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Associations between long-term exposure to ambient air pollution and renal function in Southwest China: The China Multi-Ethnic Cohort (CMEC) study☆

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ABSTRACT

Background: Limited studies have examined associations between air pollutants exposure and renal function, especially in China, with the most extensive chronic kidney disease (CKD) disease burden worldwide.
Objectives: This study examines associations between long-term exposure to ambient $PM_{2.5}$, NO_2, CO, O_3, SO_2 and renal function.
Methods: We included 80,225 participants aged 30–79 years from the baseline data of the China Multi-Ethnic Cohort (CMEC) study. Three-year average concentrations of $PM_{2.5}$, NO_2, CO, O_3, and SO_2 were estimated using satellite-based spatiotemporal models. Renal function is determined by the estimated glomerular filtration rate (eGFR) using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. After adjusting for covariates, generalized propensity scores (GPS) weighting regression was used to estimate associations between ambient air pollutants and renal function.
Results: An increase of 0.1 mg/m^3 CO (OR [odds ratio] =1.20 95% CI [confidence interval], 1.05–1.37) was positively associated with CKD. An increase of 1 μg/m^3 in SO_2 (1.07, 1.00–1.14) concentration was positively associated with CKD. An increase of 10 μg/m^3 in $PM_{2.5}$ (1.17, 0.99–1.38), NO_2 (1.12, 0.83–1.51) and O_3 (1.10, 0.81–1.50) concentration was not associated with CKD. These effects are stronger in those younger than 65, smoking and with low BMI.
Conclusions: In this study, we found that long-term exposure to ambient CO and SO_2 were positively associated with CKD. Gaseous pollutants should also arouse the concern of relevant departments.

1. Introduction

Existing research has shown that exposure to air pollutants (AP) may lead to tremendous adverse health outcomes, causing an enormous disease burden(Liu et al., 2019). However, most of them focused on cardiovascular and respiratory health effects, and little literature has

☆ on behalf of the China Multi-Ethnic Cohort (CMEC) collaborative group

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focused on kidney disease(Brook et al., 2010).

Chronic kidney disease (CKD) refers to irreversible changes in kidney function and structure that last for years and months and arise from many heterogeneous disorders. CKD is a disease with high prevalence, morbidity, and mortality rates. In recent years, the disease burden of CKD has been increasing rapidly, especially in China, where the number of people with CKD is the highest in the world, with 132 million in 2019 (Deng et al., 2021). According to WHO, 864,226 deaths (1.5% of all global deaths) in 2012 could be attributed to CKD, which ranked 14th among the leading causes of death(Angela, Webster, 2017). Apart from traditional risk factors, AP may be a new environmental risk factor for CKD (Afsar et al., 2019; Wu et al., 2020a).

The main air pollutants include particulate matter such as fine particulate matter ($PM_{2.5}$) and gaseous pollutants such as ozone (O_3), carbon monoxide (CO), nitrogen dioxide (NO_2), and sulfur dioxide (SO_2). In recent years, World Health Organization (WHO) global air quality guidelines 2021 have recommended $PM_{2.5}$, NO_2, CO, O_3 and SO_2 as classical air pollutants(WHO, 2021). Current studies concerning the association between air pollution and kidney function focus mainly on $PM_{2.5}$(Wu et al., 2020b; Ye et al., 2021). The few remaining studies concerning gaseous pollutants have mostly focused on developed regions such as the United States, Europe and South Korea, and the conclusions are inconsistent (Bowe et al., 2017; Kim et al., 2018; Kuźma et al., 2021).

In China, where the concentration of gaseous pollutants has shown an increasing trend(Lu et al., 2019; Wang et al., 2021), few epidemiology studies on gaseous pollutants and renal function have been found. An emerging question then is whether the results of the above developed regions can be extrapolated to other populations, particularly less-developed regions, such as Southwest China, where the health-related behavior and lifestyle factor differ substantially, and the concentration range of gaseous pollutants is wider(Kim et al., 2015).

Furthermore, the relevant studies mentioned above are observational and do not have causal explanations. Based on the counterfactual framework, causal models can be used to explain the extent to which reduced pollutant concentrations alter the health effects, that is, causal effects. Fitted regressions tend to be sensitive to model misspecification when the observed component characteristics differ greatly in groups, i.e., not comparable between groups(Rubin, 1979). When Generalized propensity scores weighting (GPSW) regression is taken into account, GPSW can be estimated through a regression model called the design stage. After that, a balance check is used to ensure similar covariates distribution in different groups. Then, causal effects can be estimated in pseudo-population after weighting, called the analysis stage. Since the parameters can be consistently estimated even when only one of the two stages is correctly specified, GPSW is one of the doubly robust methods, research results of which provide a critical scientific basis for policy-making(Wu et al., 2020c).

In view of the above problems, GPSW was used to analyze the baseline data of 80225 participants aged from 30–79 years based on the China Multi-Ethnic Cohort (CMEC) study, trying to get a more accurate effect of ambient $PM_{2.5}$, NO_2, CO, O_3 and SO_2 on renal function in Southwest China population.

2. Method

2.1. Study population

CMEC is a natural population-based cohort study in five provinces in southwest China, including Sichuan, Chongqing, Yunnan, Guizhou and Tibet. Baseline survey data for 99,556 participants aged 30–79 were obtained through a multistage stratified cluster sampling between May 2018 and September 2019(Zhao et al., 2021).

Based on an electronic questionnaire, face-to-face interviews were conducted to collect CMEC baseline data (Demographics and socioeconomic status, Smoking and indoor air pollution, Alcohol consumption, Tea and other beverages, Health status, Physical activity, Reproductive history (for women), Diet, Life events, Sleep, Psychological conditions and social support), medical examinations and clinical laboratory tests. The electronic questionnaires were conducted by specially trained investigators and recorded for subsequent data verification. Local community hospitals carried out medical examinations after unified personnel training and instrument calibration were carried out. Clinical laboratory tests were carried out by a third-party company with corresponding national qualifications.

Ultimately 99,556 baseline participants were collected. The exclusion criteria of this study were as follows: 1. without residential address; 2. with the length of residence at the residential address at survey < 3 years; 3. without serum creatinine data; 4. with missing information on the covariates. Finally, we included 80,225 participants in this study (Fig. S1). All of the participants had signed an informed consent form before data collection. Ethical approval was received from the Sichuan University Medical Ethical Review Board (K2016038, K2020022).

2.2. Renal function

To get comparable results, fasting venous blood was collected from each participant and tested by a third-party company with corresponding national qualifications. We used Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation to estimate the glomerular filtration rate (eGFR)(Stevens et al., 2011). Compared with the traditional modification of diet in renal disease (MDRD) equation, the CKD-EPI equation proven more suitable for Chinese for the race variable was included in the equation(Liao et al., 2011). The CKD was defined as eGFR < 60 mL/min/1.73 m^2, representing a reduction in renal function of half or more of the normal level.

