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# Associations between renal functions and exposure of arsenic and polycyclic aromatic hydrocarbon in adults living near a petrochemical complex☆

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ABSTRACT

*Background:* The understanding for the impact of petrochemical pollutants exposure on renal functions is limited.
*Objectives:* Our study examined the associations between renal functions and pollutants exposure in adult residents living in the vicinity of a petrochemical industry.
*Methods:* We recruited 2069 adult residents near a big petrochemical complex in Taiwan in 2009–2012, and they were categorized into high exposure (HE) and low exposure (LE) groups based on their address to source by 10 km radius. Study subjects were measured the urinary levels of arsenic, cadmium, mercury, thallium, and 1-hydroxypyrene (1-OHP). The estimated glomerular filtration rate (eGFR) was calculated using the Taiwanese Chronic Kidney Disease Epidemiology Collaboration equation, and the chronic kidney disease (CKD) prevalence and risks were defined according to KDIGO 2012 guidelines. Adjusted generalized linear and logistic regression models were applied to evaluate the associations between petrochemical exposure and renal functions.
*Results:* Subjects in the HE areas had significantly lower eGFR, higher CKD prevalence, and higher levels of urinary arsenic, cadmium, mercury, thallium and 1-OHP. The closer to complex and high exposure group of study subjects were significantly associated with the decrease in eGFR, higher ORs for CKD and high-intermediate risk of CKD. In addition, the study subjects who had two-fold urinary arsenic and 1-OHP levels were significantly with decreased 0.68 and 0.49 ml/min/1.73 $m^2$ of eGFR, respectively.
*Conclusions:* Residing closer and higher arsenic and polycyclic aromatic hydrocarbon exposure were associated with the renal impairment and risks of CKD among the residential population near the petrochemical industry.



## 1. Introduction

Since the late 20th century, morbidity and mortality rates for Chronic Kidney Disease (CKD) has skyrocketed (GBD 2013 Mortality and Causes of Death Collaborators, 2015). The global disease burden for CKD now accounts for a prevalence of approximately 11–13% of the adult population worldwide (Hill et al., 2016). Detection of CKD in its early stages prevents progression into End-Stage Renal Disease, which requires a validated index for assessing kidney function. The Kidney Disease: Improving Global Outcomes (KDIGO) 2012 guideline suggests that reduced glomerular filtration rate (GFR) is an accurate indicator of kidney damage (KDIGO, 2013), which is also a predictor of elevated all-cause mortality risk (Matsushita et al., 2010). Common estimating GFR (eGFR) equations are derived from plasma creatinine levels and have been adjusted for populations across the world to further account for demographic differences (Chen et al., 2014; Levey et al., 2009).

Identification of risk factors is crucial to designing public health interventions to counter the rising burden for CKD. Diabetes

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mellitus and hypertension are known co-morbid disease risk factors (Haroun et al., 2003; Lea and Nicholas, 2002; Parikh et al., 2006). Lifestyles and health behaviors, such as inactivity (Stengel et al., 2003) and smoking (Haroun et al., 2003), may also contribute to the risk of developing CKD. World Health Organization has cautioned against unhealthy environments, to which a significant number of deaths can be attributed. Interest in investigating environmental contributions to kidney function has thus increased recently. Chemical exposure from daily activities was found to adversely affect renal function among the general public (Chung et al., 2014; Kataria et al., 2015; Kim et al., 2015; Yang et al., 2017; Zheng et al., 2015). As a major source of common environmental pollutants, facilities of the petroleum industry emit sulfur dioxide ($SO_2$), nitrogen oxides (NOx), volatile organic compounds (VOCs), particulate matters (PM), polycyclic aromatic hydrocarbons (PAHs), and a variety of heavy metals (Kulkarni et al., 2007; Nadal et al., 2004; Shie et al., 2013). Of those, exposure to arsenic (As), cadmium (Cd), mercury (Hg), thallium (Tl), and PAHs has been associated with kidney impairment (ADSTR, 1992, 1999, 2007, 2012, 2019; Farzan et al., 2016).

Located in Yunlin County, the No.6 Naphtha Cracking Complex is the largest petrochemical complex in Taiwan. Operation of its oil refineries and coal-fired power plants emits pollutants to the ambient environment (Chio et al., 2014; Shie et al., 2013). In the two townships nearby this complex in Yunlin County, the obviously higher ambient concentrations of vanadium (V) and some PAHs were found (Yuan et al., 2015; Yuan et al., 2016), and the contents of many metals in $PM_{10}$ air samples were higher during the downwind season (Chan et al., 2012). A multitude of studies have validated that relevant internal biomarkers effectively modeled the degree of external pollutant exposure among the residential population in the complex vicinity. For example, urinary V and As levels displayed a concentration gradient in accordance with the distance-to-source gradient of V and As exposure (Yuan et al., 2016). Urinary 1-hydroxypyrene (1-OHP) concentration, a PAH metabolite excreted via urine, was also inversely associated with residents' distances from complex (Yuan et al., 2015). These aforementioned biomarkers have been applied in studies to establish a complete pathway from upstream pollutant exposure to downstream health effects, such as disruptions to metabolic pathways, on nearby residents (Chen et al., 2017; Yuan et al., 2016).

Studies across the world have demonstrated that occupational exposure of toxins reduces kidney function in petrochemical complex workers (Chen et al., 2006; Jarup et al., 1995; Weaver et al., 2003). Yet few have addressed the susceptibility of the residential population near petrochemical complexes to pollutant exposure and its impact on renal functioning. Therefore, our research aims to, first, investigate the health effect of renal function and, second, to investigate the relationship between petrochemical-related exposure and CKD prevalence and risk among the residents living near the big petrochemical complex.

