


ORIGINAL ARTICLE

Long-term exposure to air pollutants and increased risk of chronic kidney disease in a community-based population using a fuzzy logic inference model

Hsueh-Chun Lin^{1,*}, Peir-Haur Hung^{2,3,*}, Yun-Yu Hsieh⁴, Ting-Ju Lai⁵, Hui-Tsung Hsu⁵, Mu-Chi Chung⁶ and Chi-Jung Chung^{6,7} 

¹Department of Health Services Administration, China Medical University, Taichung, Taiwan, ²Department of Internal Medicine, Ditmanson Medical Foundation Chiayi Christian Hospital, Chiayi, Taiwan, ³Department of Applied Life Science and Health, Chia-Nan University of Pharmacy and Science, Tainan, Taiwan, ⁴Department of Health Risk Management, China Medical University, Taichung, Taiwan, ⁵Department of Public Health, China Medical University, Taichung, Taiwan, ⁶Division of Nephrology, Department of Medicine, Taichung Veterans General Hospital, Taichung, Taiwan and ⁷Department of Medical Research, China Medical University Hospital, Taichung, Taiwan

*These authors contributed equally to this work.

Correspondence to: Chi-Jung Chung; E-mail: cjchung1010@gmail.com

ABSTRACT

Background. Fuzzy inference systems (FISs) based on fuzzy theory in mathematics were previously applied to infer supplementary points for the limited number of monitoring sites and improve the uncertainty of spatial data. Therefore we adopted the FIS method to simulate spatiotemporal levels of air pollutants [particulate matter <2.5 μm (PM_{2.5}), sulfur dioxide (SO₂) and (NO₂)] and investigated the association of levels of air pollutants with the community-based prevalence of chronic kidney disease (CKD).

Methods. A Complex Health Screening program was launched during 2012–2013 and a total of 8284 community residents in Chiayi County, which is located in southwestern Taiwan, received a series of standard physical examinations, including measurement of estimated glomerular filtration rate (eGFR). CKD cases were defined as eGFR <60 mL/min/1.73 m² and were matched for age and gender in a 1:4 ratio of cases:controls. Data on air pollutants were collected from air quality monitoring stations during 2006–2016. The longitude, latitude and recruitment month of the individual case were entered into the trained FIS. The defuzzification process was performed based on the proper membership functions and fuzzy logic rules to infer the concentrations of air pollutants. In addition, we used conditional logistic regression and the distributed lag nonlinear model to calculate the prevalence ratios of CKD and the 95% confidence interval. Confounders including Framingham Risk Score (FRS), diabetes, gout, arthritis, heart disease, metabolic syndrome and vegetables consumption were adjusted in the models.

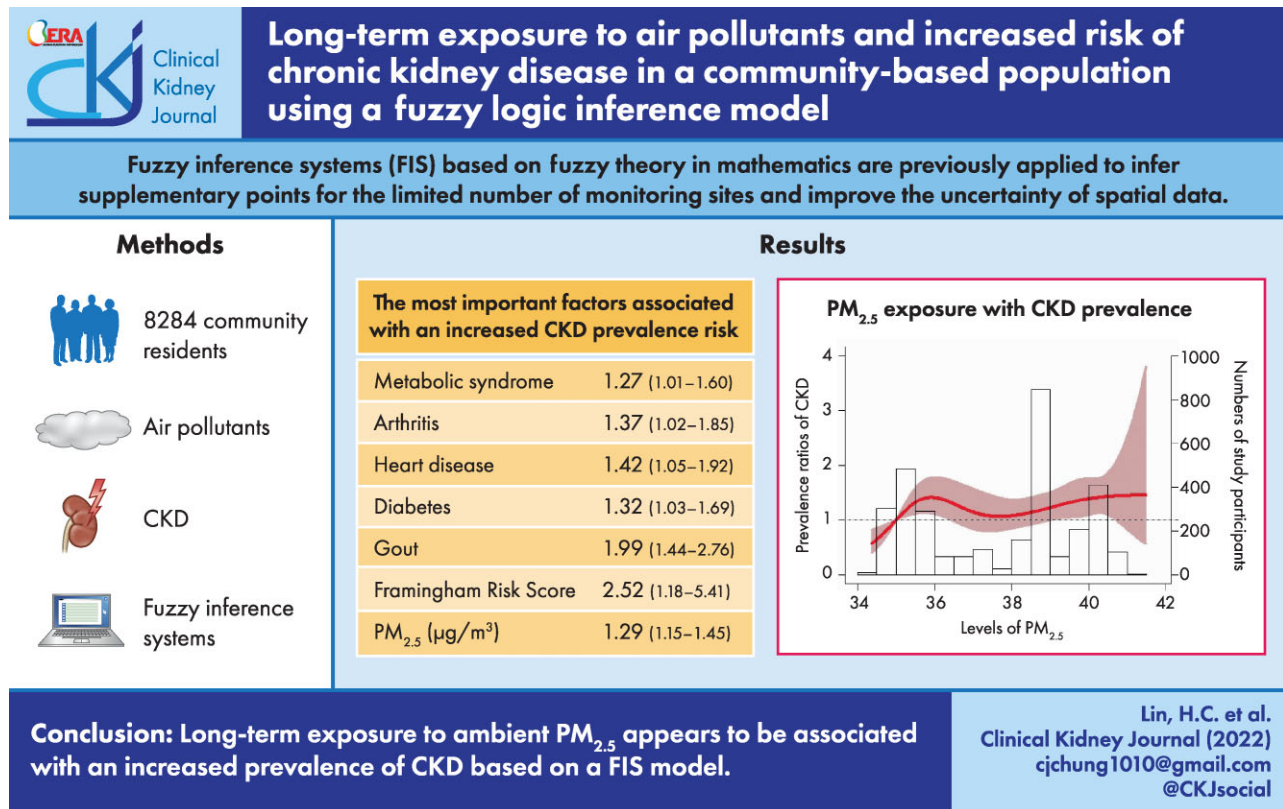
Results. Participants with a high FRS (>10%), diabetes, heart disease, gout, arthritis or metabolic syndrome had significantly increased CKD prevalence. After adjustment for confounders, PM_{2.5} levels were significantly increased in CKD cases in both single- and two-pollutant models (prevalence ratio 1.31–1.34). There was a positive association with CKD in the two-pollutant models for NO₂. However, similar results were not observed for SO₂.

