Fig. 5. The association between air pollutants and the maternal hair elements significantly associated with infant neurodevelopment. (A) Linear regression analyses of elements and air pollutants, adjusted for age and BMI. Numbers in the cells represent the standardized regression coefficients. Red and blue ellipses indicate positive and negative linear associations, respectively. The red ellipse outlines represent significant $q < 0.05$. LUR: land use regression model. (B) The correlation between the element concentration and the significant air pollutant level. The shadow around the trendline shows the 95% CI. GDM: gestational diabetes mellitus. (C) Comparison of the percentage of standardized score areas in the GDM and Non-GDM groups for two developmental domains of the Bayley Scales of Infant Development. PDI: psychomotor development index, MDI: mental development index. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

likely to be associated with GDM risk via increased insulin resistance (Fig. 6).

4.2. Maternal diet and environmental exposures associated with GDM-related elements

Maternal diet and environmental exposures may be the source of element accumulation related to GDM (Fig. 6). We found that the consumption of noodles, sweetened beverages, and poultry had positive linear associations with the elements Nb, Rb, and Cs, respectively (Fig. S4). It has been widely reported that exposure to excess inorganic elements during pregnancy was associated with GDM [30,33,44]. Various elements in water, soil, and air can bioaccumulate in meats and vegetables, which enter the food chain and are consumed by pregnant women [77]. For example, Xu et al. observed that Cs levels were positively correlated with intake from animal-sourced food [78]. Although no study has associated Nb or Rb with the specific food groups in our study (noodles and sweet beverages), several studies have reported the contamination of wheat starch and groundwater by inorganic elements. A study showed that Cd had a higher pollution load index in wheat when wastewater was used for irrigation [79]. Another study found that elements in soil and water can be transferred to wheat, and the concentrations of Cu and Pb were over the acceptable threshold in the seed [80]. Due to the high water solubility of Rb, it could be readily leached from the soil into groundwater [81].

We also found that PM10 and PM2.5 (LUR) were negatively correlated with Re and Ta, respectively (Fig. 4). Air pollutants such as particulate matter (PM) have been observed to be associated with metabolic dysfunction and increased insulin resistance [82]. Therefore, element accumulation in pregnancies affected by GDM may be partly a result of maternal diet consumption and other environmental exposures.

4.3. Maternal hair and cord serum elements and infant neurodevelopment

The elements that pregnant women are exposed to can be absorbed and detected in various biofluids and tissues, including blood, hair, and umbilical cord blood [83]. Elements are easily incorporated and retained in hair due to their high affinity for the sulfhydryl group of amino acids in hair keratin [84]. Hair has great potential as a robust biospecimen to reflect long-term element exposure during pregnancy [53]. Human hair grows approximately 10–12 mm per month, making it a time-specific marker of exposure. Umbilical cord blood is also a useful biospecimen for investigating element exposure. It can be used to understand whether maternal exposures (observed in maternal hair) cross the placental barrier and reach the fetus/infant during gestation [85]. Some studies have reported maternal hair and umbilical cord blood element levels associated with infant neurodevelopment [47,86]. In our study, we found that Rb, Er, and Tm were negatively associated with MDI scores in both hair and cord serum (Fig. 6). The lanthanide ions of rare earth elements (e.g., Er and Tm) are capable of crossing the placental barrier and blood–brain barrier to influence fetal neurodevelopment [87,88]. Recent findings have shown that lanthanide ions can cause NMDA (N-methyl-D-aspartate glutamatergic) receptor over-activation in rat hippocampal CA1 neurons, leading to glutamate-induced excitotoxic neuronal injury and damage to cognitive function and memory [89,90]. Zhao et al. found that lanthanide compounds injected into the mice's abdominal cavity could be detected in the forebrain. The same research team also claimed that lanthanide ions caused oxidative stress, damaged nervous tissue, and altered neurochemical metabolism [91]. The element Rb has been found to be positively associated with cognitive function due to its neuroprotective properties [92,93]. However, our data showed that Rb concentration was negatively associated with neurodevelopment in this cohort. As the group one elements (Alkali metals) on the periodic table, Rb and Na share some similar physical and chemical properties [94]. We speculate that Rb might act like Na to influence infant neurodevelopment through inflammation [95], activating microglia to secrete pro-inflammatory cytokine IL-1β and inhibiting the proliferation of neural progenitor cells [96]. This mechanistic hypothesis would need to be tested in an animal model. The difference in findings may also reflect a potential U-shaped relationship between Rb concentrations and neurodevelopment.

