*toxics*

MDPI

*Article*

# The TyG Index Mediates Air-Pollution-Associated Chronic Kidney Disease Incidence in HIV/AIDS Patients: A 20-Year Cohort Study

**Xiaoxia Liu [1,†], Xiuli Zhao [2,†], Lu Ye [1], Chengfeng Hu [1], Zhihao Xie [2], Jianan Ma [2], Xia Wang [3,*] and Wei Liang [2,*]**

[1] Zhenjiang Center for Disease Control and Prevention, 9# South Huangshan Road, Zhenjiang 212002, China
[2] School of Public Health, Faculty of Medicine, Yangzhou University, 136# Jiangyang Middle Road, Yangzhou 225000, China
[3] Wuhan Center for Disease Control and Prevention, 288# Machang Road, Wuhan 430024, China
* Correspondence: wangxia1973@163.com (X.W.); weiliang@yzu.edu.cn (W.L.)
† These authors contributed equally to this work.

## Abstract

Ambient air pollutants (APs) are associated with increased chronic kidney disease (CKD) risk in general populations, but their renal impact on HIV/AIDS patients remains understudied. This dynamic cohort included 7981 HIV/AIDS patients without baseline kidney disease from Wuhan and Zhenjiang, followed every 6 months with fasting blood tests to assess the triglyceride-glucose (TyG) index and estimated glomerular filtration rate (eGFR). Monthly average exposures to six APs were estimated from geocoded residential addresses. Modified Poisson regression models were used to assess associations between cumulative AP exposure and CKD incidence, with mediation analysis conducted to explore the potential role of the TyG index. Weighted quantile sum regression was applied to evaluate the joint effects of six APs. During the follow-up period, 168 new cases of CKD were identified. Each interquartile range increase in $PM_{2.5}$, $PM_{10}$, and $SO_2$ corresponded to a 16.5%, 18.9%, and 9.7% higher CKD risk, respectively, with the TyG index mediating 10.21%, 9.16%, and 5.14% of these associations. $PM_{2.5}$ demonstrated the highest attribution weight (44.4%) for CKD risk elevation in mixed-exposure models. Chronic ambient AP exposure, particularly $PM_{2.5}$, synergistically elevates CKD risk in HIV/AIDS patients with glucolipid dysregulation potentially being involved, necessitating targeted air quality policies to mitigate AP impacts on this vulnerable population.

**Keywords:** air pollutants; chronic kidney disease; HIV/AIDS; TyG; eGFR

check for updates

Academic Editor: Douglas Brugge

Received: 4 July 2025
Revised: 3 August 2025
Accepted: 7 August 2025
Published: 8 August 2025

**Citation:** Liu, X.; Zhao, X.; Ye, L.; Hu, C.; Xie, Z.; Ma, J.; Wang, X.; Liang, W. The TyG Index Mediates Air-Pollution-Associated Chronic Kidney Disease Incidence in HIV/AIDS Patients: A 20-Year Cohort Study. *Toxics* **2025**, *13*, 669. https://doi.org/10.3390/toxics13080669

**Copyright:** © 2025 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/).

## 1. Introduction

Chronic kidney disease (CKD), an irreversible chronic condition marked by persistent anomalies in kidney structure and function, poses a significant health challenge worldwide [1]. Global disease burden research highlights a rapid increase in the incidence and mortality rates of CKD worldwide [2], rendering it as a significant contributor to global mortality [3]. Since 1990, the worldwide prevalence of CKD among adults has surged by 23.9, affecting over 697 million people in 2019. Notably, China reported the highest patient count, reaching 132 million in 2020 [4]. Growing evidence suggests that CKD risk factors involve genetics, environment, underlying conditions, immune status, and lifestyle behaviors [5,6]. Recently, there has been increasing attention given to the impact of air pollutants (APs) on kidney disease [7,8].

In 2017, approximately 122 million cases of CKD worldwide were reportedly attributed to fine particulate matter ($PM_{2.5}$) exposure [9]. Multiple studies have elucidated that prolonged exposure to APs among healthy populations is linked to a decline in renal function, consequently heightening the risk of CKD [10,11]. A cohort study conducted in the United States also found that heightened exposure to elevated concentrations of $PM_{10}$, nitrogen dioxide ($NO_2$), and carbon monoxide (CO) was correlated with an augmented risk of CKD and end-stage renal diseases [8]. HIV/AIDS patients, as a group with compromised immune systems, might be more susceptible to APs [12,13]. To date, only one study has investigated the impact of ambient particulate matter exposure on kidney function in individuals living with HIV/AIDS [14], reporting that long-term $PM_{2.5}$ exposure was positively associated with incident CKD (HR: 1.599, 95% CI: 1.431–1.787 per 14.1 $\mu g/m^3$ increment). However, this work only included particulate pollutants, excluding gaseous pollutants and multi-pollutant combined effects. Our study addresses these gaps by incorporating both particulate and gaseous pollutants and applying mixture modeling to assess multi-pollutant joint effects.

The triglyceride-glucose (TyG) index, a reliable and widely used surrogate marker of insulin resistance [15], has recently gained attention in the context of chronic disease risk prediction, including CKD [16]. Emerging evidence suggests that air pollution, particularly $PM_{2.5}$ exposure, may contribute to systemic insulin resistance through oxidative stress and inflammation [17]. Given that insulin resistance is a recognized contributor to renal dysfunction, the TyG index may offer valuable insight into the biological mechanisms linking air pollution exposure and CKD development.

Recognizing the heightened vulnerability of individuals with HIV/AIDS to environmental stressors, this study investigated the association between exposure to both particulate and gaseous APs and the risk of CKD in this population. Particular emphasis was placed on the potential mediating role of the TyG index and the impact of multi-pollutant mixed exposure. Our findings can deliver actionable evidence for prioritizing particulate matter mitigation policies to alleviate air-pollution-associated CKD disparities in immunocompromised populations.

## 2. Materials and Methods

### *2.1. Study Population*

Data for this study were obtained from the HIV/AIDS Comprehensive Response Information Management System (CRIMS), maintained by the Centers for Disease Control and Prevention (CDCs) in Wuhan and Zhenjiang, covering the period from 1 January 2004, to 31 December 2023. Throughout this duration, information was collected from 11,114 HIV/AIDS patients through CRIMS, encompassing basic personal information, records of each follow-up visit, and treatment program. A total of 3133 HIV/AIDS patients were excluded from the analysis due to having an age under 18 at diagnosis ($n$ = 77), a lack of antiretroviral therapy ($n$ = 1660), missing serum creatinine (Scr) measurements ($n$ = 711), or having pre-existing kidney disease at the time of HIV diagnosis ($n$ = 685) (Figure 1). We included 7981 HIV/AIDS patients without CKD at baseline in the follow-up to assess the subsequent development of CKD. This study was granted approval by the ethics committee of Wuhan CDC (WHCDCIRB-K-2022027).

