Sex-specific differences in early renal impairment associated with arsenic, lead, and cadmium exposure among young adults in Taiwan

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Received: 25 October 2021 / Accepted: 25 February 2022 / Published online: 10 March 2022
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Abstract
Exposure to a single metal has been reported to damage renal function in humans. However, information regarding the association between multiple-metal exposure and markers for early renal impairment in different sexes among the young adult Taiwanese population is scarce. We assessed the association between exposure to arsenic (As), cadmium (Cd), and lead (Pb), and early renal impairment markers using urinary microalbumin (MA), β2-microglobulin (β2MG), and N-acetyl-beta-D-glucosaminidase (NAG) by analyzing 157 young adults aged 20–29 years, in Taiwan. Inductively coupled plasma mass spectrometry was used to determine urinary As, Cd, and Pb levels. Regression models were applied to different sex groups. The results showed that after adjusting for potential confounding factors and each metal, urinary Cd levels were significantly positively associated with urinary MA (β=0.523, 95% CI: 0.147–0.899) and β2MG (β=1.502, 95% CI: 0.635–2.370) in males. However, the urinary Cd level was significantly positively associated with only urinary NAG (β=0.161, 95% CI: 0.027–0.296) in females. This study thus indicates that the effect of exposure to metals (especially Cd) on early renal impairment among young adults in Taiwan is sex-specific. Our study results could contribute toward developing early intervention programs for decreasing the incidence of renal dysfunction. Further studies are warranted to confirm our findings and clarify the potential mechanisms involved.

Keywords Cadmium · Early renal impairment · Sex-specific · Young adults

Introduction
Arsenic (As), cadmium (Cd), and lead (Pb) cause nephrotoxicity and are widely distributed in the environment. These metals are particularly a concern in Taiwan because previous studies have revealed many human health issues associated with these metals. Regarding As, the Blackfoot disease, an endemic in Taiwan in the 1960s, was caused by As (Tseng et al. 1968); moreover, studies conducted in Taiwan in recent years have indicated that the presence of As in urine is associated with renal impairment (Yuan et al. 2020) and increased renal cell carcinoma (Hsueh et al. 2021). A previous study has also reported the associations between urinary As levels and early renal impairment and considered As to be a risk factor for tubular injury (Robles-Osorio et al. 2012). Regarding Cd, in our previous study, we found that urinary Cd levels in the general Taiwanese population had slightly increased over the past three decades, and exposure levels in Taiwan were higher than in other developed countries (Liao et al. 2019). The main route of Cd exposure in the general

Responsible Editor: Lotfi Aleya

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population is through the consumption of food, especially rice, which is a major part of the Taiwanese diet (Lien et al. 2021), or through smoking (Faroon et al. 2012). In addition, Cd exposure has been known to affect kidney function as it is associated with tubular dysfunction, hypercalciuria, and low-molecular-weight proteinuria (de Burbure et al. 2006; Goyer 1989, Prozialeck & Edwards 2012). A previous survey in the US National Health and Nutrition Examination Survey (NHANES 1999–2006) found that anything higher than a low level of urinary and blood Cd will increase the risk of chronic kidney disease (CKD) and albuminuria in participants of ≥ 20 years of age (Ferraro et al. 2010). Regarding Pb, urinary levels in the general population declined owing to the banning of leaded gasoline and the introduction of unleaded gasoline in 2000 at Taiwan; nevertheless, we found that urinary Pb levels were higher than in other developed countries (Liao et al. 2019). Some studies have reported that Pb is associated with renal dysfunction, with even low-level Pb exposure being related to the development of CKD (Brewster & Perazella 2004, Ekong et al. 2006; Staessen et al. 1992). However, there are few studies that discuss As, Cd, and Pb exposure and early renal impairment in young Taiwanese adults.