4.4. Maternal diet and environmental exposures associated with elements related to infant neurodevelopment

PM2.5, estimated by the LUR model was positively associated with K and Rb in maternal hair (Fig. 5), while oil and condiment and other seafood were positively associated with Ca and Gd in cord serum, respectively (Table S4). Although there is no previous report on the association between hair K/Rb and air pollutants, a study in Northeast China has found that the concentrations of K and Rb in the bronchoalveolar lavage fluid of patients with chronic obstructive pulmonary disease were significantly elevated in the high-risk PM2.5 inhalation period [97]. Air pollutants such as PM2.5, discharged by cars and factories, have a certain persistence and continuity [98]. Particularly, elements are likely attached to the PM surface, making PM a significant source of element exposure to air pollutants [99]. While we detected that Rb, Ta and K were associated with GDM and infant neurodevelopment (Figs. 4 and 5), Rb and Ta are generally not abundant in atmospheric PM samples, and only K is relatively abundant from biomass combustion or soil. Likewise, of the infant neurodevelopment-related elements in cord blood, only As is commonly detected in atmospheric PM samples; Gd is not frequently reported. The disparity between these results may be related to different geographic locations. Previous studies showed that twenty-seven inorganic elements were detected from PM2.5 filtered atmospheric samples in Chongqing, including K, Rb, and As [100]. Wang et al. characterized the sources of trace elements in PM2.5 from Chongqing City and reported that K accounting for 25.4% of the total analyzed trace elements [101]. Adjacent to Chongqing, the Sichuan Province has rich mineral resources of Ta [102] and Gd [103], which may influence the PM trace element concentration in the Chongqing region. Moreover, from pregnancy to the first year of infancy, the mother and infant will likely reside in the same area. Therefore, their exposure to air pollutants is likely to transcend both pregnancy and the first year post-partum, making this long-term environmental exposure likely to influence the developing infant brain. On the other hand, the high levels of Ca and Gd in cord serum may result from maternal diet. Mendil et al. found that sunflower oil from Turkey contains a high level of Ca [104]. The Gd bioaccumulation has been reported in marine species, such as mussels and sea urchins [105]. These results were consistent with our maternal dietary pattern and cord serum elements related to infant neurodevelopment. Together with our findings (Fig. 6), air pollutant exposures were only significantly associated with maternal hair elements (K and Rb), while diet exposures were only correlated with infant cord serum elements (Ca and Gd). Thus, our results demonstrated that the hair element more likely reflect environmental exposure, while the umbilical blood element may better represent the maternal diet.

4.5. Strengths and limitations

This study had several strengths. Firstly, this was the first study to explore the associations between 48 elements in hair and cord

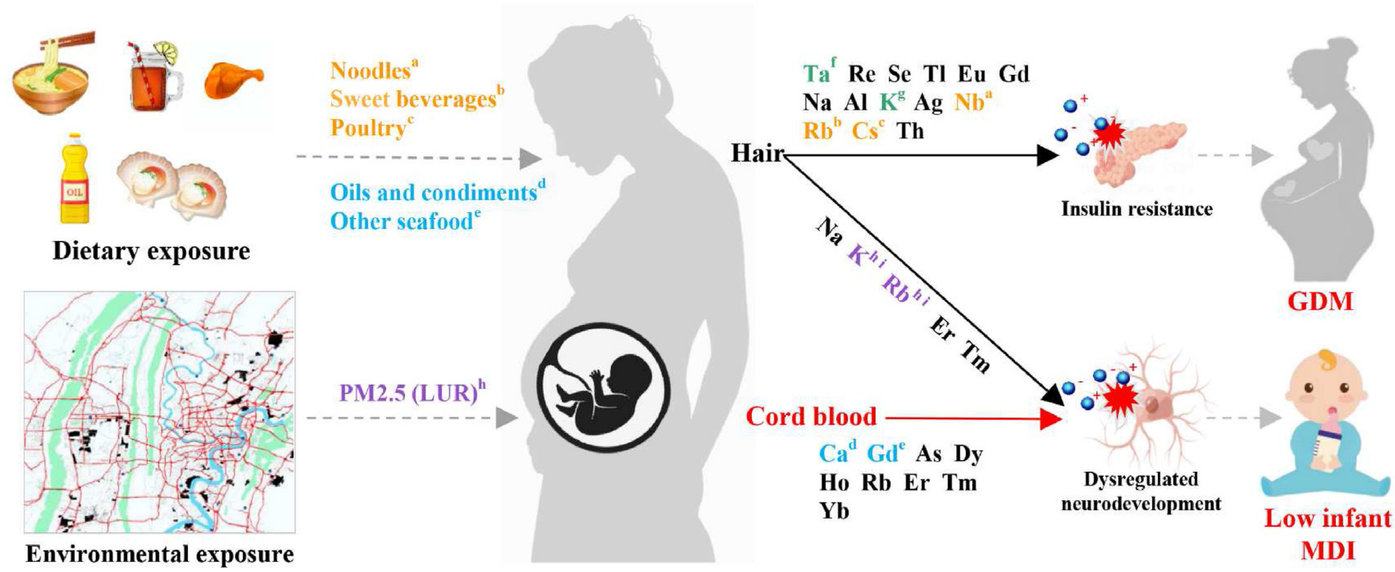

Fig. 6. The potential associations of element accumulation influence GDM risk and infant neurodevelopment through diet and air pollutant exposures. Higher noodles, sweet beverages, poultry, oil and condiment, and other seafood intakes during gestation were likely to elevate element concentrations in maternal hair (Nb, Rb, and Cs) or infant cord serum (Ca and Gd). Moreover, higher PM2.5 exposures during pregnancy might increase maternal hair's K and Rb levels. In particular, the three most prominent risk factors (Ta, Re, and Se) were associated with insulin resistance. At the same time, the elevated Rb, Er and Tm concentrations in both maternal hair and infant cord serum were associated with low infant MDI, likely related to dysregulated neurodevelopment. Therefore, we hypothesize that increased exposures to metal elements through adverse diet and air pollutants during pregnancy might promote GDM and poor infant neurodevelopment. Orange and blue letters represent dietary exposure, including noodles, sweet beverages, poultry, oils and condiments, and other seafood. Green and purple letters represent environmental exposure. Grey dashed lines indicate maternal exposure, including diet and air pollutants. Black solid lines indicate significant elements in maternal hair, while the solid red line indicates influential elements in infant cord serum related to GDM and low infant MDI. The identical superscript indicates relevant exposure factors and elements. GDM: gestational diabetes mellitus; MDI: mental development index. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

serum samples with GDM and infant neurodevelopment. Secondly, this cohort study combined exposomics and elementomics to investigate the associations between elements and pregnancy outcomes and whether there were links to modifiable lifestyle factors such as maternal diet and air pollutant exposure. Thirdly, using hair as the biospecimen for analysis in this study has great advantages. Hair sampling requires non-invasive collection, is easy to preserve, and can be used to discover long-term cumulative exposure levels. There were also several limitations to our study that should be addressed in future studies. Firstly, we only tested element concentrations in a small number of cord serum samples. Future studies should include more cord serum samples to verify the relationship between elements and infant neurodevelopment. Secondly, considering the large geographic expanse of the study area, the small sample size for the data on air pollution may not provide sufficient variability concerning exposure to PM2.5, PM10, and others. In addition, only approximate and indirect linkages can be made between elements in maternal hair and cord blood with PM mass was possible. In any future cohort, particulate matter samples should be collected for component analysis, and more representative data for pollution exposure with ICP-MS analysis of atmospheric filter samples should be considered. Thirdly, all participants in this study were recruited in Chongqing, China. Therefore, caution should be applied when trying to extrapolate our findings to other populations.