Received: 23.1.2022; Editorial decision: 23.3.2022

© The Author(s) 2022. Published by Oxford University Press on behalf of the ERA. This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (<https://creativecommons.org/licenses/by-nc/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

Conclusions. FIS may be helpful to reduce uncertainty with better interpolation for limited monitoring stations. Meanwhile, long-term exposure to ambient PM_{2.5} appears to be associated with an increased prevalence of CKD, based on a FIS model.

GRAPHICAL ABSTRACT



Keywords: air pollution, chronic kidney disease, fuzzy logic inference model, NO₂, PM_{2.5}

INTRODUCTION

Chronic kidney disease (CKD) is characterized by persistent abnormalities in kidney structure and function [1]. With >697 million patients with CKD worldwide in 2019 [2], the increased disease burden with a lower social demographic index [3] poses a major challenge to global public health [4, 5]. Exposure to particulate matter <2.5 µm (PM_{2.5}) increases mortality as well as the risk of vascular inflammation and atherosclerosis [6–8] and it is widely believed that PM_{2.5} adversely affects the development and progression of cardiovascular disease [6, 9]. The kidney, a highly vascularized organ, may also be susceptible to PM-related small vessel dysfunction and large vessel atherosclerosis [10].

Hypertension, diabetes, ethnicity, age, smoking, episodes of acute kidney injury, use of analgesic medications and genetic factors [11] are widely recognized as risk factors for the development of CKD. However, air pollution has been increasingly emphasized as a new risk factor for CKD [12, 13]. Experimental studies suggest that deregulation of renal hemodynamics, oxidative stress and an inflammatory response occurred when exposed to deeply inhaled particles. These particles damage renal tissue and eventually exacerbate acute kidney injury (AKI) and CKD in animal studies [8, 14, 15]. Mehta et al. [13] found that long-term exposure to high PM_{2.5} levels led to longitudinal changes of the

estimated glomerular filtration rate (eGFR) in a regional cohort of 669 elderly men. In another study, Xu et al. [16] reported that long-term exposure to high levels of PM_{2.5} increased the risk of membranous nephropathy. Finally, Bowe et al. [12] reported significant associations between exposure to PM_{2.5} and the risk of incident CKD, eGFR decline and end-stage renal disease (ESRD).

Several studies aimed to predict PM_{2.5} concentrations through stationary monitoring data or satellite aerosol optical depth with various spatial geostatistical algorithms and grid sizes [12, 16]. Most stationary monitoring data applied in the spatial interpolation of ambient pollutant measurements were usually from a limited number of monitoring sites. Fuzzy inference systems (FISs) based on fuzzy theory in mathematics are frequently used to infer supplementary points for a limited number of monitoring sites and improve the uncertainty of spatial data [17, 18]. The FIS for exposure estimation can design the input features, e.g. the geographic coordinates and months, to infer the reasonable outputs, such as the pollutant concentrations of PM_{2.5}. The inputs are expressed by the membership functions (MFs) for fuzzification and follow the rule-based logics for defuzzification to estimate the output [19, 20]. In our previous study, we developed and validated the FIS model to improve the uncertainty of spatial data and for application in interpolation of

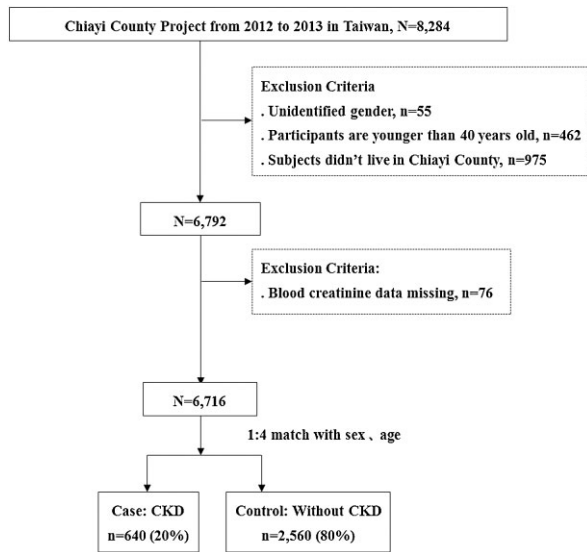


FIGURE 1: Study protocol of community-based participants recruited.

ambient levels of $PM_{2.5}$ and lead [18]. Besides $PM_{2.5}$, the FIS model was further extended in the present study to infer the levels of multiple air pollutants including sulfur dioxide (SO_2) and nitrogen dioxide (NO_2). Furthermore, we explored the prevalence ratios (PRs) of CKD associated with increasing concentrations of ambient multipollutants ($PM_{2.5}$, SO_2 and NO_2) through single- and two-pollutant models in a community-based population.

MATERIALS AND METHODS

Study area and participants

Chiayi County, a typical agricultural county located in southwestern Taiwan, comprises 18 townships and cities covering 1901.67 km² (i.e. ~5.28% of the total area of Taiwan). Chiayi County has a population of 500 000 people and the highest percentage of elderly people (18.61%) in Taiwan. We implemented a Community-based Complex Health Screening (CCHS) program to investigate the effects of environmental issues on long-term health risk assessments. Community recruitment was conducted in 2012 and 2013 and included residents ≥ 40 years of age who lived in Chiayi County. A total of 8284 community residents participated in the study. Cases with missing data of gender ($n = 55$), age < 40 years ($n = 462$) and those who did not live in Chiayi County ($n = 975$) were excluded. The detailed recruitment protocol is presented in Figure 1. A total of 6792 community residents were included in the present study. All participants provided informed consent before study enrollment and specimen collection. This study was approved by the Research Ethics Committee of China Medical University Hospital, Taichung, Taiwan (DMR101-IRB061).

Collection of questionnaire data and health examinations

All community residents ≥ 40 years of age were invited to participate in the anthropometric measurements and baseline health examinations, which included height, weight and waist and hip circumference, measured in the standing position with a special tape to the nearest centimeter at the umbilicus (waist circumference) and at the iliac spine (hip circumference). Blood

pressure in the right arm was measured by a standard mercury sphygmomanometer to record the lowest value while the individual was seated. A venous blood sample was taken after an 8-h fast to obtain the following biochemical parameters: plasma levels of triglycerides, total cholesterol, low-density lipoprotein cholesterol (LDL) and high-density lipoprotein cholesterol (HDL). In addition, blood glucose and blood creatinine were also measured. Diabetes was defined as fasting glucose ≥ 126 mg/dL or use of insulin or oral hypoglycemic medicines. Hypertension was defined as systolic blood pressure (SBP) > 140 mmHg or diastolic blood pressure (DBP) > 90 mmHg or self-reported antihypertensive medication use. Hyperlipidemia was defined as total cholesterol ≥ 200 mg/dL or triglycerides ≥ 130 mg/dL or self-reported. The presence of metabolic syndrome was further defined as individuals with three or more of the following abnormalities: SBP ≥ 130 mmHg or DBP ≥ 85 mmHg, waist circumference ≥ 90 cm for men or ≥ 80 cm for women, blood triglyceride concentration ≥ 150 mg/dL, HDL < 40 mg/dL for men or < 50 mg/dL for women or fasting glucose ≥ 100 mg/dL, using the National Cholesterol Education Program's Adult Treatment Panel III guidelines, modified for the Asian population from the International Diabetes Federation [21]. Furthermore, the gender-specific Framingham Risk Score (FRS) was calculated to assess the risk for each patient. The scores were further categorized based on the 10-year risk of cardiovascular disease ($< 10\%$, $10\text{--}20\%$ and $> 20\%$ as low risk, intermediate risk and high risk, respectively) [22].

