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CKJ REVIEW

Air pollution and kidney disease: review of current evidence

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ABSTRACT

Along with amazing technological advances, the industrial revolution of the mid-19th century introduced new sources of pollution. By the mid-20th century, the effects of these changes were beginning to be felt around the world. Among these changes, health problems due to environmental air pollution are increasingly recognized. At the beginning, respiratory and cardiovascular diseases were emphasized. However, accumulated data indicate that every organ system in the body may be involved, and the kidney is no exception. Although research on air pollution and kidney damage is recent, there is now scientific evidence that air pollution harms the kidney. In this holistic review, we have summarized the epidemiology, disease states and mechanisms of air pollution and kidney damage.

Keywords: acute kidney injury, air pollution, chronic kidney disease, heavy metals, particulate matter

INTRODUCTION

The adverse health effects of ambient (outdoor) air pollution have been recognized since increased mortality due to smog was reported in London in 1952 [1, 2]. Since then, ambient air pollution is recognized as one of the leading causes of global disease burden [3, 4]. Air pollution is a complex mixture of gaseous components and solid and liquid particles suspended in the air and can vary substantially in chemical composition between different cities. There are various sources of these pollutants (Table 1).

Particulate matter (PM), which primarily comprises solid particles derived from the combustion of coal, gasoline and diesel fuels, is the major element of air pollution that causes the most adverse health effects [12, 13]. Environmental air pollution may be composed of additional components (Figure 1), such as different sized PM (e.g. PM_{10} having an aerodynamic diameter $\leq$10 μm; $PM_{2.5}$ which are $\leq$2.5 μm and $PM_{2.5–10}$), gaseous pollutants [e.g. nitrogen dioxide (NO_2), carbon monoxide (CO), sulphur dioxide (SO_2) and ozone (O_3)] and heavy metals [e.g. cadmium (Cd), lead (Pb) and mercury (Hg)] [14–16]. Over the past

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Table 1. Major sources of common air and other environmental pollutants

Pollutant	Source	References
PM	Mostly traffic-related air pollution (mainly local emission) Other (domestic heating, industries, etc.)	[5, 6]
NO_X	Mainly derived from road traffic and the industrial burning of fuels Strongly related to diesel motor vehicles	[7, 8]
SO_X	Industrial production of sulphur-based products	[9]
O_3	Industrial combustion and processes	[10]
CO	Road traffic and industrial fuel burning	[7]
Cadmium	Diet in non-smokers Tobacco in smokers	[11]
Lead	Gasoline, batteries, pipes and ammunition In the past, paints and ceramic glazes Occupational exposure to the inorganic form of Pb (Pb^{2+}): welding manufacture of Pb-containing batteries, Pb melting and refining, and production of pottery Children ingesting Pb^{2+} contaminated soil	[11]
Mercury	Occupational, environmental and dietary sources Mainly through ingestion of food contaminated with CH_3Hg^+	[11]
Arsenic	Primary route of human exposure is ingestion of contaminated drinking water Methylated forms of As (MAs and DMAs) from pesticides used in cotton crops	[11]
Uranium	Mining and milling	[11]

decade, a growing body of research has suggested a causal relationship between ambient air pollution exposure and adverse cardiovascular health [17].

Chronic kidney disease (CKD) is another worldwide public health problem with a variety of adverse outcomes, including premature death, and it is regarded as a cardiovascular disease (CVD) risk equivalent [18]. Apart from traditional risk factors, such as hypertension and diabetes, an increasing body of evidence demonstrates that air pollution may be a novel environmental risk factor for CKD [5, 19, 20]. In the present review, we systemically summarized the current data regarding air pollution and kidney disease.

METHODS

A literature search was performed using electronic databases MEDLINE, Ovid/MEDLINE (1988–2018), PubMed/MEDLINE, EMBASE and ISI Web/Web of Science for published studies from January 1988 to March 2018. We searched for relevant studies using the keywords 'air pollution and chronic kidney disease', 'air pollution and end-stage renal disease', 'air pollution and proteinuria', 'environmental pollution and chronic kidney disease', 'air pollution and diabetes', 'air pollution and hypertension', 'toxic metals and chronic kidney disease' and 'heavy metals and chronic kidney disease', limiting the search to research articles involving humans and published in English. Neither unpublished data nor abstracts were included.