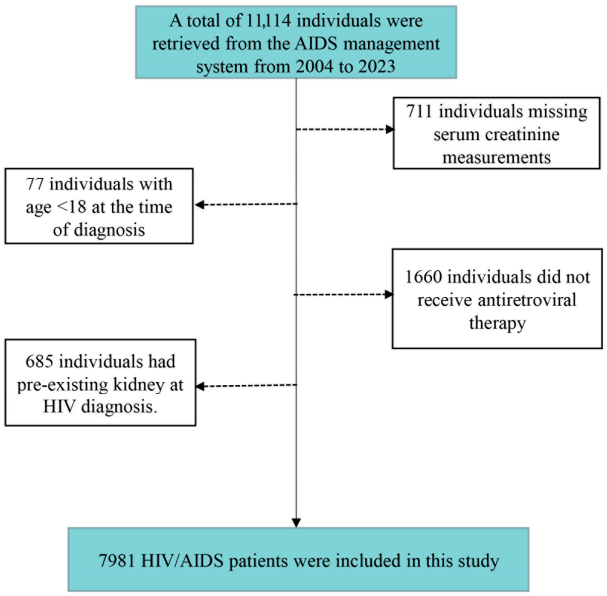


**Figure 1.** Flowchart for inclusion of study subjects.

### *2.2. Biomarker Measurements*

During each follow-up visit, conducted at six-month intervals, medical personnel collected venous blood samples (5 mL without anticoagulant) from participants after at least 8 h of fasting. Blood samples were centrifuged at 3000 revolutions per minute for 10 min to isolate serum. Serum levels of Scr, triglyceride (TG), and fasting blood glucose (FBG) were acquired using an auto-analyzer. The estimated glomerular filtration rate (eGFR) for each HIV/AIDS patient was computed utilizing the CKD Epidemiology Collaboration (CKD-EPI) equation [18]. CKD is defined as a less than 60 mL/min/1.73 $m^2$ eGFR. The TyG index is computed using the following formula: TyG index = ln [TG (mg/dL) × FBG (mg/dL)/2].

### *2.3. Exposure Assessment*

Daily AP concentration was obtained from the China High Air Pollutants dataset (CHAP, https://weijing-rs.github.io/product.html), which employs space–time extremely randomized tree models to generate full-coverage pollutant estimates. The dataset provides concentrations of particulate matter ($PM_1$, $PM_{2.5}$, $PM_{10}$) and ozone ($O_3$) at a spatial resolution of 1 km × 1 km, while $NO_2$, sulfur dioxide ($SO_2$), and CO are available at a resolution of 10 km × 10 km [19–24]. Individual exposure was estimated by geocoding each participant's residential address, which had been de-identified by professional staff at the CDC to ensure privacy protection. Pollutant concentrations from the nearest grid cell were then assigned to each participant's location using Google Maps.

### *2.4. Covariates*

We selected covariates based on previous studies that have investigated the relationship between APs and renal function [11,14,25]. The demographic information gathered encompassed age, sex, body mass index (BMI), education level (junior secondary education, senior secondary education, higher education), marital status (unmarried, married, divorced), and work types (outdoor worker, indoor worker, unknown). Details about habits and health conditions covered infection status (HIV, AIDS), smoking status, and alcohol consumption. Treatment medications were categorized based on the presence or absence of tenofovir disoproxil fumarate (TDF) (no, yes), which could potentially lead to renal impairment. TG and TC levels measured during each follow-up were taken into account,

alongside the distinction between warm (May to October) and cool (November to April) seasons at the time of follow-up, serving as confounding factors.

### 2.5. Statistical Analyses

Modified Poisson regression models were employed to assess the association between cumulative AP exposure and incident CKD. Individual cumulative exposure was defined as the average pollutant concentration experienced from baseline to either the end of follow-up or CKD onset. Risk ratios (RRs) and 95% confidence intervals (CIs) were calculated to quantify the effect of AP exposure per interquartile range (IQR) increase on CKD risk. In our analysis, two regression models were executed. Model 1 incorporated adjustments for age, sex, BMI, education level, marital status, work types, smoking status, alcohol consumption, and season. Model 2, extending model 1, encompassed additional adjustments for infection status, use of TDF, TC, and TG. Exposure–response relationships between AP concentrations and the RRs of CKD were modeled using restricted cubic splines with four degrees of freedom.

Weighted quantile sum (WQS) regression is a method for analyzing exposure mixtures, which accounts for correlations among components while estimating both the overall effect of the mixture and the relative contribution of each component. In our study, WQS regression models with 5000 bootstrap iterations were employed to comprehensively evaluate the association of mixed exposure to six APs with CKD incidence. The pollutant concentrations underwent standardization into quartiles, leading to the development of a composite exposure index. This index facilitated the assessment of mixed exposure effects through the derivation of a WQS index in both positive and negative directions. We could also infer the contribution of each pollutant within the mixed exposure model, thus identifying the primary pollutants.

Mediation analyses followed a two-step regression framework and used the mediation package with a nonparametric bootstrap approach (5000 resamples) to delineate pathways linking air pollution exposure to CKD risk and quantify the mediating role of the TyG index. Specifically, we first modeled the effect of air pollution on TyG (mediator) using a general linear model, then assessed the associations of air pollution and TyG with CKD (outcome) via modified Poisson regression. The total effect was decomposed into (1) the direct effect (DE), representing exposure's impact on outcome independent of the mediator; and (2) the indirect effect (IE), mediated through TyG index alterations. Mediation proportions were calculated as IE/(DE + IE), with bias-corrected 95% confidence intervals derived from bootstrap distributions.

Three sensitivity analyses were performed to check the robustness of our main findings. (1) We evaluated the association between AP exposure and the risk of incident CKD after excluding individuals with a history of smoking or alcohol consumption, in order to reduce potential confounding effects from lifestyle factors. (2) Cox proportional hazards models were employed to re-evaluate the association between AP exposure and incident CKD. (3) To account for multiple comparisons, we applied the False Discovery Rate (FDR) correction to the *p*-values derived from pollutant-specific models. Associations with FDR-adjusted *p*-values < 0.05 were considered statistically significant. All statistical analyses were performed using R software (Version 4.1.3). The R packages used in this study include "mediation" and "gWQS".

