Prenatal metal levels and congenital anomalies of the kidney and urinary tract: The Japan Environment and Children's Study

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Prenatal metal levels and congenital anomalies of the kidney and urinary tract: The Japan Environment and Children's Study

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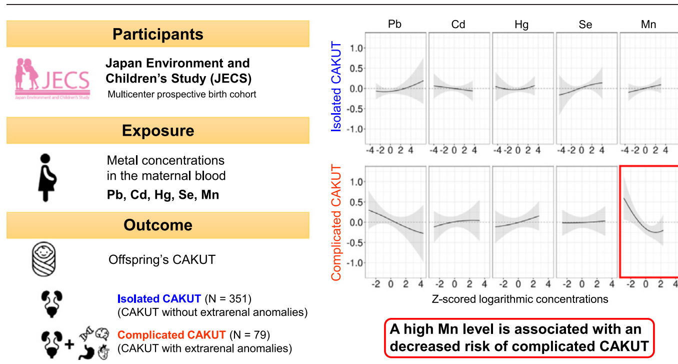
HIGHLIGHTS

- Levels of Pb, Cd, Hg, Se, and Mn were measured in maternal blood during pregnancy.
- Mn was inversely related to anomalies involving the renal and extrarenal systems.
- Prenatal Mn deficiency may increase the risk of the subtype of renal anomalies.

GRAPHICAL ABSTRACT



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ABSTRACT

Background: Prenatal exposure to metal elements has been reported as a potential risk factor for congenital malformation. However, studies on the relationship with congenital anomalies of the kidney and urinary tract (CAKUT) are very scarce.

Methods: Participants of a prospective cohort from the Japan Environment and Children's Study, conducted at 15 research centers, were recruited between January 2011 and March 2014. The exposure factors were concentrations of lead (Pb), cadmium (Cd), mercury (Hg), selenium (Se), and manganese (Mn) measured from maternal whole blood in the second or third trimester. The primary outcome was CAKUT diagnosed during the first three years of life, which was classified into isolated cases and complicated cases accompanied by extrarenal congenital defects. To conduct a nested case–control design within the cohort, we selected 351 isolated cases with 1404 matched controls, and 79 complicated cases with 316 matched controls.

Abbreviations: CAKUT, congenital anomalies of the kidney and urinary tract; BKMR, Bayesian kernel machine regression; JECS, Japan Environment and Children's Study; Mn-SOD, manganese superoxide dismutase.

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Results: A logistic regression model was used to examine the associations between individual metal concentrations and each subtype of CAKUT. A higher level of Se was associated with an increased risk of isolated CAKUT (adjusted odds ratio [95 % confidence interval]: 3.22 [1.33–7.77]). Meanwhile, higher levels of Pb and Mn were associated with a reduced risk of the complicated subtype (0.46 [0.24–0.90] and 0.33 [0.15–0.73], respectively). A Bayesian kernel machine regression model accounting for mixed effects of multiple metals further demonstrated that a higher level of Mn alone was significantly associated with a reduced occurrence of the complicated subtype.
Conclusions: Using a stringent statistical approach, the present study demonstrated that a higher Mn concentration in the maternal blood was associated with a lower risk of complicated CAKUT in offspring. Further cohort and experimental studies are needed to verify the clinical impact of this finding.

1. Introduction

Congenital anomalies of the kidney and urinary tract (CAKUT), which includes a variety of malformations in the urinary system, accounts for 20–30 % of all congenital malformations, and often results in end-stage renal disease in childhood (Nicolaou et al., 2015). CAKUT occurs in association with alteration of renal organogenesis, which begins around the 4th week of gestation and continues up to the 36th week (Murugapoopathy and Gupta, 2020). The pathogenesis of CAKUT has been investigated in genetic, epigenetic and epidemiologic studies (Murugapoopathy and Gupta, 2020; Nicolaou et al., 2015). Although a number of monogenic genes of CAKUT have been found, they explain only a small portion of the patients, suggesting the involvement of intrauterine environmental factors (van der Ven et al., 2018). Regarding environmental risk factors, previous studies have reported maternal deficiency of vitamin A (Goodyer et al., 2007) and folate (Hernández-Díaz et al., 2000), maternal ingestion of excessive alcohol (Qazi et al., 1979), folic acid (Groen In 't Woud, 2016), cocaine (Battin et al., 1995), angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers (Sekine et al., 2009), and maternal chronic diseases including obesity, diabetes, cancer, and kidney disease (Dart et al., 2015; Groen In 't Woud, 2016; Nishiyama et al., 2022). Nevertheless, the cause is unknown in the majority of cases of CAKUT.