Trained personnel interviewed each participant and completed a structured questionnaire based on the standardized assessment. The assessment information related to demographic and socioeconomic characteristics and lifestyle variables including cigarette smoking and quantity of areca nut chewing, consumption of alcohol and other beverages, participation in sports, consumption of three regular meals per day and personal and familial history of cancer or other related diseases. Prevalence of heart disease, gout, chronic liver disease, arthritis and cancer was defined if cases self-reported 'yes' to the question 'Have you ever had heart disease?' in the questionnaire on the disease history of the individual.

Definition of CKD

We used the Chronic Kidney Disease Epidemiology Collaboration equation to estimate the individual eGFR [23]. We further defined the five stages of CKD according to the relevant Kidney Disease Outcomes Quality Initiative guidelines from the National Kidney Foundation. Study participants in stages 3–5 (eGFR < 60 mL/min/1.73 m²) were defined as having CKD. In the analysis, we included 640 CKD individuals and 2560 control subjects in a 1:4 ratio of cases:controls. Controls were recruited participants whose age and gender matched the cases with CKD, but with no evidence of CKD (eGFR ≥ 60 mL/min/1.73 m²).

A FIS model for $PM_{2.5}$, SO_2 and NO_2 estimation

Data on air pollutants including $PM_{2.5}$, SO_2 and NO_2 were collected from air quality monitoring stations ($n = 73$) in Taiwan from 2006 to 2016. A map of the stationary monitors and study area in Taiwan are shown in Supplementary data, Figure S1. The monthly average concentration of $PM_{2.5}$, SO_2 and NO_2 was estimated in accordance with the FIS model. The detailed modeling procedures for $PM_{2.5}$ assessment were previously published by Chung et al. [18]. In this study, similar methods were applied to infer the concentration of SO_2 and NO_2 in Chiayi. Briefly, the

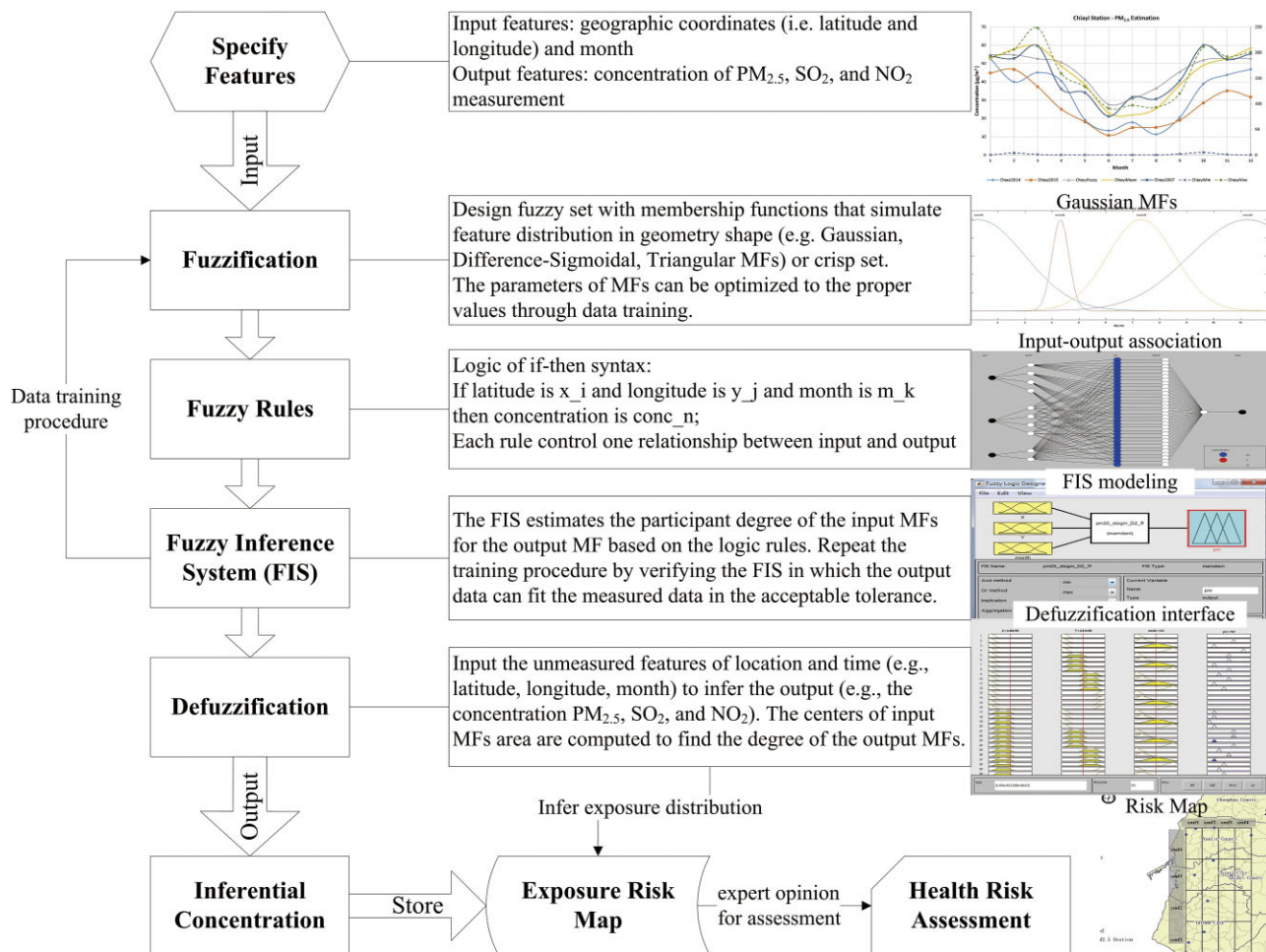


FIGURE 2: Fuzzy inference frameworks for assessing levels of air pollutants (PM_{2.5}, SO₂ and NO₂). MFs, membership functions.

analytical data of PM_{2.5}, SO₂ and NO₂ from 2006 to 2014 with filtration and imputation in data preprocessing were entered into the FIS model for the data train. The FIS model consists of four steps, as shown in Figure 2.