5. Conclusion

In conclusion, we identified associations between element levels in maternal hair with the development of GDM and infant neurodevelopment. Higher Ta, Re, and Se concentrations in maternal hair were associated with a higher risk of GDM, and higher Rb, Er, and Tm concentrations in maternal hair and cord serum were associated with impaired infant neurodevelopment. We also found that maternal diet and air pollutant exposure were associated with element concentrations linked to GDM and infant neurodevelopment, providing potential avenues for risk modification. Our study adds valuable insights to the current knowledge of GDM and infant neurodevelopment. Maternal diet and living environment should be considered early in pregnancy to reduce the likelihood of GDM and impaired infant neurodevelopment potentially. Future studies should be conducted in cohorts outside of Chongqing, China, to determine if the findings apply to other settings. Further work should also be undertaken to investigate the exact physiological mechanisms underlying the associations observed in this study.

Fundings

This work was supported by the National Natural Science Foundation of China (No. 81871185, 81971406, 82271715), The 111 Project (Yuwaizhuan (2016)32), Chongqing Science and Technology Commission (CSTC2021JCYJ-MSXMX0213, CSTB2022NSCQ-MSX1679, CSTB2022NSCQ-MSX1680), Chongqing Municipal Education Commission (KJZD-K202100407), Chongqing Health Commission and Chongqing Science & Technology Commission (2021MSXM121, 2020MSXM101), Smart Medicine Research Project of Chongqing Medical University (No. ZHYX202103), Senior Medical Talents Program of Chongqing for Young and Middle-aged [2022] 15, Kuanren Talents Programs of Second Affiliated Hospital of Chongqing Medical University, and a joint Health Research Council New Zealand–National Science Foundation of China Biomedical Research Fund (19/804).

Author contributions

The authors responsibilities were as follows - T.L.H. and H.Z. were responsible for conceptualization; Y.Y.X., Y.L., and T.L.H. were responsible for methodology and software; Y.L., X.J.Y., and Y.Y. performed the sample preparation and ICP-MS analysis; Y.L. J.dS., K.B, C.C, L.W.Z, and T.L.H. were responsible for data analysis; Y.Y.X., R.S., T.L.H., H.Z., and P.N.B. were responsible for data curation; Y.L. and Y.Y.X. were responsible for writing the original draft; Y.L., J.dS., T.M., and B.N. were responsible for data interpretation and manuscript editing; J.dS., Y.Y.X, T.L.H., and H.Z. were responsible for funding acquisition. All authors read and approved the final manuscript.

Data availability

The data that support the findings of this study are available on request from the corresponding author on reasonable request.

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.

Acknowledgments

We extend our heartfelt thanks to all collaborators involved in data collection from the study participants. We also express our gratitude to the Mass Spectrometry Center of Maternal-Fetal Medicine at Chongqing Medical University for their invaluable support in mass spectrometry analysis.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2023.08.009.