## 2. Materials and methods

### 2.1. Study area and subjects

Spanning across 2603 ha, the No.6 Naphtha Cracking Complex has undergone 4 phases of expansion and began its major operation in 1999. There are 53 plants in the complex, including, but not limited to, one thermal power plant, three oil refineries, two naphtha cracking plants, three cogeneration plants, and twelve aromatic and plastic plants. The complex has the capacity of generating 1.8 million kW of electricity from its independent thermal power plant and 2.82 million kW of electricity from its cogeneration plants. Its production capacity has expanded to 540,000 barrels of oil per day and 2.9 million tons of ethylene per year (FPC, 2019).

Our study area covered 10 townships with similar socioeconomic status in the vicinity of the No.6 Naphtha Cracking Complex in Yunlin County, Taiwan, which included Dongshi, Lunbei, Baojhong, Sihhu, Erlun, Yuanchang, Cihtong, Huwei, Mailiao, and Taisi. The 2 townships, Mailiao and Taisi, nearby the complex and mostly within the 10 km radius of the complex were classified as high exposure (HE area, while others townships farther from the complex were classified as low exposure (LE) area.

Subjects participating in the present study were adults who were at least 35 years old between 2009 and 2012 and had lived at the same address for more than 5 years in the study area at the time of recruitment. After excluding those with incomplete demographic information, missing serum creatinine measurement, or urinary creatinine $\leq$30 mg/dL or $\geq$ 300 mg/dL, the final study population comprised 2069 adults, of which 669 adults lived in HE area and 1400 adults lived in LE area.

Study subjects' home addresses were located using the Universal Transverse Mercator (UTM) coordinate system. The shortest distance from subjects' home addresses to the complex was calculated by the function of near within a Geographic Information System (GIS) (ESRI ArcGIS v.10.0). In order to show the clear renal function effects associated with the study subjects' home-to-complex distance, the shortest home-to-complex distances were transformed to negative values to make the subjects living closer with larger number representing the distance of close to complex. Then, we used the variable of close to complex to be one of the exposure variables, to investigate if the subjects living closer to the complex were with worse renal functions in all statistical analyses. Fig. 1 shows the location of the No. 6 Naphtha Cracking Complex and the distribution of home addresses of the 2069 study subjects in the study area.

### 2.2. Health data and exposure biomarkers

Our study performed a questionnaire survey and a health examination for each subject. The questionnaire survey was conducted by well-trained interviewers to obtain demographic information and common CKD risk factors including age, gender, education level, smoking, alcohol drinking, nut chewing habits, and whether subject lived near a major road. Height, weight, and blood pressure were measured during subject's health examination.

A fasting blood sample and a morning spot urine sample were collected from each subject and were analyzed by the laboratory medicine department of the Yunlin Branch of the National Taiwan University Hospital. Total cholesterol, high- and low-density lipoprotein cholesterol, fasting blood glucose, blood urea nitrogen, and serum creatinine were measured from blood samples. Serum creatinine (SCr) levels were determined with the isotope dilution mass spectrometry (IDMS)-traceable enzymatic method (Chen et al., 2014). In this study, hypertension was defined as having a systolic blood pressure $\geq$140 mm Hg or a diastolic blood pressure $\geq$90 mm Hg; diabetes mellitus was defined as having a fasting glucose $\geq$126 mg/dL, and hyperlipidemia was defined as having a cholesterol measurement $\geq$200 mg/dL.

Urinary concentrations of arsenic (As), cadmium (Cd), mercury (Hg) and thallium (Tl) were analyzed with inductively coupled plasma mass spectrometry (ICP-MS), and urinary 1-OHP concentration was analyzed with high performance liquid chromatography with fluorescence detector (HPLC-FLD) method according to procedures outlined in prior studies (Yuan et al., 2015; Yuan et al., 2016). To ensure the accurate measurements, the urinary metal levels of standard reference materials (SERO, Billingstad, Norway) analyzed by our method were all within acceptable ranges