Step 1. Specify input and output features—the sets of 'longitude, latitude and month' as well as 'concentration' were the respective features for the input and output data of the individual pollutants (PM_{2.5}, SO₂ and NO₂).

Step 2. Design the fuzzy set with proper MFs—the MFs further constitute the input features' fuzzy set for the Mamdani-type MF with the geometric shape while the output feature can be converted to the Sugeno-type MF with a numerical crisp set. For example, for PM_{2.5} we created the Gaussian MF of the month feature corresponding to the regression distributions of the studied pollutants during the four seasons, while the difference-sigmoidal (d-sigmoid) MFs of the spatial features such as longitude and latitude were designed in accordance with the concentration distribution. Similarly, we considered the Gaussian MFs for SO₂ and the d-sigmoid MFs for NO₂ cases with respect to their regression distributions including the study area of Chiayi as shown in Supplementary data, Figure S2.

Step 3. Define the fuzzy logic rules—the fuzzy logic rules are enabled with 'if-then' syntax to control the association between

the input and output features. The Mamdani-type FIS with the appropriate rules would reduce the MFs of the output features compared with the Sugeno-type FIS for the realizable inference design within the same scope. In addition, the adaptive neuro-FIS (ANFIS) can drive the data training process to optimize the Sugeno-type FIS with the appropriate FIS parameters that can be referred to as the equivalent Mamdani-type FIS. We used the triangular MF to build the fuzzy set of output features (i.e. concentration level of pollutants).

Step 4. Infer the output results—the longitude, latitude and recruitment month of the individual resident can finally be input into the trained FIS that conducted the defuzzification process with the fuzzy logic rules to deduce the concentration of PM_{2.5}, SO₂ and NO₂. We validated the output levels of PM_{2.5}, SO₂ and NO₂ with the average values of monitoring data from 2015 to 2016. The mean absolute error (MAE) and root mean square error (RMSE) of various air pollutants are shown in Supplementary data, Table S1. Both Matlab and QGIS were employed to generate the FIS model and plot the geographic-related risk map, respectively (Supplementary data, Figure S3). For every resident we calculated the overall average value of PM_{2.5}, SO₂ and NO₂ from 2006 to their corresponding year of recruitment. Descriptive data of air pollutants in the full study population, including PM_{2.5}, SO₂ and NO₂, are presented in Supplementary data, Table S2.

Table 1. Descriptive characteristics between study participants with and without CKD

Variables	Cases (n = 640)	Controls (n = 2560)	Age- and sex-adjusted PR (95% CI) ^a
eGFR (mL/min/1.73 m ²), mean ± SD	50.33 ± 9.66	74.27 ± 9.60	
Age (years), mean ± SD	66.82 ± 8.93	65.84 ± 8.89	
40–50, n (%)	14 (2.19)	56 (2.19)	
50–60, n (%)	122 (19.06)	488 (19.06)	
60–70, n (%)	267 (41.72)	1068 (41.72)	
70–80, n (%)	202 (31.56)	808 (31.56)	
≥80, n (%)	35 (5.47)	140 (5.47)	
Sex, n (%)			
Male	296 (46.25)	1184 (46.25)	
Female	344 (53.75)	1376 (53.75)	
Ethnicity, n (%)			
Holo Taiwanese	564 (97.41)	2329 (97.37)	Reference
Hakka Taiwanese	7 (1.21)	36 (1.51)	0.82 (0.36–1.85)
Mainland Chinese	8 (1.38)	27 (1.13)	1.07 (0.45–2.52)
Education, n (%)			
Elementary school or below	408 (65.38)	1631 (64.72)	Reference
High school	173 (27.72)	666 (26.43)	1.03 (0.81–1.30)
College or above	43 (6.89)	223 (8.85)	0.75 (0.52–1.08)
Marriage, n (%)			
Married	517 (82.99)	2186 (87.51)	Reference
Single	15 (2.41)	38 (1.52)	1.71 (0.90–3.24)
Widowed/divorced	91 (14.61)	274 (10.97)	1.42 (1.09–1.85)
Hypertension, n (%)	456 (71.92)	1,540 (60.87)	1.67 (1.38–2.03)**
Hyperlipidemia, n (%)	459 (72.51)	1634 (64.33)	1.48 (1.22–1.80)**
Diabetes, n (%)	210 (33.44)	584 (23.16)	1.70 (1.40–2.06)**
Metabolic syndrome, n (%)	282 (44.06)	790 (30.86)	1.81 (1.51–2.17)**
FRS, n (%)			
<10%	114 (17.81)	684 (26.72)	Reference
10–20%	214 (33.44)	868 (33.91)	1.80 (1.36–2.37)**
≥20%	312 (48.75)	1008 (39.38)	2.72 (2.02–3.68)**
Heart disease, n (%)	92 (14.77)	252 (10.04)	1.59 (1.23–2.07)**
Gout, n (%)	99 (15.99)	199 (7.93)	2.24 (1.72–2.93)**
Chronic liver disease, n (%)	27 (4.55)	90 (3.83)	1.20 (0.77–1.88)
Arthritis, n (%)	107 (17.23)	290 (11.59)	1.59 (1.24–2.04)**
Cancer, n (%)	22 (3.53)	48 (1.91)	1.84 (1.11–3.08)*
Blood pressure (mmHg), mean ± SD			
SBP	140.63 ± 19.56	138.40 ± 19.15	1.01 (1.00–1.01)**
DBP	82.86 ± 11.46	82.41 ± 10.87	1.00 (0.99–1.01)
Biochemical parameters (mg/dL), mean ± SD			
Triglycerides	142.04 ± 43.55	130.78 ± 48.26	1.01 (1.00–1.01)**
Total cholesterol	195.39 ± 38.61	197.54 ± 38.10	1.00 (0.99–1.01)
LDL	107.25 ± 31.21	109.56 ± 37.64	1.00 (0.99–1.01)
HDL	55.58 ± 14.36	58.29 ± 15.17	0.99 (0.98–0.99)***
Fasting glucose	108.28 ± 40.58	102.47 ± 32.99	1.00 (1.01–1.02)***

^aPRs and 95% CIs were calculated from conditional logistic regressions. *P > .01 – <.05, **P < .01. ***P < .001.