References

[1] Misra BB, Misra A. The chemical exposome of type 2 diabetes mellitus: opportunities and challenges in the omics era. Diabetes Metabol Syndr 2020;14:23–38. https://doi.org/10.1016/j.dsx.2019.12.001.
[2] Gao C, Sun X, Lu L, Liu F, Yuan J. Prevalence of gestational diabetes mellitus in mainland China: a systematic review and meta-analysis. J Diabetes Investig 2019;10:154–62. https://doi.org/10.1111/jdi.12854.
[3] Damm P. Future risk of diabetes in mother and child after gestational diabetes mellitus. Int J Gynaecol Obstet 2009;104(Suppl 1):S25–6. https://doi.org/10.1016/j.ijgo.2008.11.025.
[4] Chu AHY, Godfrey KM. Gestational diabetes mellitus and developmental programming. Ann Nutr Metab 2020;76(Suppl 3):4–15. https://doi.org/10.1159/000509902.
[5] Perea V, Urquizu X, Valverde M, Macias M, Carmona A, Esteve E, et al. Influence of maternal diabetes on the risk of neurodevelopmental disorders in offspring in the prenatal and postnatal periods. Diabetes Metab J 2022. https://doi.org/10.4093/dmj.2021.0340.
[6] Ornoy A, Reece EA, Pavlinkova G, Kappen C, Miller RK. Effect of maternal diabetes on the embryo, fetus, and children: congenital anomalies, genetic and epigenetic changes and developmental outcomes. Birth Defects Res C Embryo Today 2015;105:53–72. https://doi.org/10.1002/bdrc.21090.
[7] Nomura Y, Marks DJ, Grossman B, Yoon M, Loudon H, Stone J, et al. Exposure to gestational diabetes mellitus and low socioeconomic status: effects on neurocognitive development and risk of attention-deficit/hyperactivity disorder in offspring. Arch Pediatr Adolesc Med 2012;166:337–43. https://doi.org/10.1001/archpediatrics.2011.784.
[8] Camprubi Robles M, Campoy C, Garcia Fernandez L, Lopez-Pedrosa JM, Rueda R, Martin MJ. Maternal diabetes and cognitive performance in the offspring: a systematic review and meta-analysis. PLoS One 2015;10:e0142583. https://doi.org/10.1371/journal.pone.0142583.
[9] Pan SC, Huang CC, Lin SJ, Chen BY, Chan CC, Leon Guo YL. Gestational diabetes mellitus was related to ambient air pollutant nitric oxide during early gestation. Environ Res 2017;158:318–23. https://doi.org/10.1016/j.envres.2017.06.005.
[10] Yi C, Wang Q, Qu Y, Niu J, Oliver BG, Chen H. In-utero exposure to air pollution and early-life neural development and cognition. Ecotoxicol Environ Saf 2022;238:113589. https://doi.org/10.1016/j.ecoenv.2022.113589.
[11] Padula AM, Yang W, Lurmann FW, Balmes J, Hammond SK, Shaw GM. Prenatal exposure to air pollution, maternal diabetes and preterm birth. Environ Res 2019;170:160–7. https://doi.org/10.1016/j.envres.2018.12.031.
[12] Thiering E, Heinrich J. Epidemiology of air pollution and diabetes. Trends Endocrinol Metabol 2015;26:384–94. https://doi.org/10.1016/j.tem.2015.05.002.
[13] Hu H, Ha S, Henderson BH, Warner TD, Roth J, Kan H, et al. Association of atmospheric particulate matter and ozone with gestational diabetes mellitus. Environ Health Perspect 2015;123:853–9. https://doi.org/10.1289/ehp.1408456.
[14] Costa LG, Cole TB, Dao K, Chang YC, Garrick JM. Developmental impact of air pollution on brain function. Neurochem Int 2019;131:104580. https://doi.org/10.1016/j.neuint.2019.104580.
[15] Christensen GM, Rowcliffe C, Chen J, Vanker A, Koen N, Jones MJ, et al. In-utero exposure to indoor air pollution or tobacco smoke and cognitive development in a South African birth cohort study. Sci Total Environ 2022;834:155394. https://doi.org/10.1016/j.scitotenv.2022.155394.
[16] Yong HY, Mohd Shariff Z, Mohd Yusof BN, Rejali Z, Appannah G, Bindels J, et al. The association between dietary patterns before and in early pregnancy and the risk of gestational diabetes mellitus (GDM): data from the Malaysian SECOST cohort. PLoS One 2020;15:e0227246. https://doi.org/10.1371/journal.pone.0227246.
[17] Du HY, Jiang H, O K, Chen B, Xu LJ, Liu SP, et al. Association of dietary pattern during pregnancy and gestational diabetes mellitus: a prospective cohort study in northern China. Biomed Environ Sci 2017;30:887–97. https://doi.org/10.3967/bes2017.119.
[18] Sedaghat F, Akhoondan M, Ehteshami M, Aghamohammadi V, Ghanei N, Mirmiran P, et al. Maternal dietary patterns and gestational diabetes risk: a case-control study. J Diabetes Res 2017;2017:5173926. https://doi.org/10.1155/2017/5173926.
[19] Bordeleau M, Fernandez de Cossio L, Chakravarty MM, Tremblay ME. From maternal diet to neurodevelopmental disorders: a story of neuroinflammation. Front Cell Neurosci 2020;14:612705. https://doi.org/10.3389/fncel.2020.612705.
[20] Smith BL, Reyes TM. Offspring neuroimmune consequences of maternal malnutrition: potential mechanism for behavioral impairments that underlie metabolic and neurodevelopmental disorders. Front Neuroendocrinol 2017;47:109–22. https://doi.org/10.1016/j.yfrne.2017.07.007.
[21] Tozuka Y, Kumon M, Wada E, Onodera M, Mochizuki H, Wada K. Maternal obesity impairs hippocampal BDNF production and spatial learning performance in young mouse offspring. Neurochem Int 2010;57:235–47. https://doi.org/10.1016/j.neuint.2010.05.015.
[22] Kim MS, Choi MS, Han SN. High fat diet-induced obesity leads to proinflammatory response associated with higher expression of NOD2 protein. Nutr Res Prac 2011;5:219–23. https://doi.org/10.4162/nrp.2011.5.3.219.
[23] Graf AE, Lallier SW, Waidyaratne G, Thompson MD, Tipple TE, Hester ME, et al. Maternal high fat diet exposure is associated with increased hepcidin levels, decreased myelination, and neurobehavioral changes in male offspring. Brain Behav Immun 2016;58:369–78. https://doi.org/10.1016/j.bbi.2016.08.005.
[24] Bordeleau M, Fernandez de Cossio L, Lacabanne C, Savage JC, Vernoux N, Chakravarty M, et al. Maternal high-fat diet modifies myelin organization, microglial interactions, and results in social memory and sensorimotor gating deficits in adolescent mouse offspring. Brain Behav Immun Health 2021;15:100281. https://doi.org/10.1016/j.bbih.2021.100281.
[25] Urbonaite G, Knyzeliene A, Bunn FS, Smalskys A, Neniskyte U. The impact of maternal high-fat diet on offspring neurodevelopment. Front Neurosci 2022;16:909762. https://doi.org/10.3389/fnins.2022.909762.
[26] de Seymour JV, Beck KL, Conlon CA, Jones MB, Colombo J, Xia YY, et al. An investigation of the relationship between dietary patterns in early pregnancy and maternal/infant health outcomes in a Chinese cohort. Front Nutr 2022;9:775557. https://doi.org/10.3389/fnut.2022.775557.
[27] Wu J, Ying T, Shen Z, Wang H. Effect of low-level prenatal mercury exposure on neonate neurobehavioral development in China. Pediatr Neurol 2014;51:93–9. https://doi.org/10.1016/j.pediatrneurol.2014.03.018.
[28] Llop S, Ibarlucea J, Sunyer J, Ballester F. [Current dietary exposure to mercury during pregnancy and childhood, and public health recommendations]. Gac Sanit 2013;27:273–8. https://doi.org/10.1016/j.gaceta.2012.09.002.
[29] Vecchi Brumatti L, Rosolen V, Mariuz M, Piscianz E, Valencic E, Bin M, et al. Impact of methylmercury and other heavy metals exposure on neurocognitive function in children aged 7 Years: study protocol of the follow-up. J Epidemiol 2021;31:157–63. https://doi.org/10.2188/jea.JE20190284.
[30] Li X, Huang Y, Xing Y, Hu C, Zhang W, Tang Y, et al. Association of urinary cadmium, circulating fatty acids, and risk of gestational diabetes mellitus: a nested case-control study in China. Environ Int 2020;137:105527. https://doi.org/10.1016/j.envint.2020.105527.
[31] Sanders AP, Claus Henn B, Wright RO. Perinatal and childhood exposure to cadmium, manganese, and metal mixtures and effects on cognition and behavior: a review of recent literature. Curr Environ Health Rep 2015;2:284–94. https://doi.org/10.1007/s40572-015-0058-8.
[32] Tatsuta N, Iwai-Shimada M, Nakayama SF, Iwama N, Metoki H, Arima T, et al. Association between whole blood metallic elements concentrations and gestational diabetes mellitus in Japanese women: the Japan environment and Children's study. Environ Res 2022;212:113231. https://doi.org/10.1016/j.envres.2022.113231.