Differences in renal impairment according to sex have been discussed in many studies dealing with issues such as kidney cancer, CKD, hemodialysis, and end-stage renal disease (ESRD) (Carrero et al. 2018; Cobo et al. 2016; Kainz et al. 2019; Peired et al. 2021). Some previous studies have indicated that the incidence of kidney cancer is higher in men than in women (Lughezzani et al. 2019; Scelo et al. 2018). A review study concluded that while the proportion of women with predialysis CKD is higher than that of men because of their longer life expectancy, kidney function declines faster in men than in women (Carrero et al. 2018). A study in hemodialysis patients has found that fewer women than men were being treated with dialysis, and sex-specific hemodialysis data may be country and age-group specific; these differences are caused by factors beyond biology (Hecking et al. 2014). Sex-based differences related to renal impairment are well documented, but the environmental factors, such as metals, are not well understood.

CKD has been recognized as a global public issue. A study in 2014 has reported that Taiwan has the highest ESRD incidence and prevalence in the world (Lin et al. 2014), leading to serious financial burden on Taiwan’s National Health Insurance. Traditional biomarkers, such as albumin or estimated glomerular filtration rate (eGFR), only increase when a significant filtration capacity has several injuries and already occurred in renal cells (Levey & Coresh 2012, Zhang & Parikh 2019). Early identification of renal impairments is an important unmet medical need (Lousa et al. 2020). Renal is a target organ in heavy metal toxicity for its capability to reabsorb and concentrate divalent ions and metals (Lentini et al. 2017). Studies across the world have demonstrated that exposure to a single nephrotoxic metal such as As, Cd, or Pb reduces renal function in the general population (Kim et al. 2015; Sun et al. 2019). Humans are exposed to multiple metals during their lifetime, and the effects of multiple-metal exposure in humans cannot be ascertained by summing up the effects of single-metal exposures. Nevertheless, few studies have addressed metal co-exposure in young adults of both sexes, and its impact on renal functioning. Identifying risk factors, including sex and incidences of single or co-exposure to metals at a young age, or using early renal impairment markers could contribute to our knowledge of early intervenable factors for decreasing the incidence of renal dysfunction.

Therefore, our research aims to investigate the effects of As, Cd, and Pb exposures on early renal impairment markers in different sexes. Our study is valuable in that it comprehensively evaluates the associations between the co-exposure to metals (namely As, Cd, and Pb) and early renal impairment markers in different sexes.

**Materials and methods**

**Ethics statement**

This study was approved by the TMU-Joint Institutional Review Board (No. N202005041). Written informed consent from each participant was obtained prior to study enrollment.

**Study population**

This is a cross-sectional study to assess the association between metal exposure and early renal impairment among young adults in Taiwan. A total of 157 participants were recruited for this study between February and May of 2021. Participants who claimed to have no history of renal diseases were included in this study; the answer to questions pertaining to medical history of related to renal diseases was double-checked. All participants were Taiwanese, resided in northern Taiwan, and were aged 20 – 29 years.

**Data and specimen collection**

We assessed the questionnaires and specimens from each participant and obtained basic demographic information (i.e., age, body mass index (BMI), and education level), life habits (i.e., drinking, cigarette smoking, alcohol consumption), and other related factors (i.e., incense use, supplements use). Urine samples were collected from each participant and stored in polypropylene tubes. The urine specimens were stored at −20 °C until they could be
analyzed for levels of the major ubiquitous heavy metals (As, Cd, and Pb) and makers for early renal impairment.

Measurement of urinary metal levels and markers of early renal impairment

We used a published method to analyze certain metals in a urine sample (Liao et al. 2018, 2015; Tsai et al. 2015). After thawing the samples, 1-mL samples were diluted tenfold using 9 mL of 2% (v/v) nitric acid (J.T. Baker Chemical Company, Phillipsburg, NJ, USA) in 15-mL polypropylene tubes. Inductively coupled plasma-mass spectrometry (ICP-MS, Thermo Scientific X-SERIES II, Germany) was used to determine the levels of urinary As, Cd, and Pb.