Statistical analysis

In this study, the continuous and categorical variables were presented as mean [\pm standard deviation (SD)] and number (percentage), respectively. We used the univariate and multiple conditional logistic regression models to evaluate the PRs and 95% confidence intervals (CIs) to evaluate the associations between PM_{2.5}, SO₂ and NO₂ with respect to the risks of CKD. In addition, we considered the relevant risk factors in the results in Tables 1 and 2 and used stepwise logistic regressions to identify the relevant confounders. Multiple logistic regressions were then used to evaluate the risk of CKD as well as all indices of air pollutants after adjusting for relevant confounders. Furthermore, two-pollutant models were constructed to assess

the association between ambient PM_{2.5} and CKD by including other individual indices of air pollutants in these models. Similar methods were also applied to assess other pollutants. For single pollutants significantly associated with CKD, we further applied the distributed lag nonlinear model to explore the individual exposure-response relationship between pollutants and CKD prevalence [DLNM package in the R program (R Foundation for Statistical Computing, Vienna, Austria)]. The pollutant-health association was set as the natural spline (ns) function with 4 degrees of freedom in the analysis models. The model selection was through the Akaike information criterion (Supplementary data, Table S3). Finally, we used the stepwise logistic regression model to identify the factors of importance for increased risk of CKD. All data were analyzed and plotted

Table 2. Distributions of lifestyle and dietary-related factors between study participants with and without CKD

Variable	Cases (n = 640)	Controls (n = 2560)	Age- and sex-adjusted PR (95% CI) ^a
Smoking, n (%)			
No	511 (80.60)	2079 (81.82)	Reference
Yes	123 (19.40)	462 (18.18)	1.12 (0.86–1.45)
Alcohol drinking, n (%)			
No	539 (84.88)	2117 (83.58)	Reference
Yes	96 (15.12)	416 (16.42)	0.88 (0.68–1.14)
Tea drinking, n (%)			
No	434 (68.56)	1801 (71.13)	Reference
Yes	199 (31.44)	731 (28.87)	1.13 (0.93–1.37)
Coffee drinking, n (%)			
No	593 (93.39)	2366 (93.41)	Reference
Yes	42 (6.61)	167 (6.59)	1.00 (0.70–1.42)
Betel consumption, n (%)			
No	578 (90.88)	2315 (91.47)	Reference
Yes	58 (9.12)	216 (8.53)	1.08 (0.77–1.50)
Sugary drink (bottles/week), n (%)			
<3	553 (91.10)	2233 (92.58)	Reference
3–7	33 (5.44)	121 (5.02)	1.14 (0.76–1.70)
≥7	21 (3.46)	58 (2.40)	1.45 (0.87–2.41)
Fried food consumption (frequency/week), n (%)			
<1	429 (70.56)	1760 (72.52)	Reference
≥1	179 (29.44)	667 (27.48)	1.08 (0.88–1.33)
Vegetables consumption (bowls/day), n (%)			
<1	262 (41.46)	893 (35.20)	1.35 (1.12–1.62)*
1–3	314 (49.68)	1443 (56.88)	Reference
≥3	56 (8.86)	201 (7.92)	1.28 (0.92–1.77)
Fruit consumption (bowls/day), n (%)			
<1	410 (64.87)	1507 (59.35)	1.31 (1.08–1.59)
1–3	189 (29.91)	904 (35.60)	Reference
≥3	33 (5.22)	128 (5.04)	1.23 (0.81–1.86)

^aPRs and 95% CIs were calculated from conditional logistic regressions. *P > .01– <.05; **P < .01; ***P < .001.

using the SAS statistical package (version 9.4; SAS Institute, Cary, NC, USA) and R version 3.6.3. P-values of <.05 (two-sided) were considered significant.

RESULTS

After excluding missing data on blood creatinine ($n = 76$), a total of 6716 subjects with an approximate 1:1 gender ratio (640 CKD patients and 2560 healthy controls) were included in this study. The average age was 66 years (SD 8.9). In all, ~75% of subjects were 60–80 years old (Table 1). More than 95% of the study population was Holo Taiwanese and ~65% had an education level of elementary school or below. A total of 85% of the subjects were married. Study participants with heart disease, gout, arthritis, metabolic syndrome, high FRS, hypertension, diabetes, hyperlipidemia and cancer were associated with a 1.5–2.7-fold increased risk of CKD (all P-values < .05). Additionally, the estimated PRs of CKD were significantly increased per unit increments for SBP, triglycerides and fasting glucose, as well as low HDL.

We further explored the associations between CKD and non-CKD patients in lifestyle and dietary factors in (Table 2). The results showed that >70% of the study population had no history of cigarette smoking or alcohol, tea, coffee or betel consumption. About 30% consumed fried food more than once per week. Half of the study population consumed one to three servings of vegetables per day and 90% consumed less than three bottles of a sugary drink per week. However, ~60% had less than one serving

Table 3. Associations between indices of air pollutants and CKD risks from single- and two-pollutant models

Air pollutants	PR (95% CI) ^a	PR (95% CI) ^b
PM _{2.5} ($\mu\text{g}/\text{m}^3$)	1.37 (1.23–1.53)***	1.31 (1.17–1.47)***
+ SO ₂	1.37 (1.23–1.54)***	1.32 (1.18–1.48)***
+NO ₂	1.40 (1.25–1.57)***	1.34 (1.20–1.51)***
SO ₂ (ppb)	1.08 (0.99–1.17)	1.07 (0.98–1.17)
+PM _{2.5}	1.08 (0.99–1.17)	1.08 (0.99–1.17)
+NO ₂	0.96 (0.65–1.42)	1.15 (0.77–1.71)
NO ₂ (ppb)	1.03 (1.00–1.07)	1.03 (0.99–1.06)
+PM _{2.5}	1.04 (1.01–1.08)**	1.04 (1.01–1.08)*
+ SO ₂	1.05 (0.90–1.21)	0.97 (0.84–1.14)

^aAges and gender-adjusted conditional logistic regressions. ^bMultiple conditional logistic regressions included confounding factors of FRS, diabetes, gout, arthritis, heart disease, metabolic syndrome, vegetables consumption.

*P > .01–<.05; **P < .01; ***P < .001.

of fruit per day. Among these lifestyle-related risk factors, people who consumed less than one serving of vegetables per day were associated with an increased PR of CKD [odds ratio (OR) 1.35 (95% CI 1.12–1.62)].