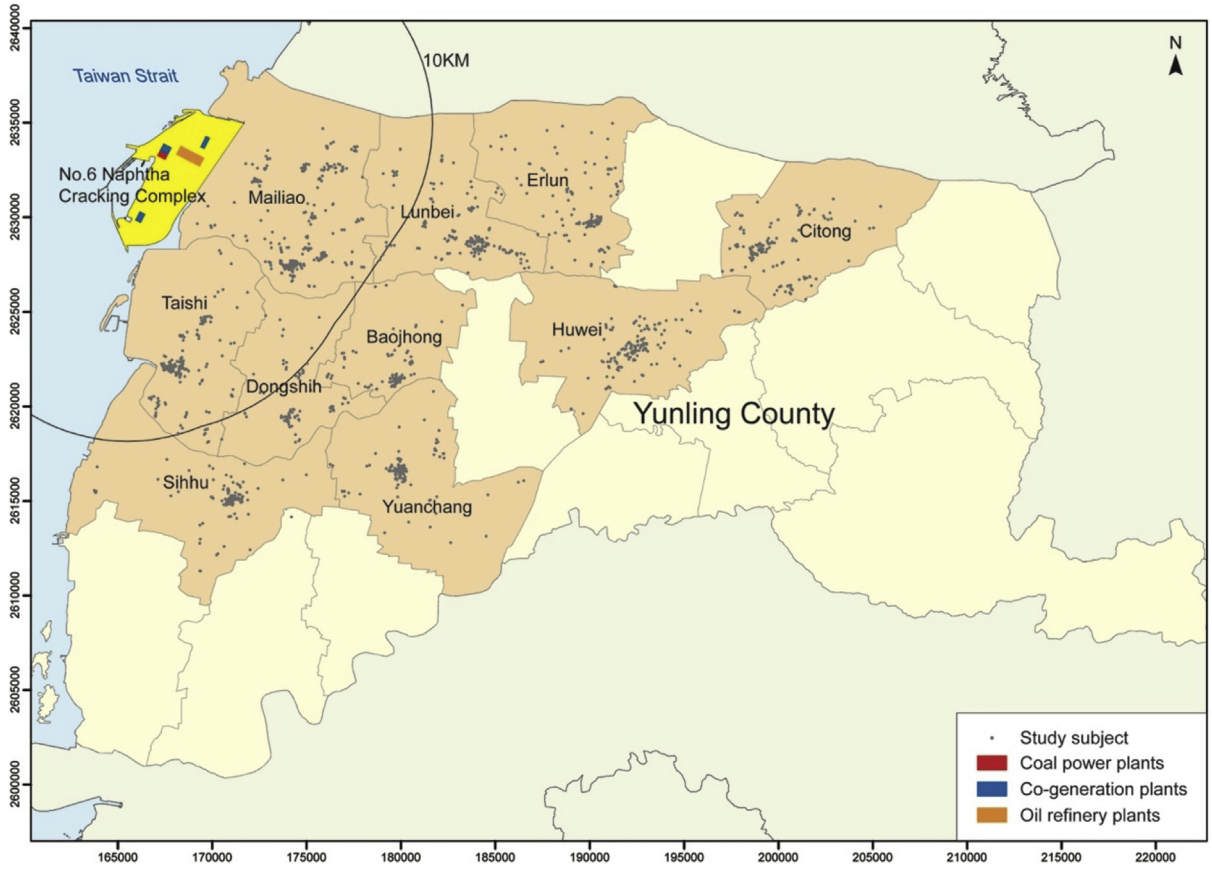


**Fig. 1.** The residential locations of 2069 study subjects living near the petrochemical complex in Yunlin County, Taiwan.

provided by the standard reference materials. And, the relative error of the ten spiked samples for each batch of the experiment was below 10% for these urinary chemicals. In addition, the measurement data was statistically analyzed when the recovery rate of each batch of the experiment higher than 85%. The detection limits for As, Cd, Hg, Tl, and 1-OHP were 3.33, 0.13, 0.44, 0.04, and 0.01 μg/L, respectively, and the proportions of study subjects with the levels below detection limits were 0.0, 2.3, 2.5, 2.0, and 0.9%, respectively. And, one half of the method detection limit was used to represent the urinary metals and 1-OHP level for samples below the method detection limits. Urine creatinine was analyzed for all urine samples to adjust for urinary exposure biomarkers. The study was approved by the Research Ethics Committee of the National Taiwan University Hospital, and written informed consent was signed by each subject.

### 2.3. Renal function

Our study used three indices to characterize subjects' renal function. Firstly, we applied the estimated glomerular filtration rate (eGFR) to be one renal function index calculated with the Taiwanese Modification of the Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI-Taiwan). The CKD-EPI-Taiwan equation was found to perform better than the abbreviated Modification of Diet in Renal Disease (MDRD) Study equation or the CKD-EPI for the Taiwanese adult population (Chen et al., 2014). The eGFR was calculated from serum creatinine, age, and gender in the following equation: $eGFR = 1.262 \times \{141 \times \min(Scr/\kappa,1)^{\alpha} \times \max(Scr/\kappa,1)^{1.209} \times 0.993^{Age} \times 1.018[\text{if female}] \times 1.159[\text{if black}]\}^{0.914}$, where Scr indicates the serum creatinine, κ for males and females are 0.9 and 0.7, α for males and females are −0.411 and −0.329; min presents the minimum of Scr/κ or 1, and max presents the maximum of Scr/κ or 1. Secondly, we defined subjects having chronic kidney disease (CKD) if eGFR ≤60 ml/min/1.73 $m^2$ which indicates that there is more than 50% reduction in normal kidney function (Levey et al., 2003). Thirdly, our study further defined subjects having a high-intermediate risk of CKD if either eGFR ≤ 60 ml/min/1.73 $m^2$ or eGFR ≥60 ml/min/1.73 $m^2$ along with a urine protein dipstick value higher than 1 + according to the KDIGO 2012 guidelines (KDIGO, 2013).

### 2.4. Statistical analysis

To compare subjects living in HE from those living in LE areas, analysis of co-variance (ANCOVA) test were conducted on continuous variables including health status, eGFR, and urinary biomarker concentrations by adjusting for potential confounders; chi-square tests were performed on categorical demographic variables. Urinary concentrations of As, Cd, Hg, Tl, and 1-OHP were $\log_2$-transformed to meet the normal distribution assumption of parametric statistics for all analyses of this study. To estimate associations between renal function and exposure to As, Cd, Hg, Tl, and PAH, generalized linear models (GLM) were applied using eGFR as the dependent variable; logistic regression models were applied using CKD prevalence and high-intermediate risk of CKD as dependent variables. GLM and regression models were adjusted for age, gender, body mass index (BMI), education level, smoking habit, cholesterol, hypertension, diabetes mellitus and living near a major road.

Furthermore, stratified analyses were conducted on associations

between exposure variables and renal function based on age (age < 65 or ≥ 65), gender (female or male), overweight (BMI ≥ 24 kg/m$^2$ or < 24 kg/m$^2$), smoking (yes or no), hypertension (yes or no), diabetes mellitus (yes or no), hyperlipidemia (cholesterol ≥ 200 mg/dL or < 200 mg/dL), education (elementary and below or junior high and above) and living near a major road (yes or no). All statistical analyses were performed using SAS software version 9.4 (SAS Institute) with a significant value $p < 0.05$.

## 3. Results

The demographic characteristics, health status, and urinary biomarker levels of 2069 study subjects living near the No.6 Naphtha Cracking Complex and comparison between HE and LE groups were summarized in Table 1. The mean age of our study population at the time of recruitment was 57.5 ± 13.3 years old, and 39.6% (N = 820) were male. Among our study population, 32.5%, 50.7%, 14.1%, and 52.1% had CKD, hypertension, diabetes mellitus, and hypercholesterolemia respectively.