The Japan Environment and Children's Study (JECS) is an ongoing nationwide prospective birth cohort study that involves >100,000 mother-child dyads, and is funded by the Ministry of the Environment of Japan (Kawamoto et al., 2014; Michikawa et al., 2018). It aims to evaluate the effects of environmental factors, especially exposures to chemicals, during fetal period and in early childhood on a variety of health outcomes including reproduction/pregnancy complications, congenital anomalies, developmental disorders, and immune/metabolic system dysfunction. Among various chemicals, the JECS measured and confirmed the concentrations of lead (Pb), cadmium (Cd), mercury (Hg), selenium (Se), and manganese (Mn) in the maternal blood of all JECS participants during the second or third trimester and then distributed them to JECS researchers in September 2019. The reason for the selection of the five metals was that these could be harmful elements as well as fundamental coexposures when seeking to evaluate the effect of other chemical contaminants on the child health (Nakayama et al., 2019).

Prenatal exposure to metals has long been considered to be a causative factor for congenital malformations. Metal elements are ingested by mothers from the daily intake of food or water, and the inhalation of air pollution, and are then transferred to the fetus through the placenta. Several studies have demonstrated positive associations of various congenital malformations with metal exposure: neural tube defects with Pb, Hg, Se, and Mn; congenital heart defects with Pb, Cd, and Se; and orofacial clefts with Pb, Cd, and Hg (Cengiz et al., 2004; Guo et al., 2019; Kundak et al., 2017; Liu et al., 2013; Liu et al., 2021; Nyanza et al., 2020; Ou et al., 2017; Pi et al., 2018; Yin et al., 2020). However, there is little information about the maternal effects of metals on the development of CAKUT in offspring.

The present study aimed to investigate the association of prenatal exposure to the metal elements Pb, Cd, Hg, Se, and Mn with the risk of CAKUT using a nested case–control design within the prospective JECS cohort. As outcomes, CAKUT was differentiated into isolated cases and complicated cases accompanied by extrarenal congenital defects because their pathomechanisms are suggested to be different (Lei et al., 2020; Nicolaou et al., 2015; Nishiyama et al., 2022; Vivante et al., 2014). We assessed the effects of each element on the occurrence of isolated and complicated CAKUT using a conventional logistic regression model and further studied the combined effects of these metals using a Bayesian kernel machine regression (BKMR) model (Bobb et al., 2018; Tian et al., 2021; Yin et al., 2020). The stringent analyses of the largest pediatric cohort in Japan first demonstrate that metal elements may influence the development of genitourinary CAKUT, offering a new perspective for intervention to optimize feto-maternal conditions.

2. Methods

2.1. Study design

The detailed design of the JECS has been described previously (Kawamoto et al., 2014; Michikawa et al., 2018). Briefly, pregnant participants were recruited at 15 research centers across Japan between January 2011 and March 2014. The basic characteristics of the mothers and children were comparable to those in national surveys, indicating that the study population of JECS is representative of the general Japanese population. The data of mothers and children used were obtained from medical records transcripts and self-report questionnaires completed by the parents. In this study, we used the "jecs-ta-20190930" fixed dataset, which was released in October 2019. The dataset contains all of the available data until children reached 36 months of age, where the data of 104,062 fetuses from 103,060 pregnancies were linked to the respective maternal data. The JECS was conducted in accordance with the Helsinki Declaration. The protocol was approved by the Ministry of Environment's Institutional Review Board for Epidemiological Studies and by the Ethics Committees of all the participating institutions (#100910001). Written informed consent was obtained from all participants.

2.2. Exposures and outcomes

Prenatal exposure to Pb, Cd, Hg, Se, and Mn was estimated by measuring concentrations of these metals in the maternal whole blood. The JECS planned to obtain the blood sample for research simultaneously with that for a regular assessment of pregnancy at a clinic visit in the second or third trimester of pregnancy. These concentrations were measured using inductively coupled plasma mass spectrometry on an Agilent 7700 device (Agilent Technologies, Tokyo, Japan). The details of the measurement methods have been described previously (Nakayama et al., 2019). The concentration was provided as gravimetric units (ng/g). For comparison with reference values and previous study reports, we converted the values to volumetric concentrations (μg/L), using 1.0506 as the specific gravity of typical human whole blood at 37 °C (Trudnowski and Rico, 1974).