## 3. Results

### 3.1. Description of the Study Sample and Exposure

The demographic profile of the 7981 HIV/AIDS patients is presented in Table 1. This study included individuals with an average age of 38.7 ± 14.6 years and a mean BMI of

22.0 ± 3.81 kg/m$^2$. The main subjects were male (89.6%), indoor workers (50.6%), and unmarried (52.2%). In addition, 63.1% of all participants were diagnosed with HIV, and 61.0% had used TDF drugs. Most participants had never smoked (68.7%) or consumed alcohol (71.0%). Table S1 shows the distribution of AP concentrations during the follow-up period. During the follow-up period, IQRs of $PM_{2.5}$, $PM_{10}$, $SO_2$, CO, $NO_2$, and $O_3$ were 13.2 μg/m$^3$, 20.2 μg/m$^3$, 2.9 μg/m$^3$, 0.2 mg/m$^3$, 13.2 μg/m$^3$, and 16.7 μg/m$^3$, respectively.

**Table 1.** Descriptive characteristics of study subjects at baseline.

| Variables | Total (N = 7981) |
|---|---|
| Age, years, (Mean ± SD) | 38.7 ± 14.6 |
| BMI, kg/m$^2$ (Mean ± SD) | 22.0 ± 3.81 |
| Sex, *n* (%) | |
| Male | 7152 (89.6) |
| Female | 829 (10.4) |
| Infection status | |
| HIV | 5033 (63.1) |
| AIDS | 2948 (36.9) |
| Education level, *n* (%) | |
| Junior secondary education | 2341 (29.3) |
| Senior secondary education | 2078 (26.0) |
| Higher education | 3562 (44.6) |
| Work types, *n* (%) | |
| Outdoor worker | 3358 (42.1) |
| Indoor worker | 4042 (50.6) |
| Unknown | 581 (7.3) |
| Marital status, *n* (%) | |
| Unmarried | 4165 (52.2) |
| Married | 2219 (27.8) |
| Divorced | 1597 (20.0) |
| Smoking status, *n* (%) | |
| Never | 5486 (68.7) |
| Former | 566 (7.1) |
| Current | 1929 (24.2) |
| Alcohol consumption, *n* (%) | |
| Never | 5670 (71.0) |
| Former | 549 (6.9) |
| Current | 1762 (22.1) |
| Use of TDF, *n* (%) | |
| No | 3116 (39.0) |
| Yes | 4865 (61.0) |
| Serum creatinine, μmol/L (Mean ± SD) | 71.2 ± 14.0 |
| Cholesterol, mmol/L (Mean ± SD) | 4.04 ± 0.881 |
| Triglyceride, mmol/L (Mean ± SD) | 1.82 ± 2.00 |
| Fasting blood glucose, mmol/L (Mean ± SD) | 5.74 ± 1.41 |

Abbreviations: SD, standard deviation; BMI, body mass index; HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome; TDF, tenofovir disoproxil fumarate.

### 3.2. Associations Between AP Exposure and Incidence of CKD

By 31 December 2023, 168 new cases of CKD were identified among the 7891 HIV/AIDS patients under follow-up. In fully adjusted models, chronic exposure to $PM_{2.5}$, $PM_{10}$, and $SO_2$ was significantly associated with increased risk of CKD. Specifically, each IQR increase in $PM_{2.5}$ was associated with a 16.5% higher risk (RR: 1.165, 95% CI: 1.030, 1.317), in $PM_{10}$ with an 18.9% higher risk (RR: 1.189, 95% CI: 1.016, 1.390), and in $SO_2$ with a 9.7% higher risk (RR: 1.097, 95% CI: 1.039, 1.159) (Table 2). However, concentrations of CO, $NO_2$, and $O_3$ did not exhibit statistically significant associations with CKD incidence. Penalized spline

analyses demonstrated near-linear increases in CKD risk with rising $PM_{2.5}$, $PM_{10}$, and $O_3$ concentrations. In contrast, $SO_2$ and $NO_2$ showed positive associations at lower exposure levels that attenuated or inverted at higher concentrations, while CO exhibited an S-shaped exposure–response trajectory (Figure 2).

**Table 2.** Associations between air pollutant exposure and CKD in HIV/AIDS patients.

| Outcomes | Pollutants | Model 1 [a] | Model 2 [b] |
|---|---|---|---|
| RR of CKD (95%CI) | $PM_{2.5}$ | 1.212 (1.078, 1.363) | 1.165 (1.030, 1.317) |
| | $PM_{10}$ | 1.244 (1.069, 1.448) | 1.189 (1.016, 1.390) |
| | $SO_2$ | 1.128 (1.074, 1.185) | 1.097 (1.039, 1.159) |
| | CO | 1.090 (0.916, 1.297) | 1.040 (0.876, 1.234) |
| | $NO_2$ | 0.975 (0.811, 1.172) | 0.950 (0.788, 1.146) |
| | $O_3$ | 1.024 (0.886, 1.184) | 1.035 (0.889, 1.205) |

[a] Model 1 was adjusted for age, sex, BMI, education, marital status, work types, smoking status, alcohol consumption, and season. [b] Model 2 was adjusted for age, sex, BMI, education, marital status, work types, smoking status, alcohol consumption, season, infection status, use of TDF, TC, and TG. All effect estimates for air pollutants correspond to an IQR increment: $PM_{2.5}$ (13.2 μg/m$^3$), $PM_{10}$ (20.2 μg/m$^3$), $SO_2$ (2.9 μg/m$^3$), CO (0.2 mg/m$^3$), $NO_2$ (13.2 μg/m$^3$), and $O_3$ (16.7 μg/m$^3$). Abbreviations: $PM_{2.5}$, the aerodynamic diameter is less than 2.5 μg/m$^3$; $PM_{10}$, the aerodynamic diameter is less than 10 μg/m$^3$; $SO_2$, sulfur dioxide; CO, carbon monoxide; $NO_2$, nitrogen dioxide; $O_3$, ozone.