The 669 subjects in the HE area (6.1 ± 1.9 km) lived significantly closer to the complex than the 1400 subjects in the LE area (18.1 ± 5.9 km). The HE group had significantly higher BMI values and lower education levels than the LE group. The mean eGFR of subjects in the HE area (63.7 ± 12.6 ml/min/1.73 m$^2$) was significantly lower than the LE area (66.9 ± 14.0 ml/min/1.73 m$^2$). CKD prevalence (eGFR ≤60 ml/min/1.73 m$^2$) in the HE area (38.3%) was also significantly higher than that in the LE area (29.7%). Urinary concentrations of As, Cd, Hg, Tl and 1-OHP were significantly higher in the HE group. There were no differences in age, gender, whether subjects lived near a major road, smoking, alcohol consumption, and nut chewing between HE and LE groups. Results from health examinations demonstrated that differences in urine protein measurement and proportions of subjects with hypertension, diabetes mellitus, and hypercholesterolemia were non-significant between HE and LE groups.

Table 2 shows the associations between exposure variables and renal function among the 2069 study subjects. Exposure was represented with one continuous (close to complex) and one categorical variable (whether subject lived in HE or LE area). Renal function was characterized with one continuous (eGFR) and two categorical variables (whether or not subject had CKD and whether or not subject had high-intermediate risk of CKD). A lower distance from home address to complex was significantly with lower eGFR ($\beta$: −2.90; 95% CI: −3.58, −2.21) and higher odds of having CKD [odds ratio (OR) = 1.55; 95% CI: 1.32, 1.81] and having a high-

**Table 1**
Comparisons of demographic characteristics, health status, and urinary biomarker levels between HE and LE groups among the study 2069 subjects living near the No.6 Naphtha Cracking Complex.

| Parameter | All (N = 2069) | HE group (N = 669) | LE group (N = 1400) | Missing (N) | *p*-value |
|---|---|---|---|---|---|
| Age(year) | 57.5 ± 13.3 | 57.7 ± 13.0 | 57.3 ± 13.4 | | 0.5153* |
| Gender(male)[k] | 820(39.6) | 263(39.3) | 557(39.8) | | 0.8369* |
| BMI(kg/m$^2$) | 25.6 ± 3.9 | 26.0 ± 4.0 | 25.4 ± 3.9 | 5 | 0.0008* |
| BUN(mg/dL) | 15.5 ± 5.1 | 15.8 ± 5.2 | 15.3 ± 5.1 | | 0.0373* |
| Creatinine(mg/dL) | 0.98 ± 0.30 | 1.00 ± 0.28 | 0.97 ± 0.31 | | <0.0001* |
| Education Level (Junior high school or above)[k] | 1018(51.3) | 266(41.9) | 752(55.7) | 83 | <0.0001* |
| Source of Drinking Water (Tap water)[k] | 1726(83.7) | 595(89.2) | 1131(81.1) | 7 | <0.0001* |
| Living Near Major Road (yes)[k] | 1246(60.9) | 379(58.1) | 867(62.2) | 24 | 0.0758* |
| Smoking (yes)[k] | 447(21.6) | 129(19.3) | 318(22.7) | | 0.0760* |
| Alcohol Consumption (yes)[k] | 363(17.6) | 107(16.1) | 256(18.3) | 7 | 0.2130* |
| Nut Chewing (yes)[k] | 278(13.5) | 92(13.9) | 186(13.3) | 10 | 0.7318* |
| Hypertension (yes)[d,k] | 1045(50.7) | 332(50.1) | 713(51.0) | 9 | 0.6831* |
| Diabetes Mellitus (yes)[e,k] | 292(14.1) | 85(12.7) | 207(14.8) | | 0.2036* |
| Hypercholesterolemia (yes)[f,k] | 1079(52.1) | 353(52.8) | 726(51.9) | | 0.6989* |
| Urine Protein[k] | | | | 1 | 0.0567* |
| − | 1794(86.8) | 587(87.9) | 1207(86.2) | | |
| +/− | 130(6.3) | 45(6.7) | 85(6.1) | | |
| + | 98(4.7) | 22(3.3) | 76(5.4) | | |
| ++ | 29(1.4) | 12(1.8) | 17(1.2) | | |
| +++ | 17(0.8) | 2(0.3) | 15(1.1) | | |
| Distance-to-Complex (km) | 14.2 ± 7.5 | 6.1 ± 1.9 | 18.1 ± 5.9 | | <0.0001* |
| Estimated Glomerular Filtration Rate (eGFR)[a,g] | 65.9 ± 13.6 | 63.7 ± 12.6 | 66.9 ± 14.0 | | <0.0001* |
| Chronic Kidney Disease (CKD)[h,k] | 672(32.5) | 256(38.3) | 416(29.7) | | 0.0001* |
| Urinary biomarker | | | | | |
| As[b,i] | 81.1 ± 118.0 | 94.6 ± 165.3 | 74.7 ± 85.9 | 7 | <0.0001* |
| Cd[b,i] | 0.88 ± 0.72 | 0.89 ± 0.66 | 0.87 ± 0.74 | 7 | 0.0257* |
| Hg[b,i] | 2.25 ± 2.39 | 2.34 ± 1.97 | 2.20 ± 2.56 | 7 | <0.0001* |
| Tl[b,i] | 0.20 ± 0.15 | 0.22 ± 0.18 | 0.19 ± 0.13 | 7 | <0.0001* |
| 1-OHP[c,j] | 0.12 ± 0.28 | 0.13 ± 0.28 | 0.11 ± 0.27 | 34 | 0.0060* |