2.3. Exposure assessment

Air pollution data were obtained from the ChinaHighAirPollutants (CHAP) Data set (https://weijing-rs.github.io/product.html, accessed data: July 9, 2020). Daily surface NO_2, CO, O_3, and SO_2 were predicted at a 10 km $\times$ 10 km spatial resolution (Wei, 2022a,b), while daily $PM_{2.5}$ was predicted at a 1 km $\times$ 1 km spatial resolution (Wei et al., 2020; Wei et al., 2021). The above daily concentrations were predicted from big data including ground-measurements, satellite remote sensing products (e.g., Moderate Resolution Imaging Spectroradiometer Multiangle Implementation of Atmospheric Correction AOD product), meteorology, land use information, pollution emissions, and other spatial and temporal predictors . A space-time extremely randomized trees model was used for the estimation. A detailed description of the estimation has been described in previous studies. The results of 10-fold cross-validation showed a high predictive ability. The R^2 (root mean square error) values for the daily prediction of $PM_{2.5}$, NO_2, CO, O_3, and SO_2 were 0.92 (10.76 $\mu g/m^3$), 0.84 (7.99 $\mu g/m^3$), 0.80 (0.29 mg/m^3), 0.87 (17.10 $\mu g/m^3$) and 0.84 (10.07 $\mu g/m^3$) respectively. According to the geocoded residential address, average concentrations of $PM_{2.5}$ NO_2, CO, O_3, and SO_2 during the three years before the baseline survey were calculated for each participant as the estimated surrogate of exposure.

2.4. Statistical analysis

We used logistic and GPSW regression to estimate the associations between increases in three-year average $PM_{2.5}$ NO_2, CO, O_3, SO_2 exposure and CKD.

In the logistic regression method (Eq. 1), Y is the status of CKD (yes or no), b_0 is the intercept, x_1 to x_m are the covariates, b_1 to b_m are the coefficients of the covariates, β is the coefficient (log odds ratio [OR]) of exposure.

$$log\ odds(Y = 1|x) = b_0 + b_1x_1 + \ldots + b_mx_m + \beta Exposure \quad (1)$$

In the GPSW regression method, we modeled the exposure on the covariates we selected; traditional linear regression (Eq. 2) and gradient boosting machine (Xgboost) with normal residuals are used to estimate GPS(Zhu et al., 2015). Then, we calculated $f(Exposure)/GPS$ as weights, where extreme weights (greater than 10) are replaced by 10. We use average absolute correlation (AC) between exposures and covariates to measure whether covariates are balanced, with average AC less than 0.1 defined as balanced. We evaluated AC before and after using the two methods (GPSW and Xgboost) separately and selected the group with the smaller average AC for subsequent analysis(Wu et al., 2020c). Ultimately, we used the logistic regression method to estimate the effects of exposure, just like Eq. 1, where the standard deviation was reestimated by the sandwich method.

$$Exposure \sim b_0 + b_1x_1 + \ldots + b_nx_n + \varepsilon \tag{2}$$

$$\varepsilon \sim N(0, \sigma^2)$$

We get the following covariates: age (≥65 years or < 65 years), sex (male or female), ethnic group (Han, Minority), region (Chengdu, Chongqing, Yunnan, Guizhou, Lhasa, Aba), annual family income (< 12,000, 12,000–19,999, 20,000–59,999, 60,000–99,999, and≥100,000 Yuan), highest education completed (bachelor degree or above, high school, junior college, junior high school, primary school, illiteracy), alcohol (never drinking, drinking or quit), body mass index (BMI[kg/m^2], low weight, < 18.5; moderate weight, 18.5–23.9; overweight, ≥24), smoking status (never smoke, smoke or quite), secondhand smoke status (yes, no), metabolic equivalent (MET) (four categories based on the percentile of length of non-sedentary time, ranging from 1 to 4, 4 represents the longest 25% of the population), Mediterranean Diet score (MED) (four categories based on the percentile of Mediterranean Diet score, ranging from 1 to 4, 4 represents the highest 25% of the population), 3-year average temperature (continuous variable), 3-year average humidity (continuous variable). Indoor air pollution is divided into three levels (light, moderate, and severe), which are a summary of three aspects: cooking behavior, fuel type, and ventilation equipment. Light is defined as occasionally cooking at home or not cooking at home. Moderate is defined as cooking regularly at home and meeting only one of the following conditions: (1) using unclean fuels or (2) not using ventilation. Severe is defined as cooking regularly at home with unclean fuels and no ventilation(Xu et al., 2021).

In addition, subgroup analyses were done by adding interaction terms in the regression model, and sex (male or female), age (≥65 years or < 65 years), alcohol (never drinking, drinking or quit), smoke (never smoke, smoke or quit), secondhand smoke (yes, no), and BMI (low weight, moderate weight, overweight) was taken into account.

Sensitivity analyses were performed to examine the robustness of the results, including:1) excluding Tibetan herdsmen in Aba for they have no fixed residence place and Tibetan in Lhasa for the concentration of survey sites and low variability in air pollution, 2) using MDRD to estimate eGFR, 3) using the 1-year, 2-year and 4-year average concentration of air pollutants as an exposure assessment.

Moreover, since hypertension and diabetes were important risk factors for CKD, we included metabolic syndrome (MetS) as a covariate. MetS was defined as the presence of at least three of the following features: glucose intolerance, obesity, hypertension, and dyslipidemia (Expert Panel On Detection et al., 2001). BMI was of high collinearity with waist circumference. Hence, we deleted BMI when MetS was taken into account as a fourth sensitivity analysis. Furthermore, we calculated E-value to evaluate the unmeasured confounding. Finally, since distributions of air pollutants were distinct between regions, we assigned regions as a random effect.

All the analyses were performed by using R software (Version 3.6.1). Xgboost and sandwich package were used to estimate Xgboost weight and adjusted standard deviations (SD) in GPSW regression.

We estimated the odds ratio (OR) of CKD associated with a 0.1 mg/m^3 increase of CO, a 1 μg/m^3 increase of SO_2 and a 10 μg/m^3 increase of $PM_{2.5}$ NO_2, O_3 respectively. Two-sided tests with *P*-values < 0.05 were

Table 1
The general characteristics and CKD results of the participants (N = 80225).