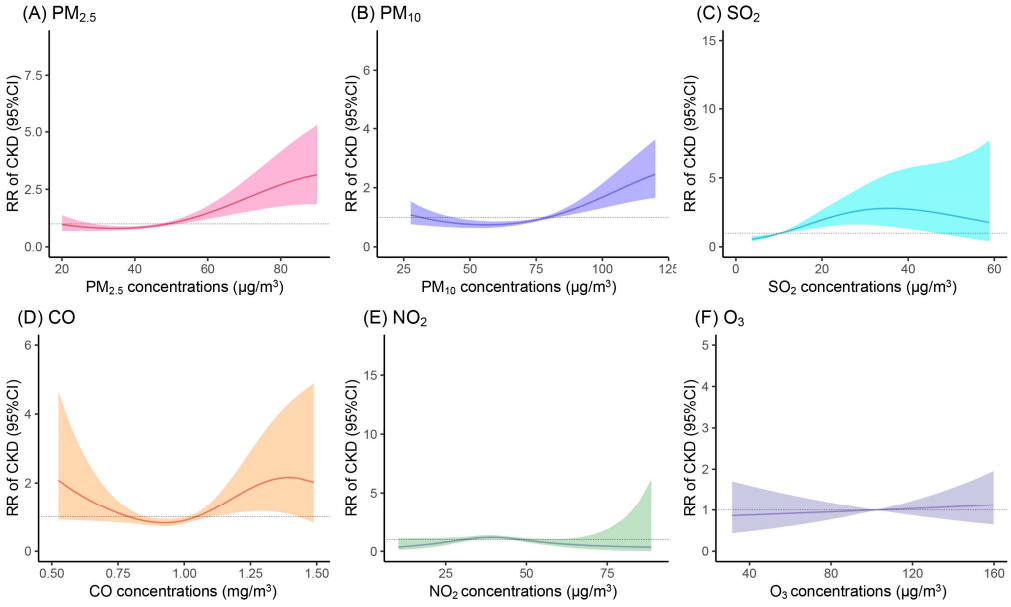


**Figure 2.** Exposure–response curves for the associations between air pollutant exposure and relative risk of CKD. Models were adjusted for age, sex, BMI, education level, marital status, work types, smoking status, alcohol consumption, season, infection status, use of TDF, TC, and TG. Abbreviations: $PM_{2.5}$, the aerodynamic diameter is less than 2.5 μg/m$^3$; $PM_{10}$, the aerodynamic diameter is less than 10 μg/m$^3$; $SO_2$, sulfur dioxide; CO, carbon monoxide; $NO_2$, nitrogen dioxide; $O_3$, ozone.

### *3.3. Mixed AP Exposure on CKD Incidence via Weighted Quantile Sum Modeling*

The WQS regression model unveiled a positive correlation between the WQS index of mixed AP exposure and incident CKD (RR: 2.405, 95% CI: 1.687, 3.428). Notably, $PM_{2.5}$ emerged as the dominant contributor, accounting for 44.4% of the overall mixture weight, followed by $O_3$ (32.6%), $PM_{10}$ (13.0%), and $SO_2$ (9.4%) (Figure 3A). Conversely, the negative-direction WQS index showed no significant inverse relationship with CKD risk (RR:1.032, 95%CI:0.682, 1.560) (Figure 3B).

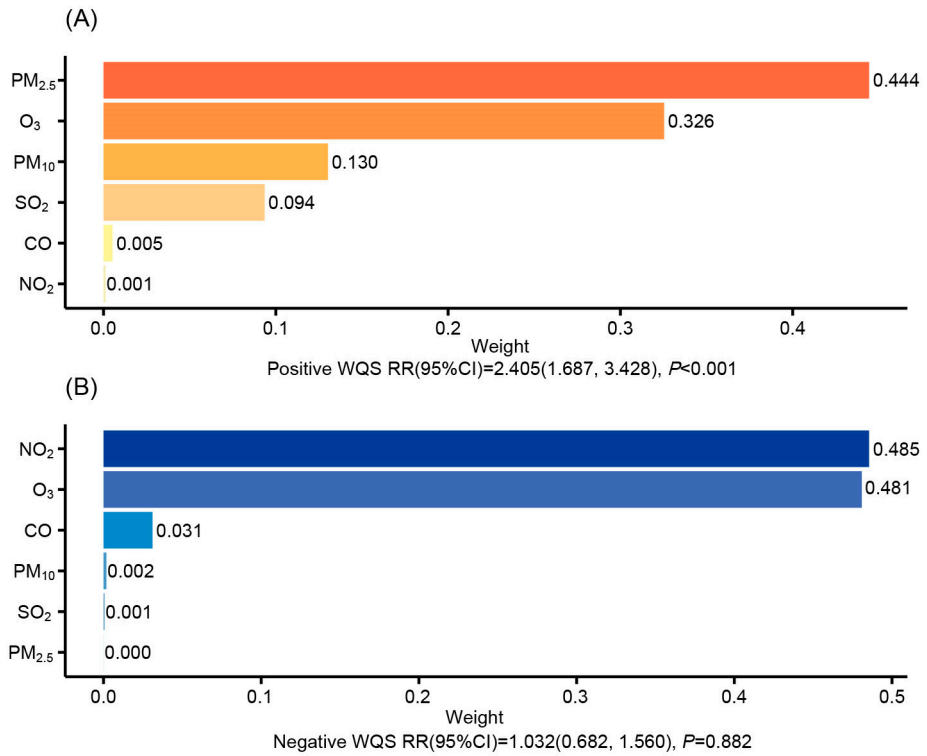


**Figure 3.** The weights of six air pollutants with the risk of CKD based on WQS regression. Models were adjusted for age, sex, BMI, education, marital status, work types, smoking status, alcohol consumption, season, infection status, use of TDF, TC, and TG. (**A**) Positive-direction WQS Regression; (**B**) Negative-direction WQS Regression. Abbreviations: $PM_{2.5}$, the aerodynamic diameter is less than 2.5 μg/m$^3$; $PM_{10}$, the aerodynamic diameter is less than 10 μg/m$^3$; $SO_2$, sulfur dioxide; CO, carbon monoxide; $NO_2$, nitrogen dioxide; $O_3$, ozone.

### *3.4. Mediation Analyses and Sensitivity Analyses*

Mediation analysis revealed that the TyG index partially mediated the association between cumulative exposure to AP and CKD risk, accounting for 10.21% (95% CI:1.70%, 32.06%) for $PM_{2.5}$, 9.16% (95% CI:1.54%, 30.95%) for $PM_{10}$, and 5.14% (95% CI:0.75%, 13.93%) for $SO_2$ (Table 3). In sensitivity analyses, consistent associations between AP exposure and CKD risk were observed after excluding individuals with a history of smoking or alcohol consumption (Table S2). Similarly, the associations between AP exposure and CKD risk remained robust when evaluated using Cox proportional hazards models (Table S3), with consistent results observed after applying FDR correction (Table S4).