[33] Liu W, Zhang B, Huang Z, Pan X, Chen X, Hu C, et al. Cadmium body burden and gestational diabetes mellitus: a prospective study. Environ Health Perspect 2018;126:027006. https://doi.org/10.1289/EHP2716.

[34] Roverso M, Di Marco V, Badocco D, Pastore P, Calanducci M, Cosmi E, et al. Maternal, placental and cordonal metallomic profiles in gestational diabetes mellitus. Metallomics 2019;11:676–85. https://doi.org/10.1039/c8mt00331a.

[35] Wu Y, Zhang J, Peng S, Wang X, Luo L, Liu L, et al. Multiple elements related to metabolic markers in the context of gestational diabetes mellitus in meconium. Environ Int 2018;121:1227–34. https://doi.org/10.1016/j.envint.2018.10.044.

[36] Rezaei M, Blaszczyk M, Tinkov AA, Binkowski LJ, Mansouri B, Skalny A, et al. Relationship between gestational diabetes and serum trace element levels in pregnant women from Eastern Iran: a multivariate approach. Environ Sci Pollut Res Int 2021;28:45230–9. https://doi.org/10.1007/s11356-021-13927-1.

[37] Zhang QQ, Li JH, Wang YD, Li XN, Wang JQ, Zhou MY, et al. Association between maternal thallium exposure and risk of gestational diabetes mellitus: evidence from a birth cohort study. Chemosphere 2021;270:128637. https://doi.org/10.1016/j.chemosphere.2020.128637.

[38] Iyengar GV, Rapp A. Human placenta as a 'dual' biomarker for monitoring fetal and maternal environment with special reference to potentially toxic trace elements. Part 3: toxic trace elements in placenta and placenta as a biomarker for these elements. Sci Total Environ 2001;280:221–38. https://doi.org/10.1016/s0048-9697(01)00827-0.

[39] Ballatori N. Transport of toxic metals by molecular mimicry. Environ Health Perspect 2002;110(Suppl 5):689–94. https://doi.org/10.1289/ehp.02110s5689.

[40] Claus Henn B, Coull BA, Wright RO. Chemical mixtures and children's health. Curr Opin Pediatr 2014;26:223–9. https://doi.org/10.1097/MOP.0000000000000067.

[41] Papadopoulou E, Haug LS, Sakhi AK, Andrusaityte S, Basagana X, Brantsaeter AL, et al. Diet as a source of exposure to environmental contaminants for pregnant women and children from six European countries. Environ Health Perspect 2019;127:107005. https://doi.org/10.1289/EHP5324.

[42] Valeri L, Mazumdar MM, Bobb JF, Claus Henn B, Rodrigues E, Sharif OIA, et al. The joint effect of prenatal exposure to metal mixtures on neurodevelopmental outcomes at 20-40 Months of age: evidence from rural Bangladesh. Environ Health Perspect 2017;125:067015. https://doi.org/10.1289/EHP614.

[43] Valvi D, Oulhote Y, Weihe P, Dalgard C, Bjerve KS, Steuerwald U, et al. Gestational diabetes and offspring birth size at elevated environmental pollutant exposures. Environ Int 2017;107:205–15. https://doi.org/10.1016/j.envint.2017.07.016.

[44] Jia X, Zhang L, Zhao J, Ren M, Li Z, Wang J, et al. Associations between endocrine-disrupting heavy metals in maternal hair and gestational diabetes mellitus: a nested case-control study in China. Environ Int 2021;157:106770. https://doi.org/10.1016/j.envint.2021.106770.

[45] Strain JJ, Love TM, Yeates AJ, Weller D, Mulhern MS, McSorley EM, et al. Associations of prenatal methylmercury exposure and maternal polyunsaturated fatty acid status with neurodevelopmental outcomes at 7 years of age: results from the Seychelles Child Development Study Nutrition Cohort 2. Am J Clin Nutr 2021;113:304–13. https://doi.org/10.1093/ajcn/nqaa338.