For single-pollutant models, study subjects with high PM_{2.5} per SD increment had a significantly increased 1.37-fold PR of CKD (95% CI 1.23–1.53) (Table 3). In addition, we considered all relevant risk factors of the above results from Tables 1 and 2 in a stepwise logistic regression and found that the most important

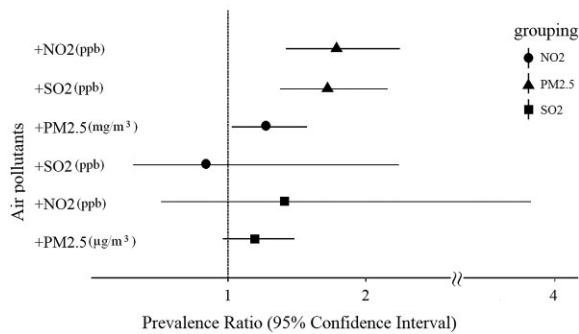


FIGURE 3: Associations between air pollutants (PM_{2.5}, SO₂ and NO₂) and CKD prevalence from a two-pollutant model by adjusting for FRS, diabetes, gout, heart disease, arthritis, metabolic syndrome and consumption of vegetables.

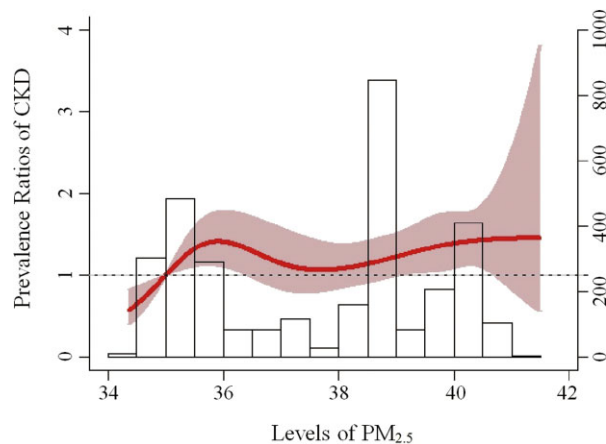


FIGURE 4: Non-linear relationships of PM_{2.5} exposure with CKD prevalence after adjusting for relevant confounders. Results are presented as PRs with 95% CIs.

factors for CKD were FRS, diabetes, gout, heart disease, arthritis, metabolic syndrome and consumption of vegetables. Therefore we adjusted these factors in the sequencing multiple conditional logistic regression analysis. After adjusting for other confounders, there were still positive associations between PM_{2.5} [PR 1.31 (95% CI 1.17–1.47)] and CKD prevalence. For PM_{2.5}, positive associations were observed in the two-pollutant models with SO₂ [PR 1.32 (95% CI 1.18–1.48)] and NO₂ [PR = 1.34 (95% CI 1.20–1.51)] after adjusting for other confounders (Figure 3 and Table 3). For NO₂, a positive association was demonstrated in the two-pollutant models with PM_{2.5} [PR 1.04 (95% CI 1.01–1.08)]. Furthermore, we tried to explore the interaction effects of PM_{2.5} and NO₂ as well as PM_{2.5} and SO₂ on CKD risk. The results showed no positive interactions were observed (all *P*-values for interaction terms in the multiplicative models > .05; data not shown). Figure 4 shows the nonlinear dose-response relationship between PM_{2.5} and CKD prevalence. The annual average PM_{2.5} of the significant CKD prevalence was identified as ~35.0–36.7 (PR range 1.01–1.42) and 39.03–40.7 µg/m³ (PR range 1.25–1.42) after adjusting for other confounders. Furthermore, we analyzed the Spearman correlation between PM_{2.5} levels and eGFR. The results presented a negative correlation of PM_{2.5} with eGFR ($r = -0.10$; $P < .0001$).

Finally, we input all relevant risk factors (including traditional factors, PM_{2.5} and NO₂) into the stepwise logistic regression model to identify the most important factors associated with an increased CKD prevalence risk (Table 4). The results

Table 4. Stepwise logistic regression analysis for increased risk of CKD

Variable	PR (95% CI)	P-value
Metabolic syndrome (yes versus no)	1.27 (1.01–1.60)	.039
Arthritis (yes versus no)	1.37 (1.02–1.85)	.035
Heart disease (yes versus no)	1.42 (1.05–1.92)	.023
Diabetes (continuous)	1.32 (1.03–1.69)	.029
Gout (yes versus no)	1.99 (1.44–2.76)	<.001
FRS	2.52 (1.18–5.41)	.017
<10%		
10–20%	1.48 (1.08–2.03)	.016
20%	1.68 (1.15–2.47)	.008
Vegetables consumption (bowls/day)		
<1	1.42 (1.16–1.75)	.001
1–3	Reference	
≥3	1.29 (0.90–1.86)	.1720
PM _{2.5} (µg/m ³)	1.29 (1.15–1.45)	<.001

All relevant factors in Tables 1–3 were included in the stepwise logistic regression model.

indicated that PM_{2.5} had an important effect on increased PRs of CKD. Other associated factors included metabolic syndrome, arthritis, heart disease, diabetes, gout, FRS and daily vegetable consumption.

DISCUSSION

This study constructed a FIS model to estimate the levels of various air pollutants and evaluate the relationship between air pollutants and PRs of CKD in a community-based population in Taiwan. The results suggest increased PRs of CKD with increasing levels of ambient PM_{2.5} across univariate- and multivariable-adjusted models and in single- and two-pollutant models. For the nonlinear dose-response relationship, the prevalence ratios of CKD were significantly increased at two peak levels of PM_{2.5} at 35.0–36.7 and 39.03–40.7 µg/m³ of PM_{2.5}.

We generated FIS models for multiple pollutants through the adaptive neural fuzzy inference process by training open data from a limited number of monitoring sites. The pollutant concentration at the geographic coordinates of residents could then be estimated for risk assessment. The proposed model consisted of MFs including Gaussian and d-sigmoid functions to simulate the spatiotemporal distribution of the measurement data within the 16 inference grids. The simulation enabled the grids with reasonable MF-based distribution to improve conventional methods such as the Kriging interpolation and inverse distance weighting (IDW), which regress an interpolation function between two known points [24, 25]. With reference to our previous study [18], the MAE and RMSE for the above evaluation of PM_{2.5} could be reduced for the FIS model in relation to the Kriging and IDW methods. In the current study, we applied consistent MFs for a pollutant, as shown in Supplementary data, Table S1 (Gaussian MF for SO₂ and d-sigmoid MF for PM_{2.5} and NO₂), which details evaluation errors of the estimated concentrations that correspond to the measured points from 2006 to 2016. The FIS model can be used to estimate the concentration distribution in the grids with more variations based on the simulation of multiple mathematical MFs. The FIS refers to a few known points and drives the MFs to establish the distribution pattern of most unknown points. In practice, the multiple MFs can be combined in the grid of distributions to simulate the nonuniform diffusion mode of pollutants. The modeling may overes-