The values shown are mean ± SD or N (%).
Unit:
[a] ml/min/1.73 m$^2$.
[b] μg/g creatinine.
[c] μmol/mol creatine.
[d] Hypertension defined as systolic blood pressure (SBP) ≥140 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg.
[e] Diabetes mellitus defined as fasting glucose ≥126 mg/dL.
[f] Hyperlipidemia defined as cholesterol≥ 200 mg/dL.
[g] eGFR was estimated with CKD-EPI-Taiwan equation.
[h] CKD defined as eGFR≤ 60 ml/min/1.73 m$^2$.
[i] After $\log_2$-transformation, compared by ANCOVA test and adjusting age, gender, smoking, alcohol drinking, nut chewing habit, fish consumption, source of drinking water, incense burning and living near major road.
[j] After $\log_2$-transformation, compared by ANCOVA test and adjusting age, gender, smoking habit, incense burning, grilled food consumption and living near major road.
[k] Categorical variables were compared with Chi-square test, and Fisher exact test would be used when 20% expectation of the cell was smaller than five.

**Table 2**
Associations of exposure variables and urinary biomarker levels with eGFR, CKD, and high-intermediate risk of CKD among the 2069 study subjects living near the No.6 Naphtha Cracking Complex.[c]

| Department | eGFR | | CKD[a] | | High-intermediate risk of CKD[b] | |
|---|---|---|---|---|---|---|
| | β | 95% CI | OR | 95% CI | OR | 95% CI |
| Close to complex[e] | −2.90* | (-3.58,-2.21) | 1.55* | (1.32,1.81) | 1.37* | (1.18,1.60) |
| Exposure area (High) | −3.18* | (-4.28,-2.08) | 1.68* | (1.32,2.01) | 1.45* | (1.15,1.82) |
| As[d] | −0.68* | (-1.12,-0.23) | 1.14* | (1.04,1.26) | 1.07* | (0.97,1.17) |
| Cd[d] | −0.26* | (-0.71,-0.19) | 0.96* | (0.87,1.06) | 0.96* | (0.88,1.06) |
| Hg[d] | −0.22* | (-0.62,-0.19) | 1.01* | (0.93,1.11) | 1.00* | (0.92,1.09) |
| Tl[d] | −0.32* | (-0.86,-0.23) | 1.03* | (0.91,1.15) | 0.94* | (0.84,1.05) |
| 1-OHP[d] | −0.49* | (-0.78,-0.20) | 1.03* | (0.97,1.10) | 1.01* | (0.95,1.08) |

*$p$-value<0.05.
[a] CKD defined by eGFR≤ 60 ml/min/1.73 $m^2$.
[b] High-intermediate risk of CKD defined by eGFR≤ 60 ml/min/1.73 $m^2$ or eGFR≥ 60 ml/min/1.73 $m^2$ and dipstick of urine protein≥ 1+.
[c] Model adjusted for age, gender, body mass index, education level, smoking, cholesterol, hypertension, diabetes mellitus and whether subject lived near a major road.
[d] Predictor parameters are expressed as the expected mean change in eGFR (ml/min/1.73 $m^2$) for 1-fold increase in exposure.
[e] Parameter is expressed as the expected mean change in eGFR (ml/min/1.73 $m^2$) for every 10 km decrease in distance from home address to complex.

intermediate risk of CKD (OR = 1.37; 95% CI: 1.18, 1.60). Similarly, living in HE areas as opposed to LE areas was significantly associated with lower eGFR ($\beta$: −3.18; 95% CI: −4.28, −2.08) and higher odds of having CKD (OR = 1.68; 95% CI: 1.32, 2.01) and having a high-intermediate risk of CKD (OR = 1.45; 95% CI: 1.15, 1.82). Based on the adjusted generalized linear models, eGFR was inversely associated with urinary concentrations of 1-OHP ($\beta$: −0.49; 95% CI: −0.78, −0.20) and As ($\beta$: −0.68; 95% CI: −1.12, −0.23). According to the adjusted logistics regression models, higher CKD prevalence was significantly associated with higher urinary concentration of As (OR = 1.14; 95% CI: 1.04, 1.26). However, high-intermediate risk of CKD was not significantly associated with any urinary biomarkers.

In addition to models relating being close to complex with renal function, Table 3 shows the associations of demographic characteristics and common CKD risk factors with renal function. All three indices of renal function indicated that renal impairment was significantly associated with older age, higher BMI values, and smoking. Moreover, a lower eGFR was associated with higher cholesterol, while CKD prevalence was significantly higher in hypertensive subjects (OR = 1.30; 95% CI: 1.03, 1.65). And, the high-intermediate risk of CKD were significantly higher in subjects with hypertension (OR = 1.32; 95% CI: 1.05, 1.66) and subjects with diabetes mellitus (OR = 1.43; 95% CI: 1.07, 1.92). Gender, education level, and whether subjects lived near a major road were not significantly associated with renal function.

Stratified analyses of the associations between eGFR, CKD, and high-intermediate risk of CKD and close to complex were summarized in Fig. 2. Negative associations between eGFR and being close to complex were stronger in females than males, in those with hypertension versus without hypertension, and in those without diabetes, while the association was null for diabetic subjects. In addition, the associations between ORs of CKD and the close to complex were obviously in females and non-diabetic subjects, while the associations with ORs of CKD were null for males and subjects with diabetes mellitus. Then, the ORs of high-intermediate risk of CKD for every 10 km decrease in distance from home to complex were higher in subjects who were elders, females, with overweight, non-smokers, with hypertension, without diabetes mellitus, with hyperlipidemia, and with an educational level of elementary school or below. However, the associations with high-intermediate risk of CKD were null for subjects with younger age, males, without overweight, smokers, without hypertension, with diabetes mellitus, without hyperlipidemia, and with an education level of junior high school and above.