Physician-diagnosed CAKUT and congenital extrarenal anomalies identified during the first three years of life were collected from multiple sources: the medical records transcripts at delivery and when the child was one month of age as well as the questionnaires when the child was 6, 12, 24 and 36 months of age. A child was judged as having an anomaly when it was reported from at least one source. CAKUT was further classified into isolated and complicated cases (Nishiyama et al., 2022). The former

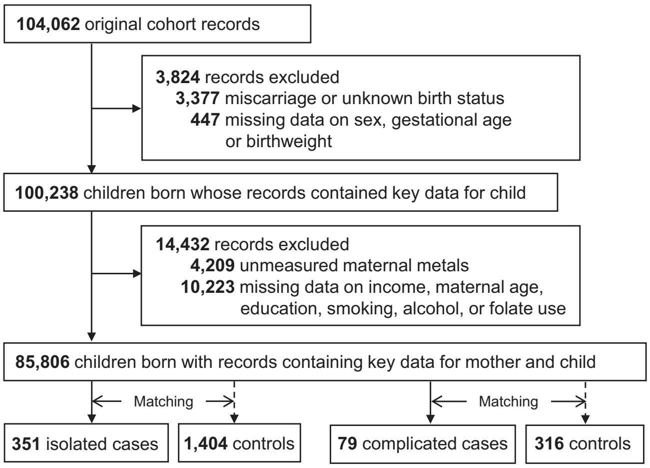

Fig. 1. Selection of cases and controls.

indicates patients in whom CAKUT manifested without extrarenal anomalies while the latter denotes patients with any extrarenal anomalies. CAKUT and extrarenal anomalies showed high variability (Supplementary Methods).

2.3. Selection of isolated and complicated CAKUT cases, and their controls

Fig. 1 shows the selection process of cases and controls using a nested case–control design in this cohort. After excluding 3377 fetuses due to miscarriage or unknown birth status and 447 children with missing data on sex, gestational age or birthweight, key data were available for 100,238 children. We then excluded 4209 children with unmeasured maternal metals and 10,223 children for whom data were unavailable on family income, maternal age, educational level, and smoking, alcohol, and folate use statuses, which could all be related to the occurrence of CAKUT, as indicated in our previous study (Nishiyama et al., 2022). Eventually, key data on mothers and children necessary for matching CAKUT cases with the controls were available for 85,806 children. The baseline characteristics and metal concentrations of the 18,256 children excluded were similar to those of the children eligible for the following steps, but they tended to have a younger gestational age and a lower birthweight (Supplementary Table S1).

The isolated cases and corresponding controls were group-matched at a 1:4 ratio, based on sex, gestational age, birthweight, family income, maternal age, educational level, smoking, alcohol, and folate use, after excluding children born to mothers with a history of kidney disease ($n = 13$) or cancer ($n = 10$), since these two diseases are closely associated with this subtype of CAKUT (Nishiyama et al., 2022). Similarly, the complicated cases and their controls were matched after the exclusion of children born to mothers with diabetes ($n = 9$) or hyperthyroidism ($n = 4$). The controls were chosen from participants who had neither CAKUT nor any extrarenal anomalies. These matching procedures selected 351 isolated cases and their matched 1404 controls as well as 79 complicated cases and their matched 316 controls. These matchings were considered successful because there were no differences in any key factors between cases and the corresponding controls (Table 1).

2.4. Statistical analyses

To estimate the associations between individual metal exposure and the risk of isolated or complicated CAKUT, we used a logistic regression model with a generalized estimating equation accounting for the clustering effect of research centers. We chose an unconditional model rather than a conditional regression model because there were no problems of sparse data (Pearce, 2016). In the model, the concentrations of each metal element were analyzed after natural log-transformation or quartile categorization (Supplementary Table S2), and all of the maternal and child factors used in the matching procedures as well as gestational age at maternal blood sampling were included as covariates (Pearce, 2016).

Table 1
Baseline characteristics of the case-control pairs in isolated and complicated CAKUT.