**Table 3.** Mediation analyses of TyG index on the associations between air pollutants and CKD.

| Exposure | Direct Effect (95% CI) | Indirect Effect (95% CI) | Proportion Mediated (95% CI) |
|---|---|---|---|
| $PM_{2.5}$ | 1.0021 (1.0008, 1.0028) | 1.0003 (1.0000, 1.0005) | 10.21% (1.70%, 32.06%) |
| $PM_{10}$ | 1.0020 (1.0008, 1.0027) | 1.0002 (1.000, 1.0005) | 9.16% (1.54%, 30.94%) |
| $SO_2$ | 1.0018 (1.0010, 1.0024) | 1.0001 (1.0000, 1.0002) | 5.14% (0.75%, 13.93%) |
| CO | 0.9996 (0.9942, 1.0015) | 1.0008 (1.0001, 1.0019) | 32.93% (−574.65%, 519.90%) |
| $NO_2$ | 0.9974 (0.9888, 1.0021) | 1.0008 (1.0002, 1.0016) | −17.41% (−383.13%, 433.09%) |
| $O_3$ | 1.0005 (0.9960, 1.0019) | 0.9996 (0.9990, 0.9999) | −14.6% (−296.35%, 310.96%) |

All effect estimates for air pollutants correspond to an IQR increment: $PM_{2.5}$ (13.2 μg/m$^3$), $PM_{10}$ (20.2 μg/m$^3$), $SO_2$ (2.9 μg/m$^3$), CO (0.2 mg/m$^3$), $NO_2$ (13.2 μg/m$^3$), $O_3$ (16.7 μg/m$^3$). Abbreviations: $PM_{2.5}$, the aerodynamic diameter is less than 2.5 μg/m$^3$; $PM_{10}$, the aerodynamic diameter is less than 10 μg/m$^3$; $SO_2$, sulfur dioxide; CO, carbon monoxide; $NO_2$, nitrogen dioxide; $O_3$, ozone.

## 4. Discussion

To our knowledge, this is the first large-scale longitudinal study examining the association between exposure to six ambient APs and CKD in HIV/AIDS patients. Our findings demonstrated that chronic exposure to $PM_{2.5}$, $PM_{10}$, and $SO_2$ was significantly associated with an elevated risk of CKD, with the TyG index partially mediating these associations. Among the six APs analyzed in mixture exposure models, $PM_{2.5}$ emerged as the most significant contributor to elevated CKD risk.

Our study revealed that chronic exposure to $PM_{2.5}$, $PM_{10}$, and $SO_2$ was related to a higher incidence of CKD, which is in agreement with the results of other studies in China. A study conducted on 72,425 Chinese adults observed that each 10 $ug/m^3$ increase in long-term $PM_{2.5}$ exposure was linked with a higher prevalence of CKD (OR, 1.71, 95CI: 1.58–1.85) [26]. A meta-analysis of 32 studies indicated that for every 10 $\mu g/m^3$ increase in $PM_{2.5}$, $PM_{10}$, $NO_2$, and $NO_X$, the risk CKD increased by 42%, 20%, 7%, and 7%, respectively. Additionally, an increase of 1 ppb $SO_2$ led to a 7% rise in CKD risk, while a 0.1 ppm rise in CO showed a 3% increase [27]. However, some studies did not find associations between long-term exposure to $PM_{2.5}$, $SO_2$, and $NO_2$ and the risk of CKD [28,29]. The existing findings are inconsistent due to variations among different population groups, disparities in exposure levels, and differences in the duration of exposure periods.

In our analysis, we found no significant associations between CO, $NO_2$, and $O_3$ and CKD risk, which may indicate a true lack of effect in our population. Biologically, particulate matter more directly induces systemic oxidative stress, inflammation, and endothelial dysfunction, key processes in CKD development. In contrast, the mechanisms by which $NO_2$ and $O_3$ impact renal function are less clear and likely weaker. Additionally, their high reactivity, shorter atmospheric lifetimes, and distinct exposure patterns may limit their renal toxicity compared to particulate matter. The null findings may be attributable to the limited statistical power caused by smaller effect sizes and the relatively low ambient concentrations of these gaseous pollutants. Further studies with larger samples and improved exposure assessments are warranted to clarify the roles of these gaseous pollutants in CKD.

Notably, this study further revealed through WQS regression that among the six mixed APs, $PM_{2.5}$ contributed the most to CKD risk, significantly more than $PM_{10}$ and $SO_2$. This finding may be attributed to the submicron particle size ($\leq$2.5 $\mu$m) of $PM_{2.5}$ and its enriched toxic components (e.g., transition metals, polycyclic aromatic hydrocarbons) and HIV-related pathophysiology, which facilitate its deep penetration through the alveolar barrier and induction of systemic oxidative stress and renal vascular endothelial damage [30,31]. HIV-related chronic immune activation and antiretroviral-therapy-associated mitochondrial dysfunction amplify these effects, driving tubulointerstitial fibrosis and vascular damage—processes further exacerbated by the inherent immunometabolic vulnerabilities of the HIV population [32]. The dominance of $PM_{2.5}$ over gas-phase pollutants highlights particle-bound toxins as key drivers of renal injury in this vulnerable population, underscoring the need for HIV-specific pollution risk assessments.

Our analysis revealed that the TyG index may be involved in the association between AP exposure and increased CKD risk. The TyG index, a novel marker for insulin resistance, is linked to $PM_{2.5}$-induced pulmonary oxidative stress, as evidenced in animal models [33]. Additionally, studies have identified a relationship between $PM_{2.5}$ exposure and elevated insulin resistance markers in humans [34], suggesting AP exposure may be linked to insulin resistance, with the TyG index potentially serving as an indicative marker. Presently, the TyG index is acknowledged as a predictive tool for CKD onset [35], with recent evidence highlighting a significant correlation between the TyG index and CKD in individuals with type 2 diabetes [36]. $PM_{2.5}$ may induce systemic oxidative stress and chronic low-grade inflammation, impairing insulin signaling and lipid metabolism. These effects can

elevate circulating glucose and triglyceride levels—key components of the TyG index—and contribute to glomerular injury, endothelial dysfunction, and renal microvascular damage. However, given the observational nature of the data and potential unmeasured confounding effects, these findings should be interpreted as exploratory and not as conclusive evidence of causality. While the mediation proportion was relatively small, this is expected given the multifactorial etiology of CKD. The TyG index may represent only one of several parallel metabolic pathways involved, and even partial mediation provides useful insight into the biological processes linking air pollution to kidney impairment.