A guideline for quality control and calculation of the method detection limit (MDL) was obtained through modified of the National Institute of Environmental Analysis (NIEA), Taiwan Environmental Protection Administration (EPA) (NIEA PA-103, PA-104, PA-107, 2005), which is modeled on the standard of the National Environmental Laboratory Accreditation (NELAC 2003). The calibration curves ranged from 0.01 to 10 ppb for As, Cd, and Pb (correlation coefficient \( R^2 > 0.995 \)), and a one-sample check for the calibration curve was performed. To ensure the quality of the analysis results, one blank, spiked, duplicated, and quality-control sample each was prepared for every 10 samples (one batch). The blank sample of all the metals was less than twice the MDL. The recovery of spiked and quality-checked samples was required to be within ±20%, and the duplicate samples were within ±10%. When the levels of the metals were below the MDL (As: 0.08 μg/L, Cd: 0.06 μg/L, and Pb: 0.03 μg/L), a value equal to half the MDL was assigned to these samples.

Urinary microalbumin (MA) was used as an indicator of early glomerular function damage, while \( \beta \)-2-microglobulin (β2MG) and N-acetyl-beta-D-glucosaminidase (NAG) were used as indicators of renal tubular dysfunction. Urinary creatinine, MA, β2MG, and NAG in the samples were measured in a laboratory certified by the Taiwan Accreditation Foundation (Nos. 1447 and 1673), which is recognized by the International Laboratory Accreditation Cooperation Mutual Recognition Arrangement. For the measurement of markers, urine levels of urinary MA were quantified using the Beckman Coulter SYNCHRON DxC 800 System (Beckman Coulter Inc., Brea, CA, USA). β2MG was measured via a chemiluminescent immunoassay by using Immulite 2000 (SIEMENS, Munich, Germany), and NAG was measured using a colorimetric NAG activity assay (ab204705, Abcam, Cambridge, UK).

Statistical analysis

The Student \( t \)-test, Mann–Whitney \( U \) test, Chi-square test, and Fisher’s exact test were used to evaluate differences between demographic data, clinical parameters, and metal levels. We further assessed the associations between exposure to metals and early renal impairment markers by using linear regression. All levels of metals and renal function markers were log-transformed (base 10) to reduce skewness. We selected covariates by following one or more of the following criteria: (1) associated with outcomes; (2) associated with exposure of interest (Szko & Nieto 2014); and (3) literature-based. Potential confounding factors (BMI, education levels, secondhand smoke exposure, incense use) and levels of urinary creatinine and each metal were adjusted for. The significance level was set at \( p < 0.05 \), and all statistical analyses were performed using the SPSS statistical software (version 19.0, IBM Corporation, Armonk, NY, USA).

Results

Characteristics of participants

The mean ages of males and females in the corresponding groups were 23.1 ± 2.1 and 23.2 ± 2.4 years (\( p = 0.818 \)), respectively. The average BMI in the male and female groups were 23.8 ± 3.8 and 21.2 ± 3.7 kg/m², respectively. More than 40% of the females had received graduate school education. None of the females were cigarette smokers. The frequency of incense use in the male group (29.4%) was significantly higher than that in the female group (13.2%, \( p = 0.026 \)). As for the clinical parameters, the median levels of urinary creatinine, MA, β2MG, and NAG were 121.5 mg/dL, 0.30 mg/dL, 45.6 ng/mL, and 24.1 mU/mL, respectively, in the male group; for the female group, the respective values were 86.9 mg/dL, 0.29 mg/dL, 31.6 ng/mL, and 30.8 mU/mL. The male group presents significantly higher median levels of creatinine (\( p = 0.008 \)), β2MG (\( p = 0.031 \)), and NAG (\( p < 0.001 \)) than those exhibited by the female group (Table 1).