## 4. Discussion

In previous, there were limited studies remarking the residents' renal effects by petrochemical industrial exposure, and the present study first revealed that the significant association between the distance-to-source and renal function for residents in the vicinity of a petrochemical complex after adjusting other confounding factors. Study subjects who lived with a 10 km closer to the petrochemical complex were significantly with decreased 0.29 ml/min/1.73 $m^2$ of

**Table 3**
Associations of demographic characteristics and common CKD risk factors with eGFR, CKD, and high-intermediate risk of CKD.

| Department | eGFR | | CKD[a] | | High-intermediate risk of CKD[b] | |
|---|---|---|---|---|---|---|
| | β | 95% CI | OR | 95% CI | OR | 95% CI |
| Close to complex[c] | −2.90* | (-3.58,-2.21) | 1.55* | (1.32,1.81) | 1.37* | (1.18,1.60) |
| Age (year) | −0.56* | (-0.61,-0.50) | 1.10* | (1.09,1.12) | 1.09* | (1.07,1.10) |
| Gender (male) | −0.90* | (-2.15,-0.35) | 1.00* | (0.75,1.32) | 0.98* | (0.75,1.28) |
| BMI (kg/$m^2$) | −0.15* | (-0.28,-0.02) | 1.04* | (1.01,1.07) | 1.03* | (1.01,1.06) |
| Cholesterol (mg/dL) | −0.02* | (-0.03,-0.00) | 1.00* | (1.00,1.01) | 1.00* | (1.00,1.01) |
| Smoking (yes) | −2.17* | (-3.60,-0.75) | 1.61* | (1.17,2.21) | 1.67* | (1.23,2.27) |
| Hypertension (yes) | −0.83* | (-1.92,-0.25) | 1.30* | (1.03,1.65) | 1.32* | (1.05,1.66) |
| Diabetes Mellitus (yes) | −0.71* | (-2.20,-0.79) | 0.99* | (0.73,1.33) | 1.43* | (1.07,1.92) |
| Education Level(Junior high school or above) | −0.62* | (-2.01,-0.77) | 0.99* | (0.74,1.33) | 0.97* | (0.73,1.29) |
| Living Near Major Road (yes) | −0.64* | (-1.66,-0.38) | 1.16* | (0.92,1.46) | 1.18* | (0.94,1.47) |

*$p$-value<0.05.
[a] CKD defined by eGFR≤ 60 mL/min/1.73 $m^2$.
[b] High-intermediate risk of CKD defined by eGFR≤ 60 mL/min/1.73 $m^2$ or eGFR≥ 60 ml/min/1.73 $m^2$ and dipstick of urine protein≥ 1+.
[c] Parameter is expressed as the expected mean change in eGFR (ml/min/1.73$m^2$) for every 10 km decrease in distance from home address to complex.