	Total	CKD		*P-value*
		Yes	No	
Sex n (%)				
male	31,809 (39.6%)	894 (45.2%)	30,915 (39.5%)	< 0.001
female	48,416 (60.4%)	1086 (54.8%)	47,330 (60.5%)	
Age, years n (%)				
<65	67,881 (84.6%)	867 (43.8%)	67,014 (85.6%)	< 0.001
≥65	12,344 (15.4%)	1113 (56.2%)	11,231 (14.4%)	
Income, Yuan n (%)				
<12,000	14,144 (17.6%)	615 (31.1%)	13,529 (17.3%)	< 0.001
12,000–19,999	14,769 (18.4%)	367 (18.5%)	14,402 (18.4%)	
20,000–59,999	29,170 (36.4%)	647 (32.7%)	28,523 (36.5%)	
60,000–99,999	11,620 (14.5%)	208 (10.5%)	11,412 (14.6%)	
≥100,000	10,522 (13.1%)	143 (7.2%)	10,379 (13.3%)	
Education n (%)				
bachelor degree or above	3350 (4.2%)	24 (1.2%)	3326 (4.3%)	< 0.001
high school	9201 (11.5%)	154 (7.8%)	9047 (11.6%)	
junior college	5375 (6.7%)	48 (2.4%)	5327 (6.8%)	
junior high school	20,375 (25.4%)	335 (16.9%)	20,040 (25.6%)	
primary school	20,613 (25.7%)	609 (30.8%)	20,004 (25.6%)	
illiteracy	21,311 (26.6%)	810 (40.9%)	20,501 (26.2%)	
Ethnic n (%)				
Han	46,339 (57.8%)	1039 (52.5%)	45,300 (57.9%)	< 0.001
Minority	33,886 (42.2%)	941 (47.5%)	32,945 (42.1%)	
Smoke n (%)				
never smoke	60,055 (74.9%)	1418 (71.6%)	58,637 (74.9%)	< 0.001
smoke or quit	20,170 (25.1%)	562 (28.4%)	19,608 (25.1%)	
Secondhand smoke n (%)				
no	41,361 (51.6%)	1084 (54.7%)	40,277 (51.5%)	0.004
yes	38,864 (48.4%)	896 (45.3%)	37,968 (48.5%)	
Indoor air pollution n (%)				
light	12,893 (16.1%)	366 (18.5%)	12,527 (16.0%)	< 0.001
moderate	63,296 (78.9%)	1464 (73.9%)	61,832 (79.0%)	
severe	4036 (5.0%)	150 (7.6%)	3886 (5.0%)	
BMI n (%)				
low weight (≤ 18.5 kg/m^2)	2815 (3.5%)	115 (5.8%)	2700 (3.5%)	< 0.001
moderate weight (18.6–23.9 kg/m^2)	36,453 (45.4%)	909 (45.9%)	35,544 (45.4%)	
overweight (≥ 24 kg/m^2)	40,957 (51.1%)	956 (48.3%)	40,001 (51.1%)	
MET n (%)				
1 (≤ 1.7 h/day)	19,724 (24.6%)	931 (47.0%)	18,793 (24.0%)	< 0.001
2 (1.8–3.2 h/day)	19,808 (24.7%)	396 (20.0%)	19,412 (24.8%)	
3 (3.3–3.7 h/day)	20,269 (25.3%)	347 (17.5%)	19,922 (25.5%)	
4 (≥ 3.8 h/day)	20,424 (25.5%)	306 (15.5%)	20,118 (25.7%)	
Alcohol n (%)				
never drinking	46,368 (57.8%)	1425 (72.0%)	44,943 (57.4%)	< 0.001

(*continued on next page*)

Table 1 (*continued*)

	Total	CKD		*P-value*
		Yes	No	
drinking or quit	33,857 (42.2%)	555 (28.0%)	33,302 (42.6%)	
MED n (%)				
1(≤ 22)	25,624 (31.9%)	845 (42.7%)	24,779 (31.7%)	< 0.001
2 (23–25)	20,133 (25.1%)	500 (25.3%)	19,633 (25.1%)	
3 (26–27)	18,562 (23.1%)	366 (18.5%)	18,196 (23.3%)	
4 (≥ 28)	15,906 (19.8%)	269 (13.6%)	15,637 (20.0%)	

Abbreviations: CKD: chronic kidney disease; BMI, body mass index; MET, metabolic equivalent; MED, Mediterranean Diet score;
$PM_{2.5}$:particulate matter with aerodynamic diameters of≤ 2.5 μm; NO_2: nitrogen dioxide; CO: carbon monoxide; O_3: ozone

considered statistically significant.

3. Results

3.1. General characteristics

We included 80,225 participants aged 30–79 years in this study. The mean age of the study population was 51.8 years. 31,809 (39.6%) of the participants were male, and 12,344 (15.4 of the participants were 65 years old or older. 1980 (2.47%) study participants had CKD. The baseline information of study participants and CKD outcome are shown in Table 1. The geographical location of participants at baseline and corresponding exposure concentrations are shown in Fig. 1.

The 3-year average $PM_{2.5}$ NO_2, CO, O_3, and SO_2 concentrations were 40.7 μg/m^3, 21.4 μg/m^3, 0.87 mg/m^3, 79.2 μg/m^3, 14.4 μg/m^3 respectively at participants' addresses (Table S1). Fig. 2 demonstrates the distribution of the 3-year average temperature, relative humidity, and concentrations of the above five pollutants in Southwest China and their correlation. The topography of Southwest China and the main sources of air pollutants are shown in Text S1.

3.2. Associations between $PM_{2.5}$ NO_2, CO, O_3, SO_2 and CKD

The balance check plot of covariates and results of average AC before and after weighting were shown in Fig. 3 and Table 2, respectively. We chose the method with a smaller average AC after weighting for the subsequent analysis, even though the average AC was greater than 0.1 ($PM_{2.5}$, NO_2, and SO_2). Ultimately, we used the GPS method for $PM_{2.5}$ and Xgboost method for NO_2, CO, O_3, and SO_2 to estimate the association.

An increase of 0.1 mg/m^3 3-year average CO concentration (OR=1.20, 95% CI, 1.05–1.37) and 1 μg/m^3 3-year average SO_2 concentration (1.07, 1.00–1.14) were positively associated with CKD. $PM_{2.5}$, NO_2, and O_3 were not associated with CKD. More details of the regression results are shown in Table 3.

3.3. Subgroup analyses

Due to the positive association of CO and SO_2 with CKD, forest plots for the CO and SO_2 subgroup analyses are presented in Fig. 4 and for the remaining pollutants in Fig. S2, Fig. S3, and Fig. S4.