Arsenic, cadmium, and lead levels in urine samples

To understand the difference in exposure levels between the male group (\( n = 51 \)) and the female group (\( n = 106 \)), the levels of As, Cd, and Pb in the two groups were compared. The median (range) levels of urinary As, Cd, and Pb in the male group were 39.51 (4.20–272.4), 0.53 (0.11–1.60), and 0.21 (ND–1.17) μg/L, respectively, while the corresponding values for the female group were 22.9
(2.78–150.1), 0.48 (0.11–20.7), and 0.12 (ND–4.8) μg/L; there were no significant differences in the exposure levels (As: \( p = 0.060 \); Cd: \( p = 0.234 \); Pb: \( p = 0.081 \)) between the two groups (Fig. 1, Table S1).

In addition, we have stratified the urinary metal levels into two groups based on their median (median levels: As: 26.58 μg/L; Cd: 0.51 μg/L; Pb: 0.14 μg/L); the results showed that the levels of urinary MA and β2MG were significantly higher in the group with urinary metal levels greater
than the median, as compared to the group where the values are less than or equal to the median for both groups (except the urinary As levels in the female group). As opposed to MA and β2MG, urinary NAG levels were significantly higher in the group with values less than or equal to the median, as compared to the group with values greater than median (Table 2).

**Association of urinary arsenic, cadmium, and lead with urinary microalbumin, β2-microglobulin, and N-acetyl-beta-D-glucosaminidase**

We assessed the association between As, Cd, and Pb levels and renal function markers in urine samples from the male and female groups. Urinary creatinine levels were adjusted for each crude model. All predictor and renal function markers were decimal logarithm–transformed. After adjusting for the potential confounding factors, we found that urinary Cd levels were significantly positively associated with MA levels ($\beta=0.523$, 95% CI: 0.147–0.899) and β2MG levels ($\beta=1.502$, 95% CI: 0.635–2.370) for the male group as a whole. The urinary NAG level was significantly positively associated with urinary Cd levels for the female group as a whole ($\beta=0.161$, 95% CI: 0.027–0.296), but not for the male group (Fig. 2, Table S2).

**Discussion**

Several studies have explored whether co-exposure to metals is associated with adverse effects on renal function in the general population (Chen et al. 2019; Sanders et al. 2019; Sun et al. 2019; Tsai et al. 2017). However, to the best of our knowledge, this is the first study to examine the sex-specific association between As, Cd, and Pb exposures and early renal impairment markers (including MA, β2MG, and NAG) in young Taiwanese adults. Our modeling strategy was two-tiered and stratified such that we pursued the analyses for single-metal exposure and multi-metal co-exposure for both male and female groups. We have discussed exposure to As, Cd, and Pb only; thus, we did not account for the whole metal exposure scenario; however, these specific metals are important because of their high toxicity. Our findings suggest that exposure to Cd poses more risk than that of exposure to Pb or As in Taiwan, thereby causing early renal impairment. There were no significant differences in Cd exposure levels between the two sex groups; however, while exposure to Cd was associated with urinary MA and β2MG levels in the male group, only NAG levels were observed in the female group, and that there were sex-specific differences in urinary metal levels and early renal impairment markers.

Most of the previous studies investigated the associations between urinary metal levels and kidney function in type 2 diabetes mellitus or chronic kidney disease patients (Moody et al. 2018; Zhou et al. 2021). In the current study, we used urinary MA, β2MG, and NAG levels that have been recognized as useful biomarkers for early renal impairment in the general population (Chen et al. 2020; Fassett et al. 2011; Jin et al. 2004; Siew et al. 2011). MA is an early marker of renal glomerular damage in the general population (Glassock 2010), whereas NAG and β2MG have been recognized to be useful clinical markers for early renal tubular damage (Gibey et al. 1981; Perez-Blanco et al. 2000). After renal impairment, the tubular epithelial cells may shrink, fall off, and even disappear, and the tissue source of NAG is lost (Kobayashi et al. 2008); once NAG is released, the excretion of urinary β2MG may be at levels higher than those of urinary NAG (Smith et al. 2012; Zhang et al. 2015). A previous study has indicated that the correlation coefficients of urinary Cd levels and urinary β2MG levels were higher than those of the urinary NAG levels, and that urinary β2MG levels could be a more sensitive marker for renal health than NAG levels (Li et al. 2020); a dose–response relationship has also been observed between the urinary β2MG positive rate and urinary Cd levels (Ishizaki et al. 1989). Another study indicated that urinary Cd and Pb co-exposure showed much better correlation with NAG levels as compared to that obtained with urinary MA levels and the eGFR; that study also demonstrated that urinary NAG could be used as an early detection marker of renal injury caused by Cd and Pb co-exposure (Chen et al. 2019).