	Isolated CAKUT		Complicated CAKUT	
	Case ($n = 351$)	Controls ($n = 1404$)	Case ($n = 79$)	Controls ($n = 316$)
Child factors				
Male, No. (%)	271 (77.2)	1084 (77.2)	46 (58.2)	184 (58.2)
Gestational age at birth, mean (SD), week	39.0 (1.8)	39.0 (1.6)	38.0 (2.5)	38.1 (2.3)
Birthweight, mean (SD), gram	3040 (453)	3045 (446)	2724 (609)	2725 (569)
Maternal factors				
Family income, No. (%)				
Low (< 4,000,000 JPY)	133 (37.9)	532 (37.9)	33 (41.8)	132 (41.8)
Middle (4,000,000–5,999,999 JPY)	113 (32.2)	452 (32.2)	25 (31.6)	100 (31.6)
High (≥ 6,000,000 JPY)	105 (29.9)	420 (29.9)	21 (26.6)	84 (26.6)
Age, mean (SD), years	31.7 (4.9)	31.6 (4.9)	31.1 (4.6)	31.3 (5.2)
Education, No. (%)				
Junior high school	11 (3.1)	44 (3.1)	4 (5.1)	16 (5.1)
High school	250 (71.2)	1000 (71.2)	64 (81.0)	256 (81.0)
University/graduate school	90 (25.6)	360 (25.6)	11 (13.9)	44 (13.9)
Smoking during pregnancy, No. (%)	46 (13.1)	184 (13.1)	19 (24.1)	76 (24.1)
Alcohol during pregnancy, No. (%)	198 (56.4)	792 (56.4)	42 (53.2)	168 (53.2)
Folate use during pregnancy, No. (%)	112 (31.9)	448 (31.9)	24 (30.4)	96 (30.4)
Metals				
Gestational age at sampling, mean (SD), week	27.5 (3.0)	27.6 (3.1)	27.0 (3.1)	27.5 (3.2)
Median (interquartile range), μg/L				
Pb	6.29 (4.90–8.19)	6.10 (4.96–7.76)	5.86 (4.99–6.87)	6.38 (5.26–7.77)
Cd	0.714 (0.522–0.952)	0.692 (0.518–0.957)	0.693 (0.546–0.903)	0.727 (0.550–1.011)
Hg	3.96 (2.61–5.69)	3.79 (2.67–5.43)	3.98 (2.72–5.56)	3.68 (2.57–5.28)
Se	180 (166–193)	175 (164–192)	177 (164–192)	179 (164–190)
Mn	16.4 (13.6–19.6)	16.0 (13.3–19.3)	15.2 (12.3–18.4)	16.4 (13.8–20.2)

Abbreviations: CAKUT, congenital anomalies of the kidney and urinary tract; JPY, Japanese yen; SD, standard deviation.

Table 2
Association between maternal metal levels (log-transformed) and offspring's CAKUT.

	Isolated CAKUT	Complicated CAKUT
Pb	1.24 (0.90–1.71)	**0.46 (0.24–0.90)**
Cd	0.98 (0.77–1.24)	1.03 (0.61–1.75)
Hg	1.15 (0.95–1.40)	1.24 (0.66–2.32)
Se	**3.22 (1.33–7.77)**	1.22 (0.41–3.70)
Mn	1.45 (0.97–2.17)	**0.33 (0.15–0.73)**

Values are presented as odds ratios (95 % confidence intervals) adjusted for sex, gestational age at birth, birthweight, family income, maternal age, education, smoking, alcohol and folate use during pregnancy, and gestational age at blood sampling. Bold text represents statistical significance ($P < 0.05$).
Abbreviations: CAKUT, congenital anomalies of the kidney and urinary tract.

However, such conventional regression models did not account for the potential mixed effects of concurrent multiple metals on the outcomes. Therefore, we further used a Bayesian kernel machine regression (BKMR) model with a probit link function for the binary outcomes of CAKUT (Bobb et al., 2018; Bobb et al., 2015). This model uses a Markov chain Monte Carlo algorithm, flexibly estimates the exposure-response function of the association between exposure and the outcome without specifying a priori functions, and then yields interpretable quantities on the scale of the latent continuous outcome (continuous marker of the binary outcome: >0 corresponds to disease while <0 corresponds to control). It can approach the combined effects of metals as well as the single effect of each metal on the outcome. In this model, exposure concentrations were natural log-transformed and the log-transformed concentrations of the metals were further converted into z scores. Because the correlations between the metal levels were not strong (Supplementary Fig. S1), component-wise variable selection was applied. In the BKMR model, the covariates included were the same as the logistic regression analyses and the clustering effect of research centers was taken into account. The BKMR model was repeated 50,000 times and then yielded a posterior inclusion probabilitiy (PIP), which is a measure of importance for each exposure within the exposure-response function and a probit coefficient (β_{probit}) that represents the estimated effect size of the association between exposure and outcome. All statistical analyses were performed using the R software program, version 4.0.3 (The R Core Team, Vienna, Austria). The R packages 'geepack' and 'bkmr' were used for the generalized estimating equation and BKMR analysis, respectively.