timate the pollution concentration for risk assessment due to the various distributions compared with the conventional methods, such as IDW based on the inverse of square root function or Kriging based on the uniform distribution function. For example, the estimated levels of SO₂ and NO₂ would be higher than with the Kriging and IDW methods. The ANFIS, which integrates the artificial neural network and FIS, can train the abundant data for machine learning to generate the prediction model. However, the FIS may have a defect to estimate the inputs out of the MF's distribution range. A conservative approach is limited to the bounds of the known input points compared with the conventional method that drives an interpolation function around the measured points. The finer grids with combinative MFs are helpful to improve the FIS model for the advanced application. Further research is required to identify the appropriate MFs and confirm the gas diffusion model.

Positive associations between CKD and NO₂ exposure by land-use regression model analysis were also presented in the findings from Chen *et al.* [26] [OR 1.07 (95% CI 1.01–1.14)] for per interquartile range increment of NO₂. Li *et al.* [27] acquired the levels of PM_{2.5} by aerosol optical depth (AOD) data and clarified the significant association of PM_{2.5} with CKD prevalence [OR 1.28 (95% CI 1.22, 1.35)]. In addition, various ambient levels of PM_{2.5}, PM₁₀, SO₂, NO₂ and ozone (O₃) were calculated by the Kriging method in the study of Wang *et al.* and they found people's exposure to high levels of PM₁₀ was associated with an increased prevalence of CKD. At present, there is a conflict between the consistency of air pollutant exposure and CKD risk, with different methods to predict the ambient levels of the pollutants in the air. In the present study, we aim to provide an additional probability to infer the ambient levels of air pollutants. Also, the finding of our study adds to the current body of literature by providing further support for the link between long-term PM_{2.5} exposure and CKD prevalence. Furthermore, the levels of PM_{2.5} in our study area were between 34.4 and 41.5 µg/m³, which exceeds the air quality guideline from World Health Organization (10 µg/m³) [28] and even higher than that in the USA [12, 13]. We tried to explore the non-linear relationship of PM_{2.5} exposure with CKD prevalence; however, with limited numbers of study participants, we merely observed two narrow ranges of PM_{2.5} exposure (35.0–36.7 and 39.03–40.7 µg/m³) with increased risk of CKD (Figure 4). In the future, it may be necessary to clarify the nonlinear dose–response relationship for CKD risk with a larger sample size. Overall, minimizing PM_{2.5} and NO₂ levels would benefit efforts for the prevention and control of CKD.

The mechanism underlying the relationship between PM_{2.5} and CKD remains unclear. Numerous studies of laboratory evidence propose that exposure to PM causes renal hemodynamic impairment and promotes oxidative stress, inflammation and DNA damage in kidney tissue, which aggravates AKI and further progresses to CKD in murine models [8, 14, 15]. In addition, it is estimated that at least 0.2% of the inhaled nanoparticles will transfer from the lungs to the systemic circulation [29]. The kidneys can only remove smaller particles (<6 nm) in the systemic circulation [30–32]. Inhaled particles that cause renal function deterioration may result from inflammation and oxidative stress [13, 33, 34]. Furthermore, recent reports have speculated that the pathogenesis mechanism of PM_{2.5}-related CKD may be similar to that of PM_{2.5}-related cardiovascular disease [35, 36].

By using the FIS model, we can infer pollutants distributed over the potential location for risk assessment. The large number of participants in our study area with a large number of events identified provides sufficient power to determine whether these patients are vulnerable with respect to the risk of CKD in an environment with high levels of air pollution. In

addition, we extensively screened and ascertained each participant's CKD risk by calculating eGFR to ensure an accurate diagnosis compared with self-reporting information. However, this study also has several limitations. First, both, selection bias and survival bias may exist because of the reliance on community volunteers with better health, which may limit the generalization of the study findings. Despite this, we still observed an association between PM_{2.5} and CKD prevalence. Our results may underestimate the PRs of CKD. In addition, more than half of the study population was older population with a high prevalence of comorbidities, including hypertension, hyperlipidemia and diabetes. Detailed information on medication usage was not acquired in the present study. Furthermore, there were ~80% non-smokers in our population. Therefore, it is difficult to evaluate the associations between the levels of PM_{2.5}, cigarette smoking and biochemical parameters, such as SBP. Second, only ambient pollution concentrations at the place of residence were available, which could potentially cause exposure misclassification. Factors such as the use of personal protective equipment and time spent outdoors may affect personal exposure. Third, data related to the development and progression of kidney diseases, such as albuminuria and inflammatory factors, are not available in this study. Finally, we constructed a FIS model using information from the quality monitoring stations in Taiwan, therefore, we did not further validate the predicted levels of air pollutants with monitoring values at distant locations. In addition, we could not exclude the effects of other air pollutants such as O₃, carbon monoxide, etc. on CKD prevalence.

This study is the first to explore the association between PM_{2.5} and PRs of CKD in a community-based population by constructing a FIS model. After considering the conventional risk factors of CKD, there is an independent effect of PM_{2.5} on CKD prevalence in either single- or two-pollutant models. CKD prevalence was significantly increased at two peak levels of PM_{2.5} (35.0–36.7 and 39.03–40.7 µg/m³) with a nonlinear dose–response relationship in the DLNM analysis. To support these findings, further studies with different study designs are warranted.

SUPPLEMENTARY DATA

Supplementary data are available at [ckj](https://ckj.oup.com/ckj) online.

FUNDING

This work was supported by China Medical University (DMR-108-164), Taichung, Taiwan, Ministry of Science and Technology (MOST 105-2314-B-039-022, MOST 105-2119-M-039-003, MOST 106-2119-M-039-002 and MOST 107-2119-M-039-002), Taipei, Taiwan and Department of Research of Ditmanson Medical Foundation Chia-Yi Christian Hospital (R110-29).

CONFLICT OF INTEREST STATEMENT

All authors have reported that they have no relationships relevant to the contents of this article to disclose.

(See related article by Copur *et al.* Increase in the global burden of chronic kidney disease: might it be attributable to air pollution? *Clin Kidney J* (2022) 15: 1800–1802.)