Sex differences with regard to renal impairment have been investigated in many studies (Garovic & August 2016, Neugarten et al. 2018). A previous review study has reported that the sex of person is significantly associated with the incidence, characteristics, and outcomes of kidney cancer, with men being more prone to renal disease–related risks (Lughezzani et al. 2019). This phenomenon may be due to the different physiology of males and females. Some studies have also observed that males are more commonly affected than females with regard to renal impairment (Aufhauser et al. 2016); testosterone is associated with tubular damage, whereas estrogen reduces albuminuria, glomerulosclerosis, and tubulointerstitial fibrosis (Maric 2009). In vitro studies have demonstrated that endogenous estrogen produces protective renal effects (Seppi et al. 2016). Some studies also
| Variables      | n (M/F) | Median (range) Male | Median (range) Female | $p^a$ | Median (range) Male | Median (range) Female | $p^a$ | Median (range) Male | Median (range) Female | $p^a$ |
|----------------|---------|---------------------|----------------------|-------|---------------------|----------------------|-------|---------------------|----------------------|-------|
| Total population | 51/106  | 0.31 (0.08–4.38)    | 0.29 (0.08–133.16)  | 0.857 | 45.60 (ND<sub>c</sub>–829.00) | 31.55 (ND<sub>c</sub>–236.00) | 0.031<sup>*</sup> | 24.10 (10.70–41.80) | 30.75 (12.20–78.30) | <0.001** |
| Arsenic        |         |                     |                      |       |                     |                      |       |                     |                      |       |
| ≤ Median (≤ 26.58 μg/L) | 20/58   | 0.17 (0.10–1.12)   | 0.27 (0.09–6.79)    | 0.066 | 24.45 (ND<sub>c</sub>–829.00) | 27.05 (ND<sub>c</sub>–111.00) | 0.753 | 30.85 (16.30–41.70) | 32.90 (12.20–78.30) | 0.145 |
| > Median (> 26.58 μg/L) | 31/48   | 0.54 (0.08–4.38)   | 0.32 (0.08–133.16)  | 0.296 | 68.20 (ND<sub>c</sub>–242.00) | 36.00 (ND<sub>c</sub>–236.00) | 0.064 | 22.30 (10.70–41.80) | 27.45 (12.50–72.70) | 0.001** |
| Cadmium        |         |                     |                      |       |                     |                      |       |                     |                      |       |
| ≤ Median (≤ 0.51 μg/L) | 22/56   | 0.16 (0.10–1.12)   | 0.24 (0.08–4.65)    | 0.044<sup>*</sup> | 21.30 (ND<sub>c</sub>–140.00) | 22.95 (ND<sub>c</sub>–160.00) | 0.697 | 28.15 (14.80–41.80) | 32.90 (13.60–78.30) | 0.034<sup>*</sup> |
| > Median (> 0.51 μg/L) | 29/50   | 0.62 (0.08–4.38)   | 0.39 (0.08–133.16)  | 0.240 | 71.10 (ND<sub>c</sub>–829.00) | 45.20 (ND<sub>c</sub>–236.00) | 0.041<sup>*</sup> | 22.30 (10.70–36.20) | 28.20 (12.20–72.70) | 0.001** |
| Lead           |         |                     |                      |       |                     |                      |       |                     |                      |       |
| ≤ Median (≤ 0.14 μg/L) | 21/59   | 0.16 (0.10–1.12)   | 0.25 (0.09–133.16)  | 0.009<sup>**</sup> | 20.30 (ND<sub>c</sub>–90.80) | 27.60 (ND<sub>c</sub>–226.00) | 0.580 | 31.10 (10.70–41.70) | 35.50 (12.20–78.30) | 0.023<sup>*</sup> |
| > Median (> 0.14 μg/L) | 30/47   | 0.58 (0.08–4.38)   | 0.42 (0.08–46.04)   | 0.321 | 72.65 (ND<sub>c</sub>–829.00) | 37.40 (ND<sub>c</sub>–236.00) | 0.013<sup>*</sup> | 22.30 (12.90–41.80) | 27.20 (12.50–72.70) | 0.007** |