3. Results

3.1. Conventional logistic regression analysis

Logistic regression models were used to examine the associations between individual metal concentrations and the risk for each subtype of CAKUT. In the analysis of log-transformed metal levels (Table 2), a higher level of Se was associated with an increased risk of isolated CAKUT (adjusted odds ratio [95 % confidence interval]: 3.22 [1.33–7.77]). Meanwhile, higher levels of Pb and Mn were associated with a reduced risk of the complicated subtype (0.46 [0.24–0.90] and 0.33 [0.15–0.73], respectively). The results of quartile analysis produced similar results (Supplementary Table S3).

3.2. BKMR analysis

BKMR models were used to account for possible nonlinear and interactive effects of concurrent multiple metals on the outcomes. The combined effects of the five metal elements on the binary outcome of isolated or complicated CAKUT were assessed by the estimated values when the concentration of all the metals were at specific percentiles (from 10th to 90th percentiles) in comparison to values when these were all at the 50th percentile (Fig. 2). With higher levels of the five metals, the risk of isolated CAKUT showed a slight increasing trend while that of complicated CAKUT had a weak decreasing trend, although these trends were not statistically significant at any of the percentiles tested. PIPs were calculated to investigate which metals mainly contributed to the occurrence of CAKUT among multiple metals to which mothers were concurrently exposed. All five metals showed low PIPs in the isolated subtype of CAKUT whereas Mn exhibited a high PIP of 0.76 (Fig. 3) in the complicated subtype.

We investigated the univariate exposure-response function between a single metal exposure and the outcome, where all the other metal exposures were fixed at their median value. There was no significant association between each metal exposure and the isolated subtype of CAKUT (Fig. 4), as was expected from the low PIPs of the five metals in this subtype. In contrast, a higher level of Mn was significantly associated with a lower occurrence of the complicated subtype (Fig. 5). To estimate the possible interaction of Mn with Pb, Cd, Hg or Se in the occurrence of complicated cases, we further visualized each exposure-response function between the primary exposure of Mn and the outcome, when a secondary exposure was fixed to the 25th, 50th, or 75th percentiles and the other three metals were at the median values (Fig. 6). There were no obvious interactions

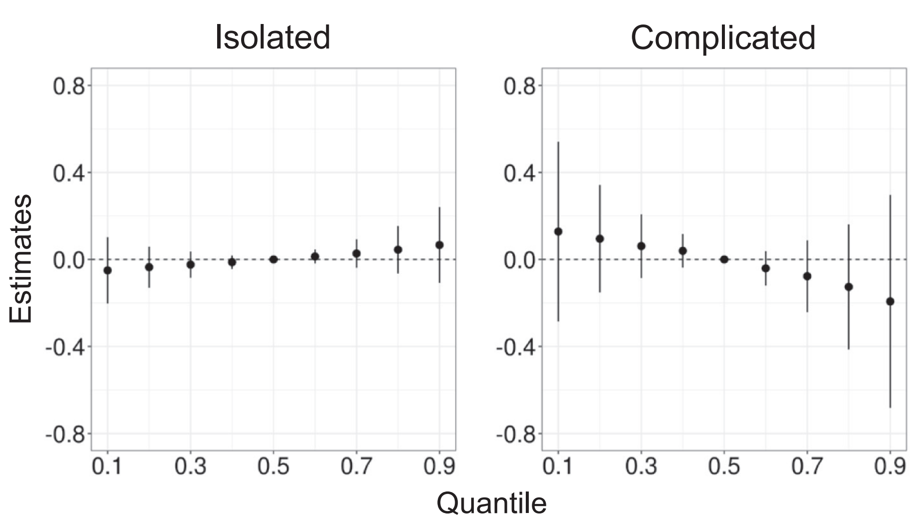

Fig. 2. The combined effects of the 5 metal elements on the risk of isolated or complicated CAKUT. The dots indicate the estimated difference in a latent continuous outcome (continuous marker of isolated or complicated CAKUT) when all of the metals were at a particular percentile (ranging from 10th to 90th percentiles) in comparison to when all of the metals were at their 50th percentile. The vertical lines represent the 95 % confidence intervals.