The effects of $PM_{2.5}$ ($p = 0.022$), CO ($p = 0.459$), O_3 ($p = 0.020$), SO_2 ($p = 0.053$) are higher in male, while the effects of NO_2 ($p = 0.632$) are higher in female. The effects of $PM_{2.5}$ ($p < 0.001$), NO_2 ($p = 0.001$), CO ($p = 0.335$), O_3 ($p = 0.432$), SO_2 ($p = 0.042$) are higher in those younger than 65 years. The effects of $PM_{2.5}$ ($p = 0.048$), NO_2 ($p = 0.882$), CO ($p = 0.349$) are higher in those not drinking alcohol, while the effects of O_3 ($p = 0.006$), SO_2 ($p = 0.680$) are higher in those drinking alcohol. The effects of $PM_{2.5}$ ($p = 0.187$), NO_2 ($p = 0.004$), O_3 ($p = 0.027$), CO ($p = 0.376$), SO_2 ($p = 0.004$) are higher in those smoking. The effects of $PM_{2.5}$ ($p = 0.705$), NO_2 ($p = 0.015$), SO_2 ($p = 0.015$) are higher in those with second-hand smoking, while the effects of O_3 ($p = 0.855$), CO ($p = 0.896$) are higher in those without second-hand smoking. Compared with those with low weight, the effects

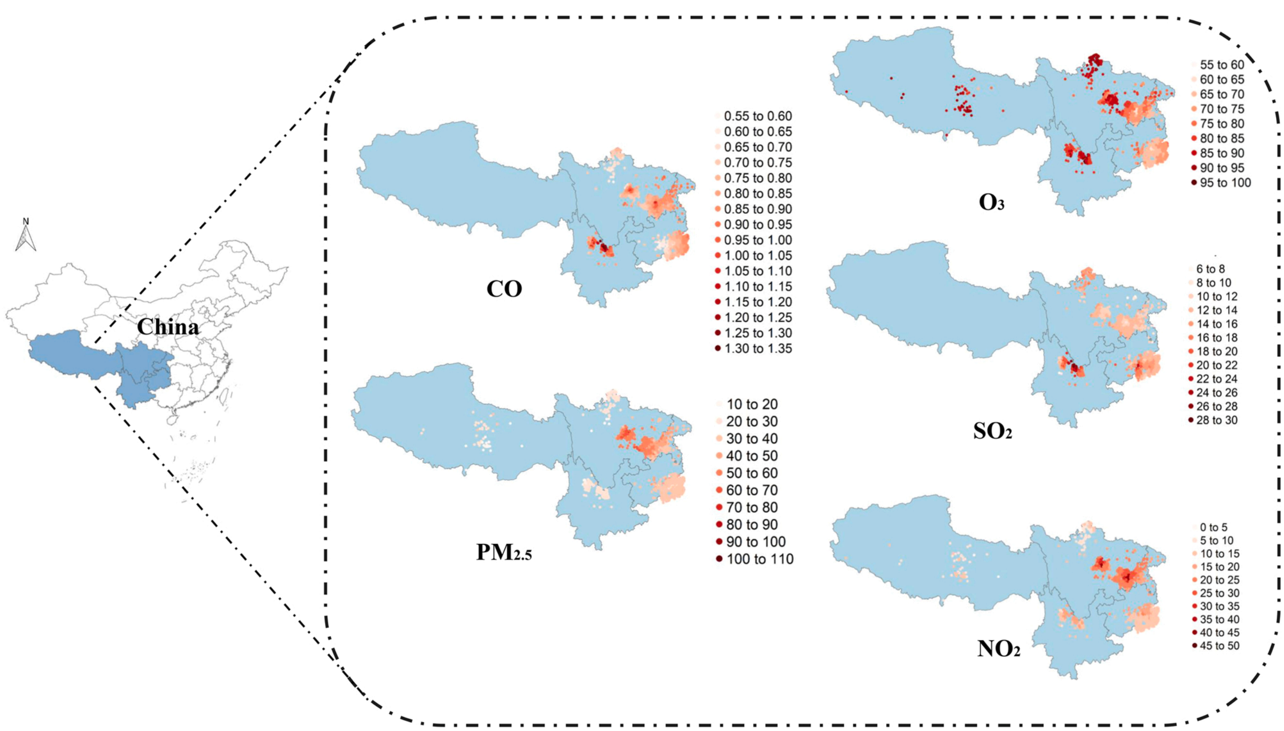

Fig. 1. The spatial distribution of the 3-year average $PM_{2.5}$ (μg/m^3), NO_2 (μg/m^3), O_3 (μg/m^3), CO (mg/m^3) and SO_2 (μg/m^3) concentration. Abbreviations: $PM_{2.5}$: particulate matter with aerodynamic diameters of≤ 2.5 μm; NO_2: nitrogen dioxide; CO: carbon monoxide; O_3: ozone; SO_2: sulfur dioxide.