<sup>a</sup>Comparison of male and female groups by the Mann–Whitney $U$ test. $^*$$p < 0.05$, $^**$$p < 0.01$

<sup>b</sup>Comparison of ≤ median and > median groups by the Mann–Whitney $U$ test. $^*$$p < 0.05$, $^**$$p < 0.01$

<sup>c</sup>ND, non-detectable, the limit of detection; $As$, 0.08 μg/L; $Cd$, 0.06 μg/L; $Pb$, 0.03 μg/L; $β2$-microglobulin, 4 ng/mL.
explored how the effect of metal exposure differed based on the sex of the person; one study reported that women seemed to be more at risk for toxic metal exposure than men under the same conditions (Berglund et al. 2011). A review study also indicated that the general population without occupational exposure to metals exhibited sex-specific differences in blood levels of manganese, Pb, and Cd, and that potential causes such as the effects of estrogen or differences in absorption rates should be investigated further (Lee & Kim 2014). Studies considering the associations between co-exposure to metals and early renal impairment in both sexes are important because the effects of putative toxicants may be different for each group (either single- or co-exposure dependent).

In the current study, no significant difference was observed in Cd exposure between the male and female groups ($p = 0.234$); comparing with our previous study (Liao et al. 2019) that reported the urinary Cd levels in 18- to 39-year-olds in the general population of Taiwan during 1993–1996 (median: 0.63 μg/L) and 2005–2008 (median: 0.61 μg/L), it can be seen that the Cd levels were higher than in the current study (male: 0.53 μg/L; female: 0.48 μg/L). Based on the studies in the USA (based on the NHANES) for 2015–2016 (CDC 2019) and Canada (based on the Canadian Health Measures Survey) for 2016–2017 (Canada 2019), the median level of urinary Cd in the group aged over 20 years in the USA was 0.179 μg/L and that in the group aged 20–39 years in Canada was 0.12 μg/L; these values were lower than those in the current study. A recent study in Taiwan has reported that median urinary Cd levels in participants without and with proteinuria are 0.8 μg/L and 1.1 μg/L ($p < 0.001$), respectively (Tsai et al. 2021); these values are higher than the Cd exposure levels indicated in this study. Based on these results, we have concluded that Cd exposure levels were higher than those in developed countries, and that associations between Cd exposure and early renal impairment markers were evident even at a low Cd exposure level.

In this study, we did not find associations between urinary As and Pb levels and early renal impairment markers. This may be due to low exposure levels in the present population. Our previous study reported that urinary Pb levels exhibited by subjects aged 18- to 39-year-old in Taiwan during 1993–1996 (median: 2.47 μg/L) and 2005–2008 (median: 1.04 μg/L) (Liao et al. 2019) were at much higher levels than in the current study; this was true for both for males (0.21 μg/L) and females (0.12 μg/L). Urinary Pb levels in our participants were lower than those in the group (older than 20 years) that participated in the NHANES 2015–2016 (0.320 μg/L). This may be due to the banning of leaded gasoline in 2000 in Taiwan, and also the removal of all lead water pipes in Taipei city (northern Taiwan, main study area of this study) in 2017. Moreover, with the study period being within the timeframe of the COVID-19 pandemic, people were likely to be wearing masks when outside. This may also have reduced exposure to Pb through ambient air. We reported the urinary As levels in the male and female groups to be 39.51 and 22.90 μg/L, respectively. The exposure levels were higher than those reported by the US NHANES 2015–2016 for the group older than 20 years (5.47 μg/L), and those reported by Canada CHMS 2016–2017 for the group aged 20–39 years (3.8 μg/L). Although previous studies have reported associations between urinary Pb and As levels and renal dysfunction (Hsueh et al. 2021; Rastogi 2008; Wang et al. 2018; Zheng et al. 2015), we analyzed multiple-metal exposure in this study; the results indicated that Cd
exposure is an important risk factor for early renal impairment in young Taiwanese adults.