The potential mechanisms behind renal damage associated with AP exposure are not yet fully understood. Prior research has indicated that elevated AP levels may activate cytokines or oxidative agents in the respiratory tract, leading to inflammation. These agents can then circulate through the body, causing damage to distant organs, including the kidneys [37,38]. Studies involving rodent models and in vitro cellular assays have demonstrated that inhibiting inflammatory pathways can mitigate kidney damage resulting from $PM_{2.5}$ exposure [39]. Moreover, individuals with pre-existing health conditions, such as HIV/AIDS patients, are already in an inflammatory state [40,41], and APs may contribute to renal damage by exacerbating the level of inflammation in patients. Meanwhile, an AP-induced high inflammatory state in HIV/AIDS patients can cause immune cells to be destroyed and can weaken immune function [12,42]. Given that HIV/AIDS patients are a vulnerable group with compromised immune systems, they exhibit heightened susceptibility to the hazards posed by APs. This vulnerability can impair their infection-fighting capabilities, potentially leading to enhanced viral replication and accelerated disease progression that affects the immune system, further exacerbating PM-related kidney damage.

There were some limitations in this study. Firstly, the exposure data used for APs were evaluated using satellite-based spatiotemporal models, calculating outdoor pollutant concentrations. This method overlooked individual indoor exposure levels, which could potentially introduce measurement biases. Secondly, information on individual-level socioeconomic status, such as income or education, was not available, which may introduce residual confounding. However, given that all participants were recruited from the same public health system and geographic area, the variability in socioeconomic status may be limited. Thirdly, while we adjusted for TDF use, detailed data on the duration and type of other ARTs were not available. Due to the complexity and variability of ART regimens, further adjustment was not feasible. Nonetheless, any potential confounding from unmeasured ART components is unlikely to be strongly associated with air pollution exposure and thus would likely result in non-differential bias. Fourthly, in this study, CKD diagnosis was based on a single eGFR measurement below 60 mL/min/1.73 $m^2$, rather than the clinical standard of two measurements 90 days apart, due to irregular follow-up intervals. While this approach deviates from clinical diagnostic criteria, it is a common practice in environmental epidemiology studies investigating the association between air pollution and kidney outcomes. We acknowledge that relying on a single eGFR measurement may overestimate CKD incidence by including cases of transient or reversible kidney function decline. However, any potential misclassification is likely to be non-differential with respect to air pollution exposure, which would bias the estimates toward the null rather than exaggerate the observed associations. Therefore, this approach, although suboptimal from a clinical standpoint, remains appropriate for etiological inference in population-based environmental research. Finally, our study was conducted in Wuhan and Zhenjiang, with findings potentially constrained by regional-specific factors (e.g., pollutant profiles, demographics). Thus, external validity in other regions requires confirmation via future studies.

## 5. Conclusions

Our study indicates that exposure to APs, particularly particulate matter, is associated with diminished renal function and an increased incidence of CKD in HIV/AIDS patients. The TyG index, as a marker of glucolipid metabolism, may offer potential insights into the metabolic pathways linking particulate matter exposure to renal damage in this population. Urgent policies are necessary to mitigate AP-induced kidney damage in vulnerable populations.

**Supplementary Materials:** The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/toxics13080669/s1, Table S1. Distribution of air pollutant concentrations during the follow-up period; Table S2. Associations between air pollutant exposure and incident chronic kidney disease after excluding individuals with a history of smoking or alcohol consumption; Table S3. Re-evaluating the associations between air pollutant exposures and chronic kidney disease using Cox proportional hazards models; Table S4. Associations between air pollutants and CKD risk with FDR correction in HIV/AIDS patients.

**Author Contributions:** Conceptualization, W.L. and X.W.; methodology, X.L.; software, X.Z.; validation, W.L., X.L., and X.W.; formal analysis, X.Z.; investigation, J.M. and Z.X.; resources, X.L., X.W.; data curation, L.Y. and C.H.; writing—original draft preparation, X.L.; writing—review and editing, X.Z.; visualization, W.L., X.L., X.Z. and X.W.; supervision, W.L.; project administration, X.W.; funding acquisition, X.W. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research was funded by Funding for Scientific Research Projects from Wuhan Municipal Health Commission, grant number WY22M02.

**Institutional Review Board Statement:** This study was granted approval by the ethics committee of Wuhan CDC (WHCDCIRB-K-2022027).

**Informed Consent Statement:** Not applicable.

**Data Availability Statement:** Data will be made available on request.

**Conflicts of Interest:** The authors declare no conflicts of interest.

## Abbreviations

The following abbreviations are used in this manuscript:

| | |
|---|---|
| $PM_{2.5}$ | the aerodynamic diameter is less than 2.5 $\mu g/m^3$; |
| $PM_{10}$ | the aerodynamic diameter is less than 10 $\mu g/m^3$ |
| $SO_2$ | sulfur dioxide |
| CO | carbon monoxide |
| $NO_2$ | nitrogen dioxide |
| $O_3$ | ozone |
| CKD | chronic kidney disease |
| AP | air pollutant |
| TyG | triglyceride-glucose |
| CRIMS | Comprehensive Response Information Management System |
| CDC | Center for Disease Control and Prevention |
| TG | triglyceride |
| WQS | weighted quantile sum |
| FBG | fasting blood glucose |
| Scr | serum creatinine |
| eGFR | estimated glomerular filtration rate |
| TDF | tenofovir disoproxil fumarate |
| RRs | risk factors |

| | |
|---|---|
| CIs | confidence intervals |
| IQR | interquartile range |
| CKD | Epidemiology Collaboration (CKD-EPI) |
| BMI | body mass index |