[46] Rothenberg SE, Yu X, Liu J, Biasini FJ, Hong C, Jiang X, et al. Maternal methylmercury exposure through rice ingestion and offspring neurodevelopment: a prospective cohort study. Int J Hyg Environ Health 2016;219:832–42. https://doi.org/10.1016/j.ijheh.2016.07.014.

[47] Rothenberg SE, Korrick SA, Liu J, Nong Y, Nong H, Hong C, et al. Maternal methylmercury exposure through rice ingestion and child neurodevelopment in the first three years: a prospective cohort study in rural China. Environ Health 2021;20:50. https://doi.org/10.1186/s12940-021-00732-z.

[48] Shekhawat DS, Janu VC, Singh P, Sharma P, Singh K. Association of newborn blood lead concentration with neurodevelopment outcome in early infancy. J Trace Elem Med Biol 2021;68:126853. https://doi.org/10.1016/j.jtemb.2021.126853.

[49] Jedrychowski W, Perera F, Jankowski J, Rauh V, Flak E, Caldwell KL, et al. Fish consumption in pregnancy, cord blood mercury level and cognitive and psychomotor development of infants followed over the first three years of life: krakow epidemiologic study. Environ Int 2007;33:1057–62. https://doi.org/10.1016/j.envint.2007.06.001.

[50] Lee JJ, Valeri L, Kapur K, Ibne Hasan MOS, Quamruzzaman Q, Wright RO, et al. Growth parameters at birth mediate the relationship between prenatal manganese exposure and cognitive test scores among a cohort of 2- to 3-year-old Bangladeshi children. Int J Epidemiol 2018;47:1169–79. https://doi.org/10.1093/ije/dyy069.

[51] Farzan SF, Gossai A, Chen Y, Chasan-Taber L, Baker E, Karagas M. Maternal arsenic exposure and gestational diabetes and glucose intolerance in the New Hampshire birth cohort study. Environ Health 2016;15:106. https://doi.org/10.1186/s12940-016-0194-0.

[52] Ettinger AS, Zota AR, Amarasiriwardena CJ, Hopkins MR, Schwartz J, Hu H, et al. Maternal arsenic exposure and impaired glucose tolerance during pregnancy. Environ Health Perspect 2009;117:1059–64. https://doi.org/10.1289/ehp0800533.

[53] Pozebon D, Scheffler GL, Dressler VL. Elemental hair analysis: a review of procedures and applications. Anal Chim Acta 2017;992:1–23. https://doi.org/10.1016/j.aca.2017.09.017.

[54] Pragst F, Balikova MA. State of the art in hair analysis for detection of drug and alcohol abuse. Clin Chim Acta 2006;370:17–49. https://doi.org/10.1016/j.cca.2006.02.019.

[55] Huang S, Mo TT, Norris T, Sun S, Zhang T, Han TL, et al. The CLIMB (Complex Lipids in Mothers and Babies) study: protocol for a multicentre, three-group, parallel randomised controlled trial to investigate the effect of supplementation of complex lipids in pregnancy, on maternal ganglioside status and subsequent cognitive outcomes in the offspring. BMJ Open 2017;7:e016637. https://doi.org/10.1136/bmjopen-2017-016637.

[56] Delplancke TDJ, de Seymour JV, Tong C, Sulek K, Xia Y, Zhang H, et al. Analysis of sequential hair segments reflects changes in the metabolome across the trimesters of pregnancy. Sci Rep 2018;8:36. https://doi.org/10.1038/s41598-017-18317-7.

[57] Chen X, Zhao X, Jones MB, Harper A, de Seymour JV, Yang Y, et al. The relationship between hair metabolites, air pollution exposure and gestational diabetes mellitus: a longitudinal study from pre-conception to third trimester. Front Endocrinol 2022;13:1060309. https://doi.org/10.3389/fendo.2022.1060309.

[58] Harper A, Baker PN, Xia Y, Kuang T, Zhang H, Chen Y, et al. Development of spatiotemporal land use regression models for PM2.5 and NO2 in Chongqing, China, and exposure assessment for the CLIMB study. Atmos Pollut Res 2021;12. https://doi.org/10.1016/j.apr.2021.101096.

[59] Loy SL, Cheung YB, Soh SE, Ng S, Tint MT, Aris IM, et al. Female adiposity and time-to-pregnancy: a multiethnic prospective cohort. Hum Reprod 2018;33:2141–9. https://doi.org/10.1093/humrep/dey300.

[60] Liu D, Cheng Y, Mi B, Zeng L, Qu P, Li S, et al. Maternal dietary patterns during pregnancy derived by reduced-rank regression and birth weight in the Chinese population. Br J Nutr 2020;123:1176–86. https://doi.org/10.1017/S0007114520000392.

[61] Lu MS, Chen QZ, He JR, Wei XL, Lu JH, Li SH, et al. Maternal dietary patterns and fetal growth: a large prospective cohort study in China. Nutrients 2016;8. https://doi.org/10.3390/nu8050257.

[62] Shourong Y, Xuerong L, Zhiwei Y, W G. The revising of the bayley scales of infant development (BSID) in China. Chin J Clin Psychol 1993;2:71–5.

[63] Kaya-Kara O, Kerem-Gunel M, Yigit S. Correlation of the Bayley scales of infant-toddler development-3rd edition and neuro-sensory motor assessment in preterm infants during the first year of life. Turk J Pediatr 2019;61:399–406. https://doi.org/10.24953/turkjped.2019.03.012.

[64] Storey JD, Bass AJ, Dabney A, qvalue DR. Q-value estimation for false discovery rate control. R package version 2.22.0. 2021. Available online at: http://github.com/jdstorey/qvalue.

[65] Wickham H. Ggplot 2: elegant graphics for data analysis. New York: Springer; 2009.