Citing high and frequent consumption of rice among Taiwanese, a previous study in Taiwan had raised an alarm about the high Cd levels in rice (Lien et al. 2021). In this study, we surveyed the frequency of rice consumption, and the results showed that there were no differences on median in urinary Cd levels between the group that consumed rice more than once per day (0.51 μg/L) and the group that consumed rice less than once per day (0.52 μg/L) (p = 0.809, data not shown). Another important source of Cd is cigarette smoke (Mortensen et al. 2011); there were four participants in the male group who smoked cigarettes, and 56 participants who claimed that they were exposed to secondhand smoke. Nevertheless, there were no significant differences between urinary Cd levels in the exposed group (cigarette smoking group: 0.50 μg/L; group exposed to secondhand smoke: 0.50 μg/L) and the non-exposed group (non-cigarette-smoking group: 0.51 μg/L, p = 0.824; group exposed to secondhand smoke: 0.50 μg/L, p = 0.409) (data not shown).

The strengths of this study include its use of human biomonitoring data as a basis for investigating co-exposure to metals in different sex groups. We provided the distribution of urinary As, Cd, and Pb levels in young Taiwanese adults. Collection of human urine specimens could avoid invasive extraction methods, and also, urinary metal levels are suitable for representing human exposure (ATSDR 2007; Ishizaki et al. 2015). Notably, we analyzed the association between co-exposure to metals and early renal impairment markers. The results indicate that Cd is a risk factor for early renal impairment, and there were sex-specific differences.

This study also has some limitations, such as a relatively small sample size. Furthermore, significant associations between exposure to metals and early renal impairment markers were identified. Studies using larger samples are needed to confirm these findings. Moreover, the cross-sectional study design (with one-time-point measurements) used in this study cannot sufficiently assess exposure over time. Another limitation is that blood samples were not analyzed in this study, rendering it impossible to assess other important renal function parameters and factors (e.g., eGFR) or determine whether the participants were afflicted with diabetes mellitus, hypertension, or autoimmune diseases, etc. Moreover, we did not conduct a detailed survey on the dietary habits of the participant and hence could not validate the contribution of heavy metals from food. Detailed food consumption data are needed for further investigations in this regard.

Conclusions

The results of sex-specific and multivariate analyses performed in this study show that Cd exposure could be a significant predictor of early renal impairment in young Taiwanese adults. Implications of low-level co-exposure to metals at a young age on early renal impairment may have far-reaching consequences later in life, leading to the development of CKD, ESRD, or renal dysfunction. Studies in this area can increase our knowledge of early intervenable factors for decreasing the incidence of renal dysfunction. Further studies are warranted to replicate our findings and elucidate the possible mechanisms involved.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11356-022-19521-3.

Acknowledgements We thank all of the participants who participated in this study.

Author contribution Kai-Wei Liao: conceptualization, supervision, data curation and validation, formal analysis, methodology, validation, writing — original draft, writing — review & editing. Ling-Chu Chien: conceptualization, supervision; Yang-Ching Chen: conceptualization, supervision; Ho-Ching Kao: investigation, formal analysis.

Funding This work was supported by the Ministry of Science and Technology (Grant No.: MOST 109–2314-B-038–140-MY2) and by the Taipei Medical University (TMU108-AE1-B29).

Availability of data and materials The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate This study was approved by the TMU-Joint Institutional Review Board (No. N202005041).

Consent for publication Not applicable.

Competing interests The authors declare no competing interests.

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