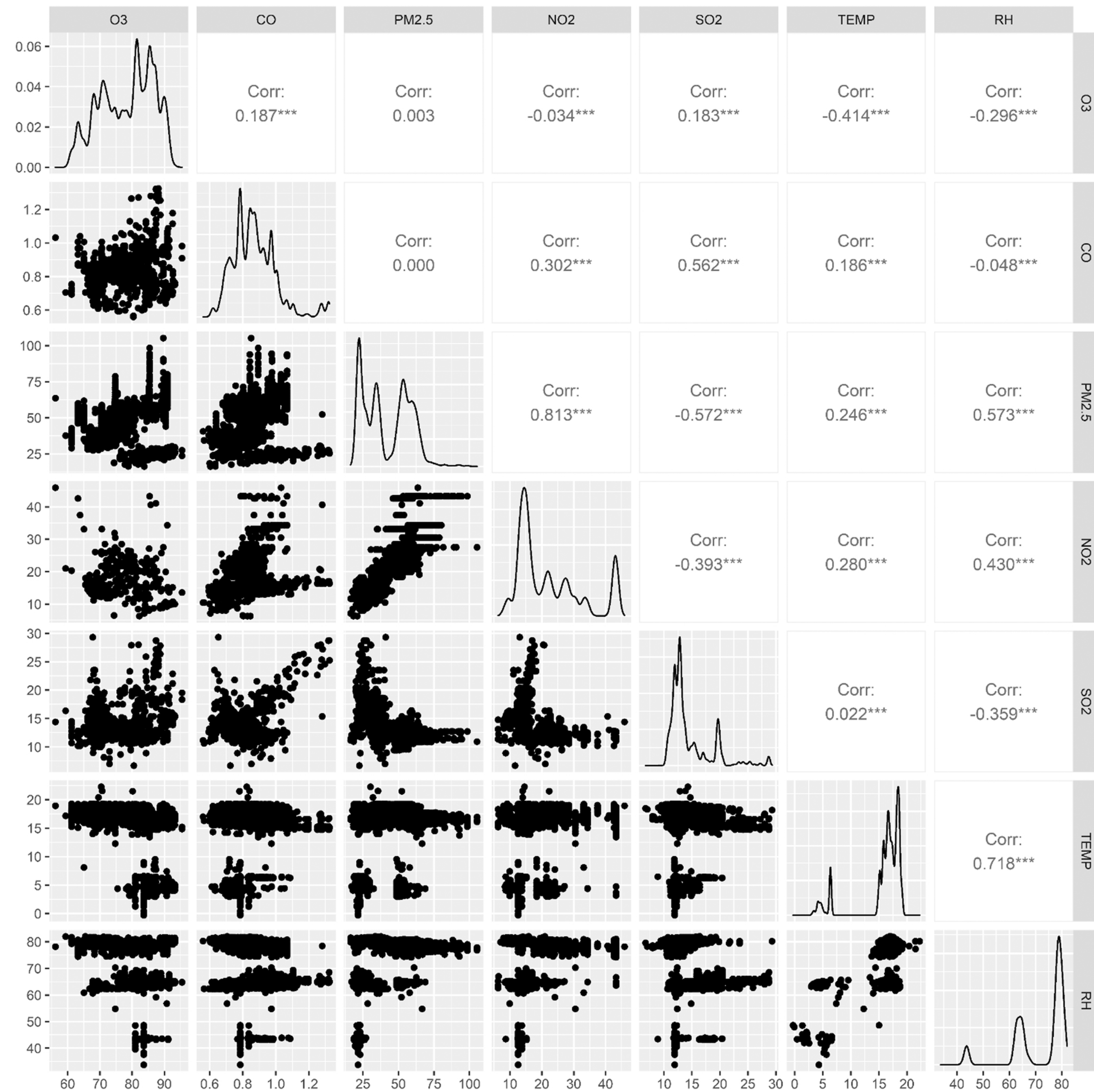

Fig. 2. Distribution of five pollutants, two meteorological factors and their correlation. The names of the five pollutants and two meteorological factors are shown at the top and far right of the figure. The first row of the vertical coordinates indicates the probability density of O_3, and the rest of the coordinate scales are the temperature/relative humidity/ concentration of the corresponding pollutant. The diagonal part of the figure shows the distribution of five pollutants and two meteorological factors. The top right part of the figure shows the correlation coefficients, and the bottom-left part plots the scatter plot between the corresponding two pollutants or meteorological factors. ***: $p < 0.001$ $PM_{2.5}$ ($\mu g/m^3$), NO_2 ($\mu g/m^3$), O_3 ($\mu g/m^3$), CO (mg/m^3), SO_2 ($\mu g/m^3$), TEMP (degrees Celsius) and RH (%). Abbreviations: $PM_{2.5}$: particulate matter with aerodynamic diameters of$\leq$ 2.5 μm; NO_2: nitrogen dioxide; CO: carbon monoxide; O_3: ozone; SO_2: sulfur dioxide; Corr: correlation; TEHP: temperature; RH: relative humidity.

of $PM_{2.5}$ ($p < 0.001$), NO_2 ($p = 0.477$), CO ($p < 0.001$), O_3 ($p = 0.003$), SO_2 ($p = 0.002$) are lower in those with moderate weight, and the effects of $PM_{2.5}$ ($p = 0.003$), NO_2 ($p = 0.760$), CO ($p = 0.011$), O_3 ($p = 0.001$), SO_2 ($p = 0.151$) are lower in those overweight.

Based on the above subgroup analysis results, we can conclude with some caution that age, smoking and BMI are the effect modifiers for the associations between the above five pollutants and CKD.

3.4. Sensitivity analyses

Sensitivity analyses (Table S2, Table S3, Table S4, Table S5, Table S6, and Table S7) showed the results were robust to 1) exclude Tibetan in Aba and Lhasa, 2) use MDRD to estimate eGFR, 3) use 1-year, 2-year and 4-year average concentrations of pollutants as exposure, 4) delete BMI and use MetS as a covariate, 5) assign the region as a random effect.

The E-value of $PM_{2.5}$ NO_2, CO, O_3, and SO_2 were 1.62, 1.49, 1.69, 1.43, and 1.34, respectively. The E value is defined as the minimum

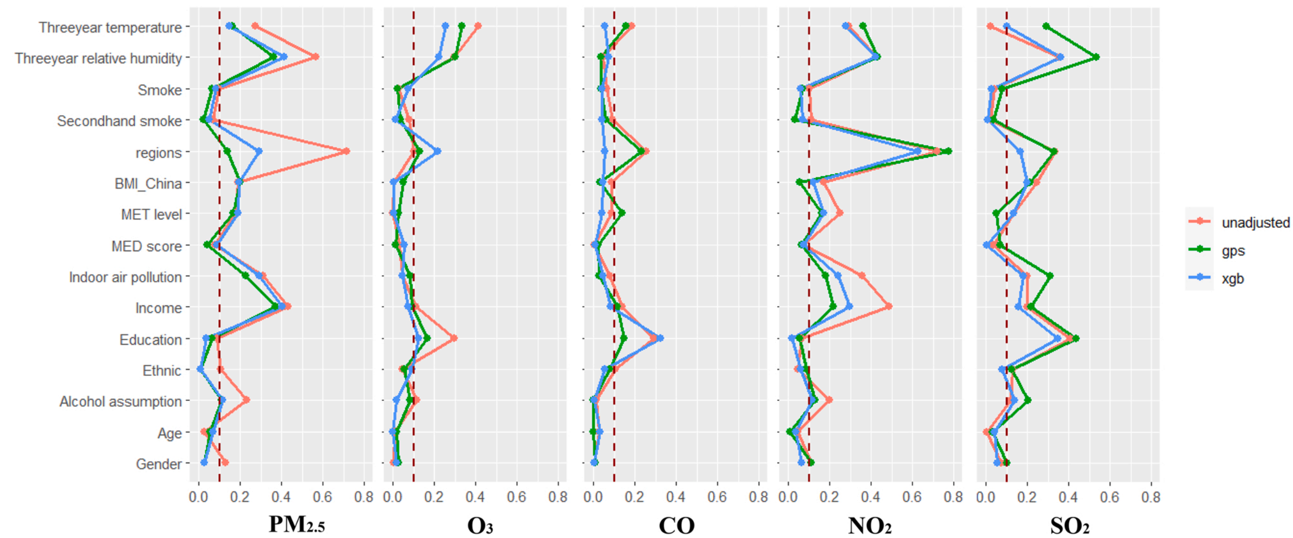

Fig. 3. Balance check plot for different pollutants scenarios. Abbreviations: $PM_{2.5}$:particulate matter with aerodynamic diameters of≤ 2.5 μm; NO_2: nitrogen dioxide; CO: carbon monoxide; O_3: ozone; SO_2: sulfur dioxide; BMI: body mass index; MET: metabolic equivalent; MED: Mediterranean Diet score; gps: generalized propensity score method; xgb: xgboost method.

Table 2
Average AC [a] between exposure and covariates.

Exposure	Original data	After gps weighting	After xgb weighting	Method selection[b]
$PM_{2.5}$	0.228	0.129	0.152	gps
NO_2	0.222	0.183	0.172	xgb
CO	0.101	0.076	0.062	xgb
O_3	0.110	0.097	0.084	xgb
SO_2	0.153	0.194	0.130	xgb

Abbreviations:
AC: absolute correlation; $PM_{2.5}$:particulate matter with aerodynamic diameters of≤ 2.5 μm; NO_2: nitrogen dioxide; CO: carbon monoxide; O_3: ozone; SO_2: sulfur dioxide; gps: generalized propensity score method; xgb: xgboost method.
[a] : Average AC represents the correlation coefficient between exposure and covariates. Smaller average AC indicates better covariates balance. AC for each covariate will be shown in Fig. 3.
[b] : Covariates are generally considered well balanced when the average AC is less than 0.1. The method with the smaller average AC will be chosen, even if the results are greater than 0.1 for both methods.

unmeasured confounding effect that is required to completely subvert the OR in your study, controlling for the measured confounding factor (Mathur et al., 2018; VanderWeele and Ding, 2017).