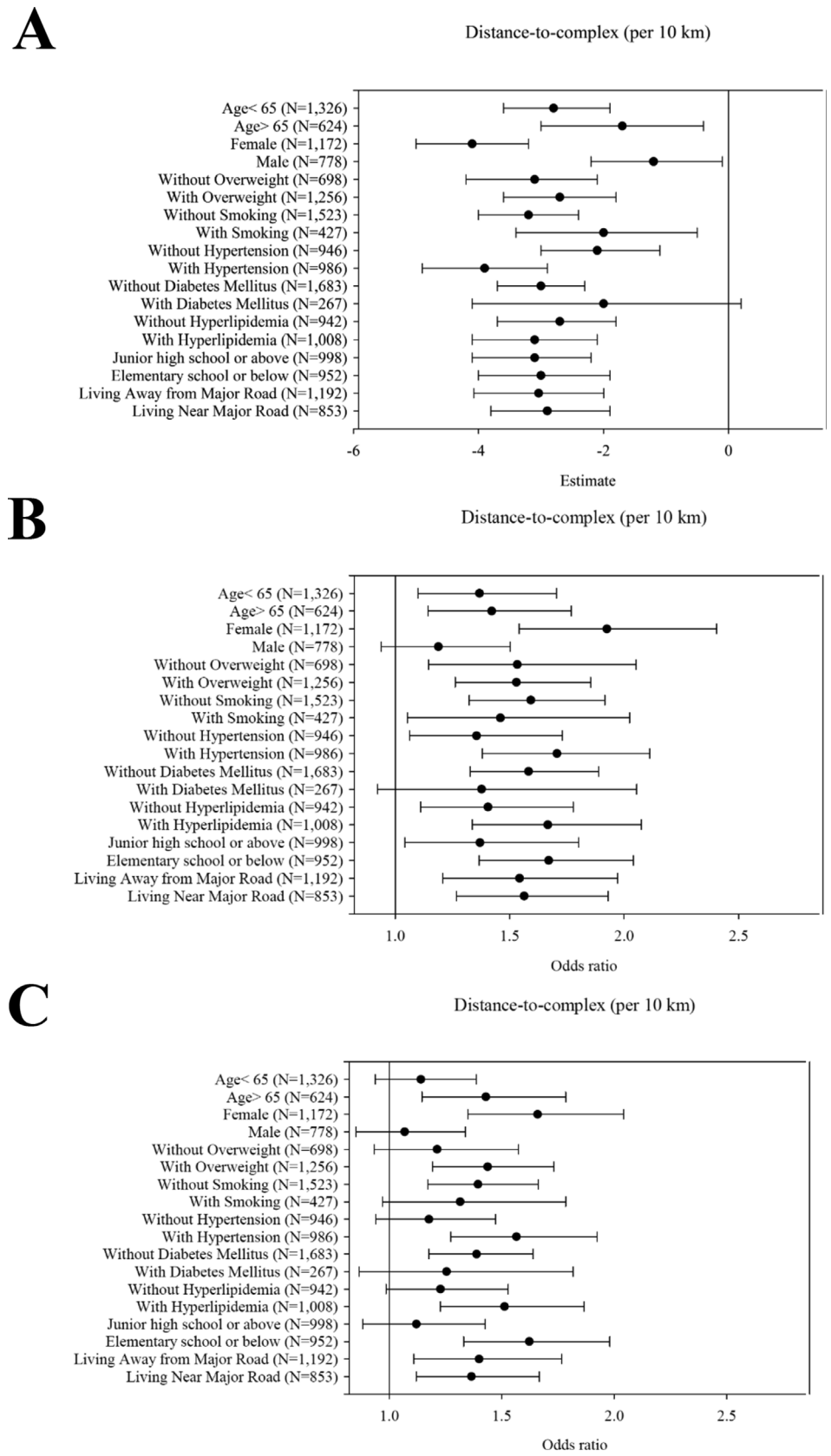


**Fig. 2.** The associations between distance to the complex and (A) eGFR or (B) CKD or (C) high-intermediate risk of CKD stratified by age, gender, overweight, smoking, hypertension, diabetes mellitus, hyperlipidemia, education level and living near major road.

eGFR, increased 1.55 OR of CKD, and increased 1.37 OR of high-intermediate risk of CKD (Table 2). And, these significant associations mostly remained even after the stratifications by the confounding factors (Fig. 2). In addition, it still showed the consistent renal effects in residents nearby after dividing their located townships in HE and LE by the distance to the complex (Table 2). Past research has confirmed that the petrochemical industry is the main source to emit many environmental pollutants with nephrotoxicity, such as aerosols, heavy metals, and VOCs, and the distance-to-source trends of these pollutants were demonstrated (Ranft et al., 2003; Sharma and Tripathi, 2009; Yuan et al., 2015). And, the HE group in the present study were with significantly higher levels of the exposure biomarkers including urinary As, Cd, Hg, Tl, and 1-OHP for the nephrotoxic pollutants when compared to those in LE group (Table 1). Therefore, the distance-to-source can be regarded as a comprehensive indicator to evaluate the potential renal hazards for residents living near a petrochemical industry.

In this study, the study subjects who were with two-fold urinary As levels were significantly with decreased 0.68 ml/min/1.73 $m^2$ of eGFR and increased 1.55 OR of CKD after adjusting confounding factors (Table 2). Previous studies showed the similar results. Two case-control studies in Taiwan found that there were significant negative correlations between urinary As levels and eGFR (Hsueh et al., 2009; Huang et al., 2011). In Bangladesh, a cross-sectional study showed the healthy study subjects who were with increased 10% urinary As levels were with decreased 0.21 ml/min/1.73 $m^2$ of eGFR (Peters et al., 2015). In addition, animal experiment also confirmed the kidney damage by the As exposure, and it observed that dogs developed glomerular sclerosis and severe tubular damage at high doses of As exposure and formed vacuolar formation in renal tubular epithelial cells under low dose exposure (Tsukamoto et al., 1983). Previous studies have pointed out that the kidney damage might be related to the production of excessive reactive oxygen species (ROS) caused by heavy metal exposure (Scibior and Zaporowska, 2007). Arsenic not only produce active oxygenates during metabolism but also reduce the enzymes responsible for the detoxification of exogenous toxicants to cause the oxidative stress increasing in human body (Nesnow et al., 2002). In addition, arsenic exposure can activate the signaling pathway of caspase-3, 9, increase the expression of interleukin-6, 8 (IL-6, 8), and activate the apoptotic pathway of p-53 tumor protein. These effects lead to increase the free radicals in the body, decrease DNA damage repair and produce inflammatory responses, which in turn damage renal tubules (Jimi et al., 2004; Tsukamoto et al., 1983). On the other hand, previous studies have shown that occupational exposure to Cd and Hg can cause kidney damage, and the similar outcomes were observed in the present study, but it was not statistically significant. It is speculated that the possible cause is the difference in exposure levels between workers and residents. Cadmium occupational exposure workers, such as smelters, radiators, and welding workers, have an average urinary Cd level about 4–10 times that of the present study subjects (Chen et al., 2006; Jarup et al., 1995). And, Mercury occupational exposure workers, such as chlor-alkali industry and chlorine-containing factory workers, have an average urine Hg level about 10 times that of the present study subjects (Boogaard et al., 1996; Langworth et al., 1992).

For the PAHs exposure, the present study found that the study subjects who were with two-fold urinary 1-OHP levels were significantly with decreased 0.49 ml/min/1.73 $m^2$ of eGFR after adjusting confounding factors (Table 2). There were limited studies to focus on the association between PAHs exposure and renal function in the past. One research conducted in USA observed the youth study subjects who were with two-fold of 3-hydroxyphenanthrene, one kind of PAHs metabolites, were significantly with decreased 2.66% eGFR levels (Farzan et al., 2016). Besides, an India occupational study found that exposure group who were with higher urinary PAH metabolites were with significantly higher ratio of abnormal urinary albumin-to-creatinine ratio (ACR) than those of control group (Singh et al., 2016). Previous studies have shown that PAHs are potential oxidative stressors to further lead to progression of inflammatory or chronic diseases (Araujo et al., 2008). In an epidemiological study, it showed the dose-response effect between PAHs urinary metabolites and the oxidative stress biomarker of 8-hydroxy-2-deoxyguanosine (8-OHdG) (Li et al., 2015). The occupational epidemiological studies found that the adults exposure to PAHs were with higher levels of oxidative stress and lipid peroxidation (Kuang et al., 2013; Noh et al., 2015). The PAH exposure studies of the general population also found that the concentration of PAH metabolites in urine is positively correlated with the indicators of inflammation and oxidative stress in serum, such as C-reactive protein (CRP) and gamma glutamyl transferase (GGT) (Alshaarawy et al., 2013; Farzan et al., 2016; Kuang et al., 2013). Based on the above findings, it is inferred that PAHs may cause kidney damage by causing inflammatory reactions and increasing oxidative stress in the body, but the exact mechanism requires more research to clarify. In addition to the independent chemical exposure, the weighted quantile sum (WQS) regression was applied to observe the association of combined chemical exposures with the renal function index, eGFR, after adjusting confounding factors, and the result showed remaining significantly negative association between eGFR levels and combined chemical exposure. The As contributed to about half of the mixture index negatively associated with eGFR levels (46.5%), and the descending contributions were found in 1-OHP (35.1%) and Hg (18.4%) (data not shown).