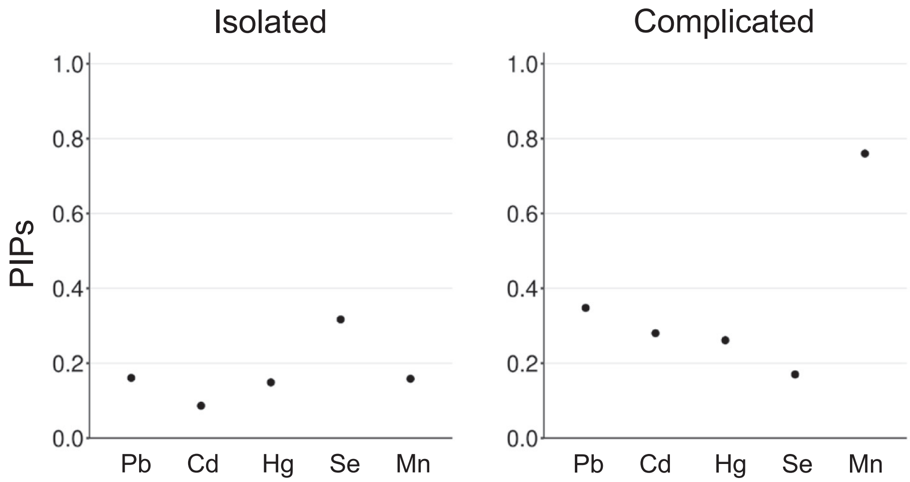

Fig. 3. Posterior inclusion probabilities (PIPs) for each of the metals in isolated or complicated CAKUT.

between Mn and other metals although the curves of the functions may have been slightly steeper when Pb was at a higher level (75th percentile) in comparison to lower levels (50th and 25th percentiles).

4. Discussion

Using a nested case–control design within a large prospective cohort study, we investigated the association between metal concentrations in the maternal blood and CAKUT in offspring. Conventional logistic regression models for individual metals showed a positive association between Se and the isolated subtype as well as inverse associations between Pb and Mn and the complicated subtype. However, in a probit BKMR model that flexibly accounted for mixed effects of multiple metal exposures, the association between Mn and complicated CAKUT was the only association that remained, demonstrating that the risk of complicated CAKUT decreased as Mn levels increased.

The current study revealed a lower risk of complicated CAKUT with a higher level of Mn in maternal blood. A very limited number of studies have shown an association between maternal Mn levels and congenital malformations. Some studies have demonstrated that higher Mn levels in maternal blood or placenta are associated with an elevated risk of neural tube defects in offspring (Özel et al., 2019; Yin et al., 2020). Conversely, another study showed that hair Mn levels were significantly lower in mothers of infants with congenital malformations than in mothers of control infants (Saner et al., 1985). Mn is an essential trace element that is found in all tissues and is involved in a number of enzymes, such as arginase, glutamine synthetase, phosphoenolpyruvate decarboxylase, and Mn superoxide dismutase. Because Mn is required for normal immune function, regulation of blood sugar and cellular energy, reproduction, digestion, bone growth, and antioxidant defense against superoxide free radicals (Aschner and Aschner, 2005), insufficient Mn may have adverse effects on the developing organs of the fetus. Although increased metal exposure usually receives much attention in relation to the association with the occurrence of congenital malformations, the association between decreased metal exposure and congenital malformations is also worth noting.

Among the various potential effects of Mn insufficiency on congenital anomalies, dysfunction of antioxidant defenses may be involved in the pathogenesis of complicated CAKUT. In the developing embryo and fetus, the formation of reactive oxygen species, or oxidative stress, has been suggested to cause fetal structural abnormalities and death by damaging cellular lipids, protein and DNA and by altering signal transduction (Wells et al., 2009). Mn is an important cofactor of manganese superoxide dismutase (Mn-SOD), which catalyzes the dismutation of superoxide radicals into oxygen and hydrogen peroxide. The Mn levels in pregnant women are much higher than those in nonpregnant women (Kim, 2018). Furthermore, Mn crosses the placental barrier by active transport (Krachler et al., 1999); thus, its levels in cord blood are as much as three times higher than those in maternal blood (Zhou et al., 2019). Such increased Mn levels may underscore its importance for the organogenesis of the fetus. Several studies have demonstrated the involvement of oxidative stress in teratogenesis of multiple organs, such as the central nervous system, heart, and gastrointestinal tract (Impellizzeri et al., 2020; Wells et al., 2005; Wells et al., 2009). A rat model revealed that prenatal exposure to oxidative stress could lead to kidney dysplasia and renal fibrosis, which was ameliorated by an antioxidant agent, vitamin C (Zhu et al., 2017). As Mn-SOD activity is correlated with serum Mn concentration in humans (Davis and Greger, 1992), Mn insufficiency could result in dysfunction of Mn-SOD and might then increase the risk of congenital malformations in the renal and extrarenal systems via oxidative stress.