4. Discussion

Current literature on air pollutants exposure and CKD remains relatively limited, especially for gaseous pollutants. To our knowledge, this is the first large population-based study in China to examine the relationship between not only particulate matter ($PM_{2.5}$) exposure but also gaseous pollutants (NO_2, CO, O_3, and SO_2) exposure and kidney function. We found that long-term exposure to CO and SO_2 was associated with CKD. Although the association between $PM_{2.5}$ NO_2, O_3 and CKD was insignificant, we concluded the following pattern from the subgroup analysis that the risk to kidney function from the five pollutants mentioned above was stronger in men, smokers and those with low BMI.

This study gives us the following insights: First, the effects of $PM_{2.5}$, which has been widely demonstrated to be associated with CKD, may be geographically heterogeneous, and caution is needed when comparing and extrapolating across different previous studies. Second, for researchers, it is essential to focus on gaseous pollutants alongside particulate matter and to consider further susceptible populations for the association of gaseous pollutants and CKD. Third, policy makers could develop policies to control sources of CO and SO_2 in Southwest China to curb the gaseous pollutants related to CKD burden.

The mechanism of renal damage by CO and SO_2 remains unclear. Oxidative stress and inflammation are shown to be the link between cardiovascular disease and CKD(Cachofeiro et al., 2008). Both epidemiological and experimental animal studies have demonstrated that exposure to SO_2 was associated with cardiovascular risk(Hong et al., 2002; Zhang et al., 2014). As for CO, intermittent CO exposure is associated with arterial wall damage and atherogenesis(Huang et al., 2016). Davutoglu et al. found that chronic CO exposure was positively associated with high-sensitivity C-reactive protein and carotid intima-media thickness(Davutoglu et al., 2009). The inflammatory mediators induced by CO and SO_2 and other pollutants in the lungs could spill over into the circulation, resulting in systemic inflammation, oxidative stress and damage to distant organs, including kidneys. However, studies on the direct renal toxicity of CO and SO_2 are still scarce, and further research is needed.

Several studies have found that long-term exposure to ambient $PM_{2.5}$ was associated with CKD(Bowe et al., 2018; Li et al., 2021a). However, we found that $PM_{2.5}$ was not associated with CKD and the findings were relatively stable in the sensitivity analysis. Existing studies have confirmed that the association between $PM_{2.5}$ and CKD varies greatly geographically(Bowe et al., 2020). Heterogeneity of study populations might lead to different conclusions on the same scientific issues. In addition, the statistical approach used in this study yields larger estimates of variance and thus more conservative conclusions. When estimating the effect of $PM_{2.5}$, we found the lower limit of the confidence interval is close to 1, which also suggests that we may draw false negative conclusions due to the inadequate sample size or the conservative feature of the method. The existing literature examining SO_2 and CKD is still relatively limited. We only found two studies with consistent findings, and our study provides positive results on this issue for a different population(Jeong et al., 2020; Lee et al., 2022).

There are several studies on CO exposure and CKD, but little attention has been paid to the general population, and the results were inconsistent(Bowe et al., 2017; Chin et al., 2018; Kim et al., 2018). For example, Bowe et al. found an interquartile range (IQR) increase of CO was positively associated with CO and CKD (HR=1.09, 95% CI, 1.08–1.10) in US veterans(Bowe et al., 2017). While Chin et al. found CO was positively associated with an annual urinary albumin-to-creatinine ratio (ACR) increase in patients with type 2 diabetes(Chin et al., 2018).

Table 3
Estimated effects of five pollutants exposure on CKD in Southwest China using three different methods.

Exposure	Method[a]	Outcome					
		β[b]	*OR*	*LCI*	*HCI*	*P-value*	*STD*
$PM_{2.5}$	logistic regression	0.0101	1.11	0.97	1.26	0.129	0.00665
	gps weighting[c]	**0.0153**	**1.17**	**0.99**	**1.38**	**0.070**	**0.00848**
	xgb weighting	0.00863	1.09	0.88	1.35	0.435	0.0111
NO_2	logistic regression	0.0044	1.05	0.93	1.18	0.478	0.00621
	gps weighting	0.00896	1.09	0.93	1.29	0.288	0.00843
	xgb weighting	**0.0113**	**1.12**	**0.83**	**1.51**	**0.456**	**0.0151**
CO	logistic regression	0.698	1.07	1.01	1.14	0.021	0.302
	gps weighting	0.958	1.10	1.01	1.20	0.037	0.458
	xgb weighting	**1.82**	**1.20**	**1.05**	**1.37**	**0.007**	**0.675**
O_3	logistic regression	-0.000310	1.00	0.87	1.15	0.966	0.00719
	gps weighting	-0.00243	0.98	0.82	1.16	0.782	0.00879
	xgb weighting	**0.00968**	**1.10**	**0.81**	**1.50**	**0.541**	**0.0158**
SO_2	logistic regression	0.0146	1.01	0.99	1.04	0.283	0.0136
	gps weighting	0.0294	1.03	0.97	1.09	0.316	0.0293
	xgb weighting	**0.0649**	**1.07**	**1.00**	**1.14**	**0.032**	**0.0324**

Abbreviations:
$PM_{2.5}$:particulate matter with aerodynamic diameters of≤ 2.5 μm; NO_2: nitrogen dioxide; CO: carbon monoxide; O_3: ozone; SO_2: sulfur dioxide; gps: generalized propensity score method; xgb: xgboost method; *β*: regression coefficients of exposure in the model; *OR*: odds ratio; *LCI*: low confidence interval; *HCI*: high confidence interval; STD: standard error.

[a] : The same covariates were adjusted in all three different methods: age, sex, ethnic group, region, annual family income, highest education completed, alcohol, body mass index, smoking status, secondhand smoke status, indoor air pollution status, metabolic equivalent, Mediterranean diet score, 3-year average temperature, 3-year average humidity.

[b] : Due to the wide variation in results between exposures, three significant digits have been retained for both *β* and *STD* to ensure readability. By convention, *OR*, *LCI*, *HCI* and *P-value* are retained to two and three decimal places respectively.

[c] : For every single exposure, we chose one of the two weighting methods as a representative result (**bold**) based on the conditions in Table 1, and the results of the remaining methods were used as a comparison.