REFERENCES

- Chen TK, Knicely DH, Grams ME. Chronic kidney disease diagnosis and management: a review. *JAMA* 2019; 322: 1294–1304

2. GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet* 2020; **396**: 1204–1222
3. GBD Chronic Kidney Disease Collaboration. Global, regional, and national burden of chronic kidney disease, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2020; **395**: 709–733
4. Yang G, Wang Y, Zeng Y et al. Rapid health transition in China, 1990–2010: findings from the Global Burden of Disease Study 2010. *Lancet* 2013; **381**: 1987–2015
5. Stanifer JW, Muir A, Jafar TH et al. Chronic kidney disease in low- and middle-income countries. *Nephrol Dial Transplant* 2016; **31**: 868–874
6. Brook RD, Rajagopalan S, Pope CA, 3rd et al. Particulate matter air pollution and cardiovascular disease: An update to the scientific statement from the American Heart Association. *Circulation* 2010; **121**: 2331–2378
7. Hoffmann B, Moebus S, Kroger K et al. Residential exposure to urban air pollution, ankle-brachial index, and peripheral arterial disease. *Epidemiology* 2009; **20**: 280–288
8. Nemmar A, Karaca T, Beegam S et al. Prolonged pulmonary exposure to diesel exhaust particles exacerbates renal oxidative stress, inflammation and DNA damage in mice with adenine-induced chronic renal failure. *Cell Physiol Biochem* 2016; **38**: 1703–1713
9. Lin CK, Lin RT, Chen PC et al. A global perspective on sulfur oxide controls in coal-fired power plants and cardiovascular disease. *Sci Rep* 2018; **8**: 2611
10. Lue SH, Wellenius GA, Wilker EH et al. Residential proximity to major roadways and renal function. *J Epidemiol Community Health* 2013; **67**: 629–634
11. Kazancioglu R. Risk factors for chronic kidney disease: an update. *Kidney Int Suppl* 2013; **3**: 368–371
12. Bowe B, Xie Y, Li T et al. Particulate matter air pollution and the risk of incident CKD and progression to ESRD. *J Am Soc Nephrol* 2018; **29**: 218–230
13. Mehta AJ, Zanutti A, Bind MA et al. Long-term exposure to ambient fine particulate matter and renal function in older men: the Veterans Administration Normative Aging Study. *Environ Health Perspect* 2016; **124**: 1353–1360
14. Nemmar A, Al-Salam S, Zia S et al. Diesel exhaust particles in the lung aggravate experimental acute renal failure. *Toxicol Sci* 2010; **113**: 267–277
15. Yan YH, CKC C, Wang JS et al. Subchronic effects of inhaled ambient particulate matter on glucose homeostasis and target organ damage in a type 1 diabetic rat model. *Toxicol Appl Pharmacol* 2014; **281**: 211–220
16. Xu X, Wang G, Chen N et al. Long-term exposure to air pollution and increased risk of membranous nephropathy in China. *J Am Soc Nephrol* 2016; **27**: 3739–3746
17. Gorzalczany MB. An interval-valued fuzzy inference method: some basic properties. *Fuzzy Sets Syst* 1989; **31**: 243–251
18. Chung CJ, Hsieh YY, Lin HC. Fuzzy inference system for modeling the environmental risk map of air pollutants in Taiwan. *J Environ Manage* 2019; **246**: 808–820
19. Chiu SL. Fuzzy model identification based on cluster estimation. *J Intell Fuzzy Syst* 1994; **2**: 267–278
20. Zadeh LA. Outline of a new approach to the analysis of complex systems and decision processes. *IEEE Syst. Man Cybern* 1973; **3**: 28–44
21. Yen AM, Boucher BJ, Chiu SY et al. Longer duration and earlier age of onset of paternal betel chewing and smoking increase metabolic syndrome risk in human offspring, independently, in a community-based screening program in Taiwan. *Circulation* 2016; **134**: 392–404
22. D'Agostino RB, Sr., Vasan RS, Pencina MJ et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation* 2008; **117**: 743–753
23. Levey AS, Stevens LA, Schmid CH et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009; **150**: 604–612
24. Lee SJ, Serre ML, van Donkelaar A et al. Comparison of geostatistical interpolation and remote sensing techniques for estimating long-term exposure to ambient PM_{2.5} concentrations across the continental United States. *Environ Health Perspect* 2012; **120**: 1727–1732
25. Rivera-Gonzalez LO, Zhang Z, Sanchez BN et al. An assessment of air pollutant exposure methods in Mexico City, Mexico. *J Air Waste Manag Assoc* 2015; **65**: 581–591
26. Chen SY, Chu DC, Lee JH et al. Traffic-related air pollution associated with chronic kidney disease among elderly residents in Taipei City. *Environ Pollut* 2018; **234**: 838–845
27. Li G, Huang J, Wang J et al. Long-term exposure to ambient PM_{2.5} and increased risk of CKD prevalence in China. *J Am Soc Nephrol* 2021; **32**: 448–458
28. World Health Organization. WHO global air quality guidelines: particulate matter (PM_{2.5} and PM₁₀), ozone, nitrogen dioxide, sulfur dioxide and carbon monoxide. Geneva: World Health Organization, 2021
29. Miller MR, Raftis JB, Langrish JP et al. Inhaled nanoparticles accumulate at sites of vascular disease. *ACS Nano* 2017; **11**: 4542–4552
30. Sarin H. Physiologic upper limits of pore size of different blood capillary types and another perspective on the dual pore theory of microvascular permeability. *J Angiogenes Res* 2010; **2**: 14
31. Choi HS, Liu W, Misra Pet al. Renal clearance of quantum dots. *Nat Biotechnol* 2007; **25**: 1165–1170
32. Balasubramanian SK, Poh KW, Ong CN et al. The effect of primary particle size on biodistribution of inhaled gold nanoagglomerates. *Biomaterials* 2013; **34**: 5439–5452
33. Yang YR, Chen YM, Chen SY et al. Associations between long-term particulate matter exposure and adult renal function in the Taipei metropolis. *Environ Health Perspect* 2017; **125**: 602–607
34. O'Neill MS, Diez-Roux AV, Auchincloss AH et al. Airborne particulate matter exposure and urinary albumin excretion: the Multi-Ethnic Study of Atherosclerosis. *Occup Environ Med* 2008; **65**: 534–540
35. Afsar B, Elsurer Afsar R, Kanbay A et al. Air pollution and kidney disease: review of current evidence. *Clin Kidney J* 2019; **12**: 19–32.
36. Zhang Y, Liu D, Liu Z. Fine Particulate Matter (PM_{2.5}) and Chronic Kidney Disease. *Rev Environ Contam Toxicol* 2021; **254**: 183–215.