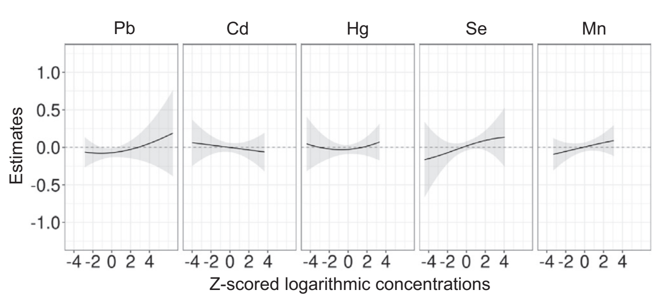

Fig. 4. The univariate exposure-response relationships between a single metal exposure and isolated CAKUT. The line and band indicate the estimated value and 95 % confidence interval of the association, where the other metal exposures were fixed at their median levels, respectively.

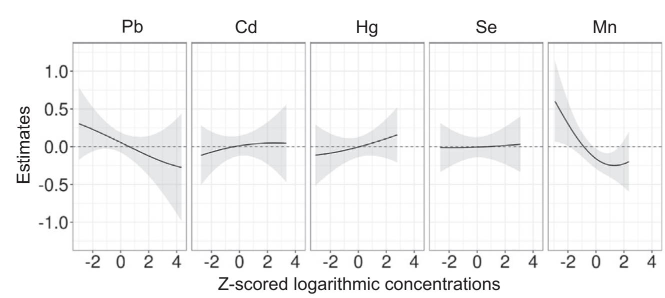

Fig. 5. The univariate exposure-response relationships between a single metal exposure and complicated CAKUT. The line and band indicate the estimated value and 95 % confidence interval of the association, where the other metal exposures were fixed at their median levels, respectively.

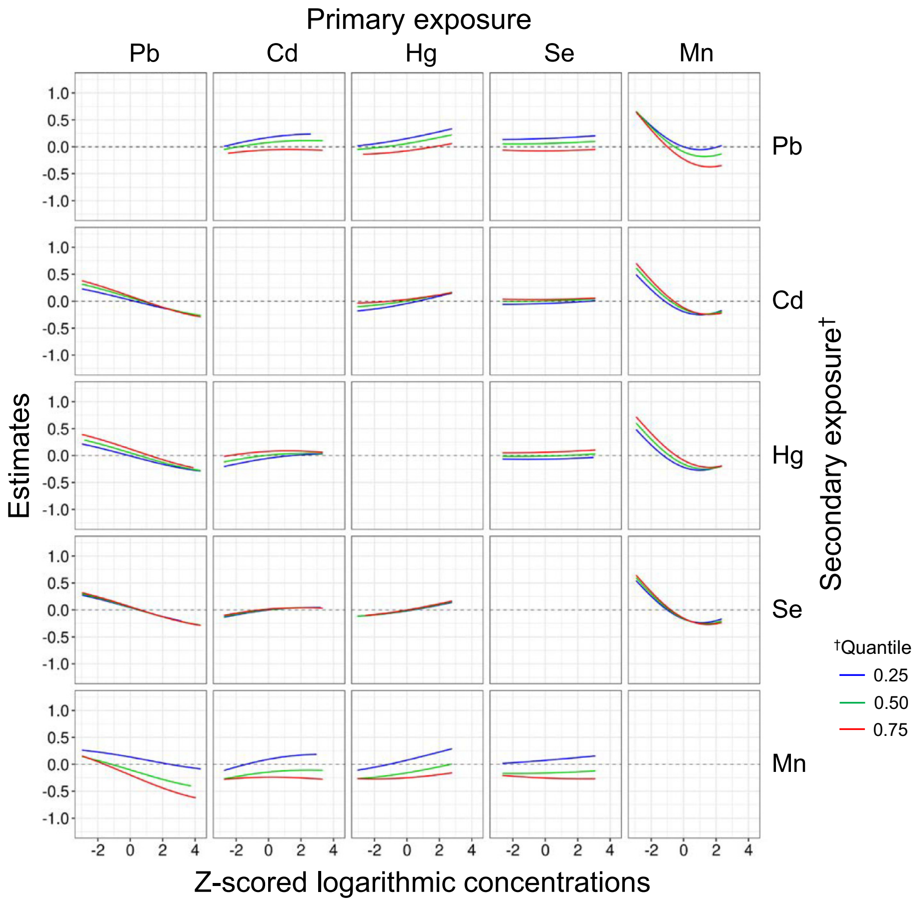

Fig. 6. The estimated values of the bivariate exposure-response functions of every two metals in the complicated CAKUT. For example, the rightmost top panel indicates the association between Mn levels and the outcome when Pb is fixed at the 25th (blue), 50th (green), or 75th (red) percentile and other metals (Cd, Hg, and Se) are fixed to their 50th percentiles (medians).