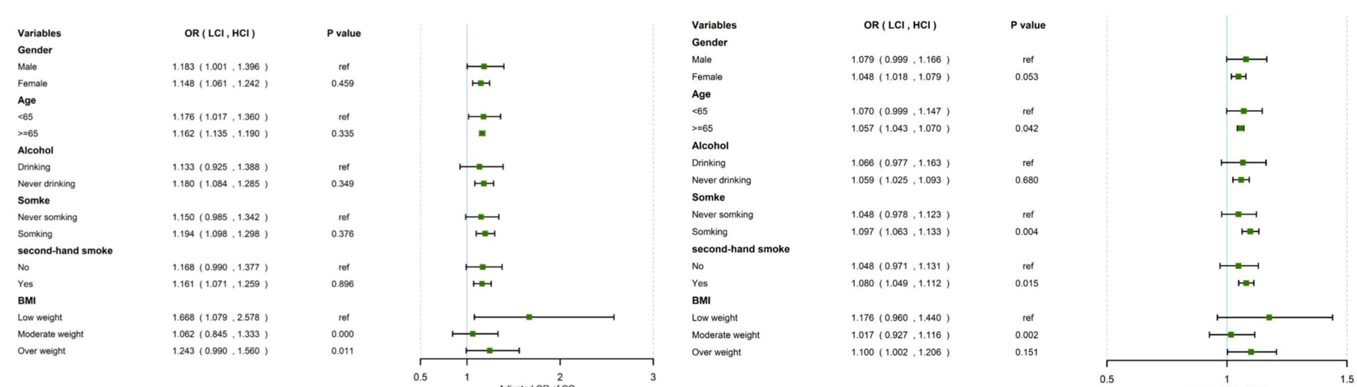

Fig. 4. The associations between long-term CO, SO_2 exposure and CKD in participants with different subgroups in Southwest China. Abbreviations: CO: carbon monoxide; SO_2: sulfur dioxide; *OR*: odds ratio; *LCI*: low confidence interval; *HCI*: high confidence interval; BMI: body mass index.

Unlike all of the above results, Kim et al. found that a 0.1 ppm increase of CO was not significantly associated with CKD (OR=1.02, 95% CI, 0.95–1.09) in Korean adults(Kim et al., 2018). In our study, CO concentration was positively associated with CKD. In addition to differences in populations, differences in pollutants concentrations may result in our analysis not being comparable to existing studies. For example, the median concentration of CO in our study is 0.69 ppm. In the above three studies on CO, the median concentrations are 0.51 ppm, 0.9 ppm, and 0.6 ppm, respectively. Thus, our study provides additional evidence for medium to high concentrations of CO.

The association of air pollutants with CKD risk was stronger in those smoking. The effect modification of smoking was generally consistent with Li and his colleagues(Li et al., 2021b). Air pollutants may act synergistically with chemicals in tobacco. The association of air pollutants with CKD risk was stronger in men. The effect modification of sex was generally consistent with Li and his colleagues(Li et al., 2021b). However, Yang and his colleagues came to a different conclusion(Yang et al., 2017). Previous studies have shown that women have slightly higher respiratory reactivity and lung particle deposition than men, which may account for their susceptibility to air pollution(Zhang et al., 2018). However, in our study, smoking rates were much higher in men (61.3%) than in women (1.4%). The effect of sex can also be explained considering the positive interaction between smoking and air pollution mentioned earlier. It is worth noting that this paper focuses on gaseous pollutants and the mechanism of effect modifiers needs further research.

Trying to accurately estimate the effects of air pollutants on renal function, we used robust causal inference methods in this study. In general, not only traditional approaches but also causal inference methods need assumption, without which the results we get will not hold. The assumption that guarantees we draw accurate conclusions in this study is accounting for all confounders. GPSW method provides protection against confounding by measured covariates and interactions for a better balance of covariates after a balance check. Traditional sensitivity analyses and the calculation of E-value were conducted to unmeasured confounding and showed that our results are robust. We found that even after weighting, the average AC for $PM_{2.5}$ NO_2 and SO_2

was still greater than 0.1. Although GPSW is a doubly robust method, and we chose a weighted method with a more minor average AC for further effect estimation, causal associations for pollutants whose covariates were not fully balanced still need to be interpreted with caution. Besides, the standard deviation in GPSW regression consists of variance in GPS estimate and in GPSW regression itself, and we used the sandwich method to reestimate it. Consequently, the standard deviation in GPSW regression is relatively larger, seen in Table 3. This also shows that this method is conservative because it is more difficult to get significant results.

Our study has several strengths. First, data collection was carried out by uniformly trained investigators, and the suspected unqualified questionnaires were checked and corrected by recording. All biochemical tests were performed by the same third-party company, ensuring data comparability across a wide range of surveys. Second, we ended up involving 80,225 participants aged from 30 to 79. We obtained robust associations between air pollutants exposure and CKD based on the large sample size and we further identified age, smoking and BMI as effect modifiers. Finally, we use GPSW regression to estimate the effect. This robust causal inference method can improve the robustness of statistical methods and the interpretability of statistical results, which provide a critical scientific basis for policy-making.

Our study also has some limitations. First, the data for this study were derived from baseline data from the CMEC study and were cross-sectional. Although we have collected exposure data for the three years before the baseline survey, the strength of the evidence is still relatively weak. We can improve this problem in the follow-up investigation. Second, our exposure data is based on the residential addresses of participants. Other influencing factors of individual environmental exposure such as indoor or outdoor and travel patterns have not been taken into account. Finally, this study estimated eGFR using SCr to make inferences about renal function. On the one hand, SCr has limited accuracy in estimating GFR. Due to limited research conditions, we did not use the gold standard to measure GFR. On the other hand, renal function is also affected by various factors, and even if we include various possible covariates, some related diseases may be omitted, resulting in biased results.

5. Conclusion

In conclusion, long-term exposure to ambient CO and SO_2 was positively associated with CKD among Southwest China aged 30–79. Smoke, age and BIM might modify the above associations. This study was expected to provide a scientific basis for relevant departments to make policies.

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Credit authorship contribution statement

S. Li and Q. Meng designed the study, analyzed the data, and drafted the article. B. Guo, R Lu, C Laba, and H. Guan searched the literature and analyzed the data. Z. Wang, Y. Pan, H. Hu, C. Zeng, and X. Wang edited the article and contributed to the discussion. J. Wei provided exposure data. B. Guo, R Lu and X. Zhao supervised this study. All authors critically revised the article.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ecoenv.2022.113851.