[66] Paithankar JG, Saini S, Dwivedi S, Sharma A, Chowdhuri DK. Heavy metal associated health hazards: an interplay of oxidative stress and signal transduction. Chemosphere 2021;262:128350. https://doi.org/10.1016/j.chemosphere.2020.128350.

[67] Renu K, Chakraborty R, Myakala H, Koti R, Famurewa AC, Madhyastha H, et al. Molecular mechanism of heavy metals (lead, chromium, arsenic, mercury, nickel and cadmium) - induced hepatotoxicity - a review. Chemosphere 2021;271:129735. https://doi.org/10.1016/j.chemosphere.2021.129735.

[68] Chen H, Zhu C, Zhou X. Effects of lead and cadmium combined heavy metals on liver function and lipid metabolism in mice. Biol Trace Elem Res 2022. https://doi.org/10.1007/s12011-022-03390-5.

[69] Huang Y, Li X, Zhang W, Su W, Zhou A, Xu S, et al. Aluminum exposure and gestational diabetes mellitus: associations and potential mediation by n-6 polyunsaturated fatty acids. Environ Sci Technol 2020;54:5031–40. https://doi.org/10.1021/acs.est.9b07180.

[70] Liu Y, Xia YY, Zhang T, Yang Y, Cannon RD, Mansell T, et al. Complex interactions between circulating fatty acid levels, desaturase activities, and the risk of gestational diabetes mellitus: a prospective cohort study. Front Nutr 2022;9:919357. https://doi.org/10.3389/fnut.2022.919357.

[71] Kleinewietfeld M, Manzel A, Titze J, Kvakan H, Yosef N, Linker RA, et al. Sodium chloride drives autoimmune disease by the induction of pathogenic TH17 cells. Nature 2013;496:518–22. https://doi.org/10.1038/nature11868.

[72] Barron A, McCarthy CM, O'Keeffe GW. Preeclampsia and neurodevelopmental outcomes: potential pathogenic roles for inflammation and oxidative stress? Mol Neurobiol 2021;58:2734–56. https://doi.org/10.1007/s12035-021-02290-4.

[73] Sultana Z, Maiti K, Aitken J, Morris J, Dedman L, Smith R. Oxidative stress, placental ageing-related pathologies and adverse pregnancy outcomes. Am J Reprod Immunol 2017;77. https://doi.org/10.1111/aji.12653.

[74] Kyozuka H, Murata T, Fukuda T, Yamaguchi A, Kanno A, Yasuda S, et al. Effect of preconception selenium intake on the risk for gestational diabetes: the Japan environment and children's study. Antioxidants 2021;10. https://doi.org/10.3390/antiox10040568.

[75] Misu H, Takamura T, Takayama H, Hayashi H, Matsuzawa-Nagata N, Kurita S, et al. A liver-derived secretory protein, selenoprotein P, causes insulin resistance. Cell Metabol 2010;12:483–95. https://doi.org/10.1016/j.cmet.2010.09.015.