The BKMR method used in this study was very useful to identify Mn as a key exposure among the five metals in relation to the complicated subtype of CAKUT. The logistic regression models of individual metals additionally showed a positive association between Se and the isolated subtype as well as an inverse association between Pb and the complicated subtype. Pb and Se have been reported to show positive associations with congenital malformations including neural tube, heart, and orofacial defects (Cengiz et al., 2004; Guo et al., 2019; Kundak et al., 2017; Ou et al., 2017; Pi et al., 2018; Yin et al., 2020). To the best of our knowledge, there have been no reports demonstrating an association between prenatal exposure to Se or Pb and CAKUT. In reality, pregnant women were concurrently exposed to mixtures of multiple metals, and such concurrent exposures may modify the associations that are estimated by logistic models. Our BKMR models addressed this issue and revealed the sole significant association between increased Mn and a decreased risk of complicated CAKUT.

The strength of this study was the nested case–control design, in which the controls were rigorously matched to cases according to maternal and child characteristics. The anomalies among children were collected consecutively until the children were three years of age, and included malformations of the renal system, as well as malformations of other organs, enabling discrimination between isolated and complicated cases. Moreover, our main result, which was drawn from the logistic regression models was refined using a BKMR model that accounted for the nonlinear and nonadditive effects of multiple metal elements.

The present study was associated with several limitations. Although the diagnoses of CAKUT were made by physicians, the questionnaires did not collect any detailed information about the onset, severity, or diagnostic procedures. Some cases of CAKUT in offspring would have been missed because not all of the participants received extensive renal examinations, which possibly resulted in a bias. Furthermore, 18,256 children were excluded before the selection of cases and controls because of missing information on key factors, which might have led to another bias. To measure exposure, maternal blood was sampled at different times during the second or third trimester of pregnancy. Because considerable amounts of the five metals, especially Pb, Cd, and Hg, are contained in blood cells, measuring them in whole blood would be advantageous. However, such later time ranges may not directly reflect maternal exposure during the pivotal window for development of the kidney and urinary tract. In addition, although CAKUT is considered to result from the interaction between genetic and environmental factors, at this time, genetic analyses were not performed in this study. Thus, the results regarding complicated CAKUT, in particular, should be interpreted with caution because this type is generally considered more influenced by genetic factors, and the sample size of our analysis was small.

5. Conclusion

The current study used the novel approach of the BKMR model, which accounted for mixed effects of exposure to multiple metals and found that a higher concentration of Mn in the maternal blood during pregnancy was associated with a lower risk of complicated CAKUT in offspring. For the prevention of congenital malformations in offspring, it may be necessary to pay more attention to not only the excess trace elements during pregnancy but also the deficiency of trace elements. This finding should be verified by further research, including replication studies and Mn-loading tests in pregnant animals.

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CRediT authorship contribution statement

Yuka Iwaya: Conceptualization, Investigation, Writing – original draft. **Masafumi Sanefuji:** Conceptualization, Investigation, Methodology, Formal analysis, Resources, Writing – original draft. **Kei Nishiyama:** Conceptualization, Investigation, Writing – review & editing. **Yuri Sonoda:** Investigation, Writing – review & editing. **Norio Hamada:** Investigation, Writing – review & editing. **Reiko Suga:** Investigation, Writing – review & editing. **Masayuki Ochiai:** Investigation, Writing – review & editing. **Masayuki Shimono:** Investigation, Writing – review & editing. **Koichi Kusuhara:** Supervision, Project administration, Writing – review & editing. **Shouichi Ohga:** Supervision, Project administration, Writing – review & editing.

Data availability

Data are unsuitable for public deposition due to ethical restrictions and legal framework of Japan. It is prohibited by the Act on the Protection of Personal Information (Act No. 57 of 30 May 2003, amendment on 9 September 2015) to publicly deposit data containing personal information. Ethical Guidelines for Medical and Health Research Involving Human Subjects enforced by the Japan Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labour and Welfare also restricts the open sharing of epidemiological data. All inquiries about access to data should be sent to: jecs-en@nies.go.jp. The person responsible for handling enquiries sent to this e-mail address is Dr. Shoji F. Nakayama, JECS Programme Office, National Institute for Environmental Studies.

Declaration of competing interest

The authors declare that they have no competing interests in association with the present study.

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Appendix A. Supplementary data

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