References

Afsar, B., et al., 2019. Air pollution and kidney disease: review of current evidence. Clinical Kidney. Journal 12, 19–32.
Angela, C., Webster, E.V.N.R., 2017. Chronic kidney disease. Lancet 389, 1238–1252.
Bowe, B., et al., 2020. The global and national burden of chronic kidney disease attributable to ambient fine particulate matter air pollution: a modelling study. BMJ Glob. Health 5, e002063.
Bowe, B., et al., 2017. Associations of ambient coarse particulate matter, nitrogen dioxide, and carbon monoxide with the risk of kidney disease: a cohort study. Lancet Planet Health 1, e267–e276.
Bowe, B., et al., 2018. Particulate matter air pollution and the risk of incident CKD and progression to ESRD. J. Am. Soc. Nephrol. 29, 218–230.
Brook, R.D., et al., 2010. Particulate matter air pollution and cardiovascular disease. Circulation 121, 2331–2378.
Cachofeiro, V., et al., 2008. Oxidative stress and inflammation, a link between chronic kidney disease and cardiovascular disease. Kidney Int. (Supplement), S4–S9.
Chin, W.-S., et al., 2018. Effects of long-term exposure to CO and PM on microalbuminuria in type 2 diabetes. Int. J. Hyg. Environ. Health 221, 602–608.
Davutoglu, V., et al., 2009. Chronic carbon monoxide exposure is associated with the increases in carotid intima-media thickness and c-reactive protein level. Tohoku J. Exp. Med. 219, 201–206.
Deng, Y., et al., 2021. Global, regional, and national burden of diabetes-related chronic kidney disease fom 1990 to 2019. Front. Endocrinol. 12.
Expert Panel On Detection, E., et al., 2001. Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). JAMA: J. Am. Med. Assoc. 285, 2486–2497.
Hong, Y.C., et al., 2002. Effects of air pollutants on acute stroke mortality. Environ. Health Perspect. 110, 187–191.
Huang, W.-H., et al., 2016. Environmental NO2 and CO Exposure: ignored factors associated with uremic pruritus in patients undergoing hemodialysis. Sci. Rep. 6.
Jeong, S.-M., et al., 2020. Effects of abdominal obesity on the association between air pollution and kidney function. Int. J. Obes. 44, 1568–1576.
Kim, H.-J., et al., 2018. Association between exposure to ambient air pollution and renal function in Korean adults. Ann. Occup. Environ. Med. 30, 14.
Kim, K.-H., et al., 2015. A review on the human health impact of airborne particulate matter. Environ. Int. 74, 136–143.
Kuźma, Ł., et al., 2021. Exposure to air pollution and renal function. Sci. Rep. 11, 11419.
Lee, W., et al., 2022. Short-term exposure to air pollution and attributable risk of kidney diseases. Epidemiology 33, 17–24.
Li, Q., et al., 2021a. Association between airborne particulate matter and renal function: an analysis of 2.5 million young adults. Environ. Int. 147, 106348.
Li, Q., et al., 2021b. Association between airborne particulate matter and renal function: An analysis of 2.5 million young adults. Environ. Int 147, 106348.
Liao, Y., et al., 2011. Assessment of the CKD-EPI equation to estimate glomerular filtration rate in adults from a Chinese CKD population. J. Int. Med. Res. 39, 2273–2280.
Liu, C., et al., 2019. Ambient particulate air pollution and daily mortality in 652 cities. N. Engl. J. Med. 381, 705–715.
Lu, H., et al., 2019. Overview on the spatial-temporal characteristics of the ozone formation regime in China. Environ. Sci. Process Impacts 21, 916–929.
Mathur, M.B., et al., 2018. Web site and R package for computing e-values. Epidemiology 29, e45–e47.
Rubin, D.B., 1979. Using multivariate matched sampling and regression adjustment to control bias in observational studies. J. Am. Stat. Assoc. 74, 318–324.
Stevens, L.A., et al., 2011. Evaluation of the chronic kidney disease epidemiology collaboration equation for estimating the glomerular filtration rate in multiple ethnicities. Kidney Int 79, 555–562.
VanderWeele, T.J., Ding, P., 2017. Sensitivity analysis in observational research: introducing the e-value. Ann. Intern Med 167, 268–274.

Wang, Z., et al., 2021. Spatial and temporal characteristics of environmental air quality and its relationship with seasonal climatic conditions in Eastern China during 2015–2018. Int. J. Environ. Res. Public Health 18, 4524.

Wei, J., et al., 2020. Improved 1 km resolution PM_{2.5} estimates across China using enhanced space–time extremely randomized trees. Atmos. Chem. Phys. 20, 3273–3289.

Wei, J., et al., 2021. Reconstructing 1-km-resolution high-quality PM2.5 data records from 2000 to 2018 in China: spatiotemporal variations and policy implications. Remote Sens. Environ. 252, 112136.

WHO, WHO global air quality guidelines. Particulate matter (PM2.5 and PM10), ozone, nitrogen dioxide, sulfur dioxide and carbon monoxide. Executive summary. Geneva: World Health Organization. Vol. 368, 2021.

Wei, J., et al., 2022a. Full-coverage mapping and spatiotemporal variations of ground-level ozone (O3) pollution from 2013 to 2020 across China. Remote Sens. Environ. 270, 112775.

Wei, J., et al., 2022b. Ground-level NO_2 surveillance from space across China for high resolution using interpretable spatiotemporally weighted artificial intelligence. Environ. Sci. Technol. https://doi.org/10.1021/acs.est.2c03834.

Wu, M.-Y., et al., 2020a. Association between air pollutants and development of chronic kidney disease: a systematic review and meta-analysis. Sci. Total Environ. 706, 135522.

Wu, M.Y., et al., 2020b. Association between air pollutants and development of chronic kidney disease: a systematic review and meta-analysis. Sci. Total Environ. 706, 135522.

Wu, X., et al., 2020c. Evaluating the impact of long-term exposure to fine particulate matter on mortality among the elderly. Sci. Adv. 6 eaba5692-eaba5692.

Xu, H., et al., 2021. Dietary pattern and long-term effects of particulate matter on blood pressure: a large cross-sectional study in chinese adults. hypertension (Dallas. Tex.: 1979). 78 184–194.

Yang, Y.R., et al., 2017. Associations between long-term particulate matter exposure and adult renal function in the taipei metropolis. Environ. Health Perspect. 125, 602–607.

Ye, J.J., et al., 2021. Ambient air pollution exposure and risk of chronic kidney disease: a systematic review of the literature and meta-analysis. Environ. Res 195, 110867.

Zhang, Q., et al., 2014. Effects of gaseous sulfur dioxide and its derivatives on the expression of KATP, BKCa and L-Ca2+ channels in rat aortas in vitro. Eur. J. Pharmacol. 742, 31–41.

Zhang, Z., et al., 2018. Long-term exposure to fine particulate matter, blood pressure, and incident hypertension in Taiwanese Adults. Environ. Health Perspect. 126, 017008.

Zhao, X., et al., 2021. Cohort Profile: the China Multi-ethnic cohort (CMEC) study. Int. J. Epidemiol. 50, 721–721 l.

Zhu, Y., et al., 2015. A boosting algorithm for estimating generalized propensity scores with continuous treatments. J. Causal Inference 3, 25–40.