## References


1. Chen, T.K.; Knicely, D.H.; Grams, M.E. Chronic Kidney Disease Diagnosis and Management: A Review. *Jama* **2019**, *322*, 1294–1304. [CrossRef]
2. Jung, J.; Park, J.Y.; Kim, Y.C.; Lee, H.; Kim, E.; Kim, Y.S.; Lee, J.P.; Kim, H. Effects of air pollution on mortality of patients with chronic kidney disease: A large observational cohort study. *Sci. Total Environ.* **2021**, *786*, 147471. [CrossRef]
3. Li, Z.H.; Song, W.Q.; Qiu, C.S.; Li, H.-M.; Tang, X.-L.; Shen, D.; Zhang, P.-D.; Zhang, X.-R.; Ren, J.-J.; Gao, J.; et al. Long-term air pollution exposure, habitual physical activity, and incident chronic kidney disease. *Ecotoxicol. Environ. Saf.* **2023**, *265*, 115492. [CrossRef] [PubMed]
4. 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. [CrossRef] [PubMed]
5. Kazancioğlu, R. Risk factors for chronic kidney disease: An update. *Kidney Int. Suppl.* **2013**, *3*, 368–371. [CrossRef] [PubMed]
6. Kataria, A.; Trasande, L.; Trachtman, H. The effects of environmental chemicals on renal function. *Nat. Rev. Nephrol.* **2015**, *11*, 610–625. [CrossRef]
7. Blum, M.F.; Surapaneni, A.; Stewart, J.D.; Liao, D.; Yanosky, J.D.; Whitsel, E.A.; Power, M.C.; Grams, M.E. Particulate Matter and Albuminuria, Glomerular Filtration Rate, and Incident CKD. *Clin. J. Am. Soc. Nephrol.* **2020**, *15*, 311–319. [CrossRef]
8. Bowe, B.; Xie, Y.; Li, T.; Yan, Y.; Xian, H.; Al-Al, Z. Associations of ambient coarse particulate matter, nitrogen dioxide, and carbon monoxide with the risk of kidney disease: A cohort study. *Lancet Planet. Health* **2017**, *1*, e267–e276. [CrossRef]
9. Bowe, B.; Artimovich, E.; Xie, Y.; Yan, Y.; Cai, M.; Al-Aly, Z. The global and national burden of chronic kidney disease attributable to ambient fine particulate matter air pollution: A modelling study. *BMJ Glob. Health* **2020**, *5*, e002063. [CrossRef]
10. Lin, Y.T.; Lo, Y.C.; Chiang, H.Y.; Jung, C.-R.; Wang, C.-M.; Chan, T.-C.; Kuo, C.-C.; Hwang, B.-F. Particulate Air Pollution and Progression to Kidney Failure with Replacement Therapy: An Advanced CKD Registry-Based Cohort Study in Taiwan. *Am. J. Kidney Dis.* **2020**, *76*, 645–657.e1. [CrossRef]
11. Li, G.; Huang, J.; Wang, J.; Zhao, M.; Liu, Y.; Guo, X.; Wu, S.; Zhang, L. Long-Term Exposure to Ambient $PM_{2.5}$ and Increased Risk of CKD Prevalence in China. *J. Am. Soc. Nephrol.* **2021**, *32*, 448–458. [CrossRef] [PubMed]
12. Liang, W.; Wang, X.; Xie, N.; Yan, H.; Ma, H.; Liu, M.; Kong, W.; Zhu, Z.; Bai, W.; Xiang, H. Short-term associations of $PM_{2.5}$ and $PM_{2.5}$ constituents with immune biomarkers: A panel study in people living with HIV/AIDS. *Environ. Pollut.* **2023**, *317*, 120743. [CrossRef] [PubMed]
13. Ma, H.; Zhang, Q.; Liang, W.; Han, A.; Xie, N.; Xiang, H.; Wang, X. Short-Term Exposure to $PM_{2.5}$ and $O_3$ Impairs Liver Function in HIV/AIDS Patients: Evidence from a Repeated Measurements Study. *Toxics* **2023**, *11*, 729. [CrossRef]
14. Ma, H.; Liang, W.; Han, A.; Zhang, Q.; Gong, S.; Bai, Y.; Gao, D.; Xiang, H.; Wang, X. Ambient particulate matter and renal function decline in people with HIV/AIDS. *Aids* **2024**, *38*, 713–721. [CrossRef] [PubMed]
15. Wang, S.; Wang, Q.; Yan, X. Association between triglyceride-glucose index and hypertension: A cohort study based on the China Health and Nutrition Survey (2009–2015). *BMC Cardiovasc. Disord.* **2024**, *24*, 168. [CrossRef]
16. Wang, X.; Zheng, K.; Hu, X.; Pei, J. The impact of sex-related disparities on the association between triglyceride-glucose index and renal function decline in patients with type 2 diabetes: Insights from the ACCORD trial. *Diabetes Res. Clin. Pr.* **2025**, *224*, 112163. [CrossRef]
17. Lu, Y.; Qiu, W.; Liao, R.; Cao, W.; Huang, F.; Wang, X.; Li, M.; Li, Y. Subacute PM2.5 Exposure Induces Hepatic Insulin Resistance Through Inflammation and Oxidative Stress. *Int. J. Mol. Sci.* **2025**, *26*, 812. [CrossRef]
18. Levey, A.S.; Stevens, L.A.; Schmid, C.H.; Zhang, Y.L.; Castro, A.F.; Feldman, H.I.; Kusek, J.W.; Eggers, P.; Van Lente, F.; Greene, T.; et al. A new equation to estimate glomerular filtration rate. *Ann. Intern. Med.* **2009**, *150*, 604–612. [CrossRef]
19. Wei, J.; Li, Z.; Guo, J.; Sun, L.; Huang, W.; Xue, W.; Fan, T.; Cribb, M. Satellite-Derived 1-km-Resolution $PM_1$ Concentrations from 2014 to 2018 across China. *Environ. Sci. Technol.* **2019**, *53*, 13265–13274. [CrossRef]
20. Wei, J.; Li, Z.; Xue, W.; Sun, L.; Fan, T.; Liu, L.; Su, T.; Cribb, M. The ChinaHighPM$_{10}$ dataset: Generation, validation, and spatiotemporal variations from 2015 to 2019 across China. *Environ. Int.* **2021**, *146*, 106290. [CrossRef]
21. Wei, J.; Li, Z.Q.; Lyapustin, A.; Sun, L.; Peng, Y.; Xue, W.; Su, T.; Cribb, M. Reconstructing 1-km-resolution high-quality $PM_{2.5}$ data records from 2000 to 2018 in China: Spatiotemporal variations and policy implications. *Remote Sens. Environ.* **2021**, *252*, 112136. [CrossRef]
22. Wei, J.; Li, Z.Q.; Cribb, M.; Huang, W.; Xue, W.; Sun, L.; Guo, J.; Peng, Y.; Li, J.; Lyapustin, A.; et al. Improved 1 km resolution PM2.5 estimates across China using enhanced space-time extremely randomized trees. *Atmos. Chem. Phys.* **2020**, *20*, 3273–3289. [CrossRef]