After pooling the all study subjects, this study showed that some life habits and personal characteristics including age, BMI, total cholesterol in the blood, smoking habits, and hypertension were significantly associated with the decreased renal function and the increased risk of chronic kidney disease (Table 3). It is consistent with the findings of previous studies that age, overweight, dyslipidemia, smoking habits, and hypertension were the important renal function risk factors (Haroun et al., 2003; Levey et al., 2003; Parikh et al., 2006). In addition to the effects of above risk factors on renal functions, we also observed the potential exaggerated effects of environmental exposure on study subjects with overweight, hypertension, or hyperlipidemia after conducting the stratified analysis, especially for the high-intermediate risk of CKD (Fig. 2). In the present study, there were 2069 subjects with 40% males and average age of 57.5 years old, and they were with the eGFR of 65.9 ml/min/1.73 $m^2$ calculated by the CKD-EPI-Taiwan and the prevalence rate of chronic kidney disease (eGFR $\leq$60 ml/min/1.73 $m^2$) in 32.5%. Previous studies also conducted some survey on kidney function for people in Taiwan. One study analyzed the health examination data of 462,293 people which were 49.8% male and with the average age of 41.8 years old, and it found that the subjects were with the eGFR of 84.3 ml/min/1.73 $m^2$ calculated by abbreviated MDRD and 7.1% with chronic kidney disease (Wen et al., 2008). Compared with the study by Wen et al., our study subjects with the lower eGFR might be due to the higher age, even with the different formulas to calculate the eGFR. The age was considered to be a risk factor for renal function in the past (Lindeman et al., 1985). The results of our present study also show the same trend that the study subjects who were with the increase per one year of age were significantly with the decreased 0.56 ml/min/1.73 $m^2$ of eGFR after adjusting for other renal function risk factors (Table 3). Another study was conducted the renal function survey in New Taipei City, Taiwan, and there were 21,656 subjects with the average age of 53.7 years old and 33% male. Then, they

were with the eGFR of 77.1 ml/min/1.73 $m^2$ calculated by the CKD-EPI-Taiwan, and 10% subjects were with the eGFR less than 60 ml/min/1.73 $m^2$ (Yang et al., 2017). Compared with the study by Yang et al., our study subjects were with the similar basic characteristic distributions, but they were with obviously lower eGFR value and 3 times prevalence of chronic kidney disease. One reason might be the higher prevalence of hypertension in our study subjects, and it cannot be ignored about the environmental pollution effects near the petrochemical industry. The effect of the petrochemical industry on the renal function of residents was greater than or equal to the influence of smoking and hypertension (Table 3). Therefore, the potential exact impact on renal function and chronic kidney disease for local residents needs further in-deep evaluation.

The research presented in this study has the following limitations. First, this is a cross-sectional study to show that the residential population nearby were with the increase of urinary exposure biomarker levels, the decreased renal function, and the increased risk of chronic kidney disease. However, the causal relationship cannot be confirmed, and it is recommended to further clarify it by a long-term follow-up study. Second, the urinary metals and 1-OHP are the short-term exposure biomarkers, and it might be difficult to represent the long-term exposure scenario for the local residents. Nevertheless, the petrochemical industry operated for a long period coupled with several main extensions since 1999, and all the study subjects have lived at the current address for more than five years. Therefore, it can be expected that these residents are affected by long-term exposure from the petrochemical industry, and it should not have a directional impact on the results of the present study. Third, potential pollutants emitted from the complex might affect the renal functions in the residents in the study areas, such as PM and VOCs. In fact, our previous study found the two townships nearby the complex were with lower $PM_{10}$ or $PM_{2.5}$ levels but with higher petrochemical-related VOCs levels when compared to other farther townships (Chan et al., 2012). Therefore, it is necessary to clarify the effects of external and internal exposure of these VOCs on renal functions in the residents nearby in advanced studies. Fourth, previous study have pointed out that renal function may affect the excretion of heavy metals in the body (Buser et al., 2016). The present study also investigated the associations between the urinary arsenic concentrations and eGFR values in three groups divided by eGFR values. The results showed that there were no significant differences on the association among three groups (data not shown). However, the potential impact of renal function deterioration on heavy metal excretion should be concerned in further study. Fifth, the eGFR is a good and widely used renal function index, but studies have indicated that the obviously changes in eGFR value might be observed when the kidneys with more severe affection. In the present study, we did not have the information for some other renal function related index, such as albuminuria data. In the further advanced study, it could simultaneously use some early-stage renal function index, such as urinary albumin and creatinine ratio, to comprehensively evaluate the effects of environmental exposure on the renal functions.

In conclusion, adults who lived in the high exposure areas or closer to the petrochemical complex were associated with significantly decreased renal function and increased risks of CKD. In addition, the subjects with the higher urinary arsenic and 1-OHP levels which are potential polluted from the petrochemical complex were obviously related to the lower renal function and the higher risk of chronic kidney disease. Therefore, these two biomarkers would be appropriate to explore the associations between environmental exposure by petrochemical industry and the renal injury of residents. Further detailed and comprehensive longitudinal cohort studies are essential to clarify the mechanisms of these petrochemical-related pollutants and their potential renal function effects.

## Declaration of competing interest

The authors declare they have no actual or potential competing financial interests.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envpol.2019.113457.

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