[76] Mita Y, Nakayama K, Inari S, Nishito Y, Yoshioka Y, Sakai N, et al. Selenoprotein P-neutralizing antibodies improve insulin secretion and glucose sensitivity in type 2 diabetes mouse models. Nat Commun 2017;8. ARTN 165810.1038/s41467-017-01863-z.
[77] Stasinos S, Nasopoulou C, Tsikrika C, Zabetakis I. The bioaccumulation and physiological effects of heavy metals in carrots, onions, and potatoes and dietary implications for Cr and Ni: a review. J Food Sci 2014;79:R765–80. https://doi.org/10.1111/1750-3841.12433.
[78] Xu L, Liu Y, Zhao Q, Du H, Gao Y, Bai M, et al. Urinary element profiles and associations with cardiometabolic diseases: a cross-sectional study across ten areas in China. Environ Res 2022;205:112535. https://doi.org/10.1016/j.envres.2021.112535.
[79] Ahmad K, Wajid K, Khan ZI, Ugulu I, Memoona H, Sana M, et al. Evaluation of potential toxic metals accumulation in wheat irrigated with wastewater. Bull Environ Contam Toxicol 2019;102:822–8. https://doi.org/10.1007/s00128-019-02605-1.
[80] Shahbazi F, Ghasemi S, Sodaiezadeh H, Ayaseh K, Zamani-Ahmadmahmoodi R. The effect of sewage sludge on heavy metal concentrations in wheat plant (Triticum aestivum L.). Environ Sci Pollut Res Int 2017;24:15634–44. https://doi.org/10.1007/s11356-017-9178-z.
[81] Khosravi K, Barzegar R, Golkarian A, Busico G, Cuoco E, Mastrocicco M, et al. Predictive modeling of selected trace elements in groundwater using hybrid algorithms of iterative classifier optimizer. J Contam Hydrol 2021;242:103849. https://doi.org/10.1016/j.jconhyd.2021.103849.
[82] Andersen ZJ, Raaschou-Nielsen O, Ketzel M, Jensen SS, Hvidberg M, Loft S, et al. Diabetes incidence and long-term exposure to air pollution: a cohort study. Diabetes Care 2012;35:92–8. https://doi.org/10.2337/dc11-1155.
[83] Grassin-Delyle S, Martin M, Hamzaoui O, Lamy E, Jayle C, Sage E, et al. A high-resolution ICP-MS method for the determination of 38 inorganic elements in human whole blood, urine, hair and tissues after microwave digestion. Talanta 2019;199:228–37. https://doi.org/10.1016/j.talanta.2019.02.068.
[84] Popescu C, Hocker H. Hair - the most sophisticated biological composite material. Chem Soc Rev 2007;36:1282–91. https://doi.org/10.1039/b604537p.
[85] Bocca B, Ruggieri F, Pino A, Rovira J, Calamandrei G, Martinez MA, et al. Human biomonitoring to evaluate exposure to toxic and essential trace elements during pregnancy. Part A. concentrations in maternal blood, urine and cord blood. Environ Res 2019;177:108599. https://doi.org/10.1016/j.envres.2019.108599.
[86] Yu X, Chen L, Wang C, Yang X, Gao Y, Tian Y. The role of cord blood BDNF in infant cognitive impairment induced by low-level prenatal manganese exposure: LW birth cohort, China. Chemosphere 2016;163:446–51. https://doi.org/10.1016/j.chemosphere.2016.07.095.
[87] Deval G, Boland S, Fournier T, Ferecatu I. On placental toxicology studies and cerium dioxide nanoparticles. Int J Mol Sci 2021:22. https://doi.org/10.3390/ijms222212266.
[88] Palasz A, Segovia Y, Skowronek R, Worthington JJ. Molecular neurochemistry of the lanthanides. Synapse 2019;73:e22119. https://doi.org/10.1002/syn.22119.
[89] Hu XY, Yang JH, Sun YL, Gao X, Zhang LJ, Li YQ, et al. Lanthanum chloride impairs memory in rats by disturbing the glutamate-glutamine cycle and over-activating NMDA receptors. Food Chem Toxicol 2018;113:1–13. https://doi.org/10.1016/j.fct.2018.01.023.
[90] Sun Y, Yang J, Hu X, Gao X, Li Y, Yu M, et al. Conditioned medium from overly excitatory primary astrocytes induced by La(3+) increases apoptosis in primary neurons via upregulating the expression of NMDA receptors. Metallomics 2018;10:1016–28. https://doi.org/10.1039/c8mt00056e.
[91] Zhao HQ, Cheng Z, Hu RP, Chen J, Hong MM, Zhou M, et al. Oxidative injury in the brain of mice caused by lanthanid. Biol Trace Elem Res 2011;142:174–89. https://doi.org/10.1007/s12011-010-8759-1.
[92] Rahimi N, Hassanipour M, Yarmohammadi F, Faghir-Ghanesefat H, Pourshadi N, Bahramnejad E, et al. Nitric oxide and glutamate are contributors of anti-seizure activity of rubidium chloride: a comparison with lithium. Neurosci Lett 2019;708:134349. https://doi.org/10.1016/j.neulet.2019.134349.
[93] Xiao L, Zan G, Qin J, Wei X, Lu G, Li X, et al. Combined exposure to multiple metals and cognitive function in older adults. Ecotoxicol Environ Saf 2021;222:112465. https://doi.org/10.1016/j.ecoenv.2021.112465.
[94] Wu H, Zhou W, Yildirim T. Alkali and alkaline-earth metal amidoboranes: structure, crystal chemistry, and hydrogen storage properties. J Am Chem Soc 2008;130:14834–9. https://doi.org/10.1021/ja806243f.
[95] Hu L, Zhu S, Peng X, Li K, Peng W, Zhong Y, et al. High salt elicits brain inflammation and cognitive dysfunction, accompanied by alternations in the gut microbiota and decreased SCFA production. J Alzheimers Dis 2020;77:629–40. https://doi.org/10.3233/JAD-200035.
[96] Kaushik DK, Thounaojam MC, Kumawat KL, Gupta M, Basu A. Interleukin-1 beta orchestrates underlying inflammatory responses in microglia via Kruppel-like factor 4. J Neurochem 2013;127:233–44. https://doi.org/10.1111/jnc.12382.
[97] Che C, Li J, Dong F, Zhang C, Liu L, Sun X, et al. Seasonal characteristic composition of inorganic elements and polycyclic aromatic hydrocarbons in atmospheric fine particulate matter and bronchoalveolar lavage fluid of COPD patients in Northeast China. Respir Med 2020;171:106082. https://doi.org/10.1016/j.rmed.2020.106082.
[98] Hassan NA, Hashim Z, Hashim JH. Impact of climate change on air quality and public health in urban areas. Asia Pac J Publ Health 2015;28:38S–48S. https://doi.org/10.1177/1010539515592951.
[99] Fireman Klein E, Klein I, Ephrat O, Dekel Y, Kessel A, Adir Y. Trajectory of inhaled cadmium ultrafine particles in smokers. BMJ Open Respir Res 2021;8. https://doi.org/10.1136/bmjresp-2021-001000.
[100] Yu J, Wang J, Xu L, Li L, Liu R, Liu J. Characteristics of chemical components of PM2.5 and its seasonal variations in Chongqing urban area. Chin J Environ Eng 2017;11(12):6372–8.
[101] Wang H, Qiao B, Zhang L, Yang F, Jiang X. Characteristics and sources of trace elements in PM(2.5) in two megacities in Sichuan Basin of southwest China. Environ Pollut 2018;242:1577–86. https://doi.org/10.1016/j.envpol.2018.07.125.
[102] Bin C. [Beneficiation test of a lithium polymetallic mine in Sichuan]. Modern Mining 2019:216–8.
[103] Li S, Wei G, Yu X, Yu J, Kang Y. Research Progress in Environmental Risk Assessment and Pollution Control of Light Rare Earth Mines. Agric Res Appl 2021;34(1):65–70.
[104] Mendil D, Uluozlu OD, Tuzen M, Soylak M. Investigation of the levels of some element in edible oil samples produced in Turkey by atomic absorption spectrometry. J Hazard Mater 2009;165:724–8. https://doi.org/10.1016/j.jhazmat.2008.10.046.
[105] Trapasso G, Chiesa S, Freitas R, Pereira E. What do we know about the ecotoxicological implications of the rare earth element gadolinium in aquatic ecosystems? Sci Total Environ 2021;781:146273. https://doi.org/10.1016/j.scitotenv.2021.146273.