23. Wei, J.; Li, Z.Q.; Li, K.; Dickerson, R.R.; Pinker, R.T.; Wang, J.; Liu, X.; Sun, L.; Xue, W.; Cribb, M. Full-coverage mapping and spatiotemporal variations of ground-level ozone ($O_3$) pollution from 2013 to 2020 across China. *Remote Sens. Environ.* **2022**, *270*, 112775. [CrossRef]
24. Wei, J.; Li, Z.Q.; Wang, J.; Li, C.; Gupta, P.; Cribb, M. Ground-level gaseous pollutants ($NO_2$, $SO_2$, and CO) in China: Daily seamless mapping and spatiotemporal variations. *Atmos. Chem. Phys.* **2023**, *23*, 1511–1532. [CrossRef]
25. Oh, J.; Ye, S.; Kang, D.H.; Ha, E. Association between exposure to fine particulate matter and kidney function: Results from the Korea National Health and Nutrition Examination Survey. *Environ. Res.* **2022**, *212*, 113080. [CrossRef] [PubMed]
26. Duan, J.W.; Li, Y.L.; Li, S.X.; Yang, Y.-P.; Li, F.; Li, Y.; Wang, J.; Deng, P.-Z.; Wu, J.-J.; Wang, W.; et al. Association of Long-term Ambient Fine Particulate Matter ($PM_{2.5}$) and Incident CKD: A Prospective Cohort Study in China. *Am. J. Kidney Dis.* **2022**, *80*, 638–647.e1. [CrossRef] [PubMed]
27. Xu, W.; Jia, L.; Lin, Y.; Zhang, C.; Sun, X.; Jiang, L.; Yao, X.; Wang, N.; Deng, H.; Wang, S.; et al. Association of air pollution and risk of chronic kidney disease: A systematic review and meta-analysis. *J. Biochem. Mol. Toxicol.* **2024**, *38*, e23610. [CrossRef]
28. Yang, Y.R.; Chen, Y.M.; Chen, S.Y.; Chan, C.C. Associations between Long-Term Particulate Matter Exposure and Adult Renal Function in the Taipei Metropolis. *Environ. Health Perspect.* **2017**, *125*, 602–607. [CrossRef]
29. Lin, H.C.; Hung, P.H.; Hsieh, Y.Y.; Lai, T.-J.; Hsu, H.-T.; Chung, M.-C.; Chung, C.-J. Long-term exposure to air pollutants and increased risk of chronic kidney disease in a community-based population using a fuzzy logic inference model. *Clin. Kidney J.* **2022**, *15*, 1872–1880. [CrossRef]
30. Liang, K.H.; Colombijn, J.M.T.; Verhaar, M.C.; Ghannoum, M.; Timmermans, E.J.; Vernooij, R.W.M. The general external exposome and the development or progression of chronic kidney disease: A systematic review and meta-analyses. *Environ. Pollut.* **2024**, *358*, 124509. [CrossRef] [PubMed]
31. Chen, H.; Nguyen, L.T.; Feng, M.; Wang, B.; Xu, B.; Yarak, R.A.; Chan, Y.L.; Viswanathan, S.; Komala, M.G.; Pollock, C.A.; et al. Cross-Generational Impact of Maternal Exposure to Low Level of PM2.5 on Kidney Health. *Am. J. Nephrol.* **2025**, *56*, 222–235. [CrossRef]
32. Joshi, K.S.; Jadhao, V.F.; Gujarathi, R.; Churiwala, W.; Natu, A.A. Human Immunodeficiency Virus-positive Patients on Highly Active Antiretroviral Therapy Continue to Have a Decline in Renal Function Irrespective of Tenofovir Usage. *J. Glob. Infect. Dis.* **2024**, *16*, 111–116. [CrossRef]
33. Ribble, A.; Hellmann, J.; Conklin, D.J.; Bhatnagar, A.; Haberzettl, P. Fine particulate matter ($PM_{2.5}$)-induced pulmonary oxidative stress contributes to increases in glucose intolerance and insulin resistance in a mouse model of circadian dyssynchrony. *Sci. Total Environ.* **2023**, *877*, 162934. [CrossRef]
34. Zhao, L.; Fang, J.; Tang, S.; Deng, F.; Liu, X.; Shen, Y.; Liu, Y.; Kong, F.; Du, Y.; Cui, L.; et al. $PM_{2.5}$ and Serum Metabolome and Insulin Resistance, Potential Mediation by the Gut Microbiome: A Population-Based Panel Study of Older Adults in China. *Environ. Health Perspect.* **2022**, *130*, 27007. [CrossRef]
35. Ren, X.; Jiang, M.; Han, L.; Zheng, X. Association between triglyceride-glucose index and chronic kidney disease: A cohort study and meta-analysis. *Nutr. Metab. Cardiovasc. Dis.* **2023**, *33*, 1121–1128. [CrossRef]
36. Low, S.; Pek, S.; Moh, A.; Ang, K.; Khoo, J.; Shao, Y.-M.; Tang, W.E.; Lim, Z.; Subramaniam, T.; Sum, C.F.; et al. Triglyceride-glucose index is prospectively associated with chronic kidney disease progression in Type 2 diabetes—Mediation by pigment epithelium-derived factor. *Diabetes Vasc. Dis. Res.* **2022**, *19*, 14791641221113784. [CrossRef]
37. Brook, R.D.; Rajagopalan, S.; Pope, C.A., 3rd; Brook, J.R.; Bhatnagar, A.; Diez-Roux, A.V.; Holguin, F.; Hong, Y.; Luepker, R.V.; Mittleman, M.A.; 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. [CrossRef] [PubMed]
38. Xu, X.; Nie, S.; Ding, H.; Hou, F.F. Environmental pollution and kidney diseases. *Nat. Rev. Nephrol.* **2018**, *14*, 313–324. [CrossRef] [PubMed]
39. Chenxu, G.; Minxuan, X.; Yuting, Q.; Tingting, G.; Jinxiao, L.; Mingxing, W.; Sujun, W.; Yongjie, M.; Deshuai, L.; Qiang, L.; et al. iRhom2 loss alleviates renal injury in long-term PM2.5-exposed mice by suppression of inflammation and oxidative stress. *Redox Biol.* **2018**, *19*, 147–157. [CrossRef]
40. Decrion, A.Z.; Dichamp, I.; Varin, A.; Herbein, G. HIV and inflammation. *Curr. HIV Res.* **2005**, *3*, 243–259. [CrossRef] [PubMed]
41. Peterson, T.E.; Baker, J.V. Assessing inflammation and its role in comorbidities among persons living with HIV. *Curr. Opin. Infect. Dis.* **2019**, *32*, 8–15. [CrossRef] [PubMed]
42. Chen, X.; Chen, H.; Zhang, Z.; Fu, Y.; Han, X.; Zhang, Y.; Xu, J.; Ding, H.; Cui, H.; Dong, T.; et al. Elevated CD54 Expression Renders CD4+ T Cells Susceptible to Natural Killer Cell-Mediated Killing. *J. Infect. Dis.* **2019**, *220*, 1892–1903. [CrossRef] [PubMed]


**Disclaimer/Publisher's Note:** The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.