NEPHROTOXIC METALS AND RENAL DISEASE

Heavy metals are among the best-known environmental pollutants causing kidney disease. It is less well known that they are also air pollutants, particularly Cd, Pb and Hg, but also arsenic (As) and uranium (http://www.euro.who.int/__data/assets/pdf_file/0007/78649/E91044.pdf).

Arsenic and CKD

Environmental, occupational and dietary exposure to As appear to contribute to the incidence of renal injury and the development of renal disease [11]. Contamination of drinking water with As has been linked to the development of hypertension and renal injury [21, 22]. Findings from a cross-sectional study of patients in Taiwan showed a positive correlation between urinary As and the incidence of CKD. It was concluded that high levels of urinary As may increase the risk of developing CKD by 4-fold [23]. Acute As-induced renal intoxication may lead to tubulointerstitial nephritis and acute tubular necrosis manifested by hypercalciuria, albuminuria, nephrocalcinosis and necrosis of the renal papillae [24, 25].

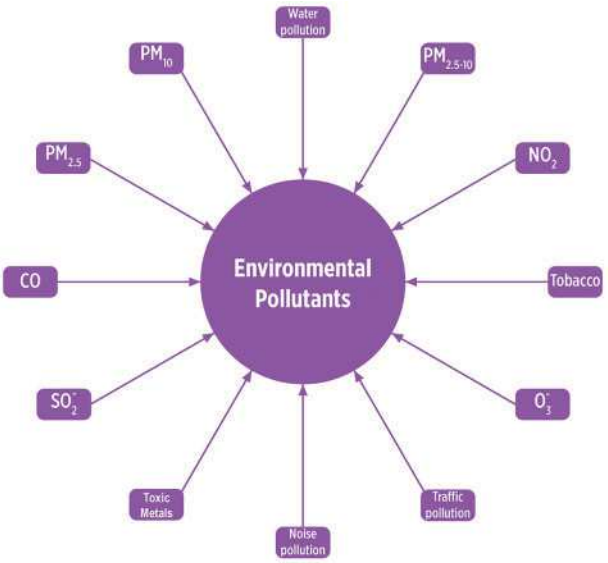


FIGURE 1: Components of environmental pollution.

Cadmium and CKD

Cd is a prevalent nephrotoxic environmental pollutant. In non-smokers, diet is the primary source for Cd exposure. However, in smokers, the major source of exposure is related to tobacco products that contain high concentration of Cd. As paediatric

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age increases, Cd exposure is also increased [26]. Environmental tobacco smoke exposure was the most important determinant of Cd status in school-aged children. Moreover, serum Cd levels were higher in active smoker teenagers than in non-smokers. Interestingly, higher serum Cd concentration was associated with higher alpha-1-microglobulinuria in adolescents, suggesting subclinical renal toxicity after several years of cumulative exposure [27]. Cd is also present in air and drinking water, although the concentration of Cd in air is relatively low, and drinking water is normally not a major source of exposure for the general population. However, Cd contamination of drinking water and vegetables has been observed in some cities and regions [26]. Exposure to Cd is often assessed by measuring the concentration of Cd in urine and/or blood. In fact, urinary Cd excretion is considered as one of the most reliable indicators of renal and body burden of Cd [11].

Cd is directly nephrotoxic and can induce renal tubular damage (polyuria, generalized tubular dysfunction, i.e. Fanconi syndrome) and progressive loss of glomerular filtration rate (GFR) [28–30]. Long-term Cd exposure is thought to accelerate the CKD-related decline in GFR [31–33]. Cross-sectional studies have shown that Cd exposure is a risk factor for the development of CKD [34, 35]. Epidemiological studies have demonstrated a positive correlation between CKD and the renal accumulation of Cd in individuals exposed chronically to this metal [36, 37]. The most frequent long-term consequence of Cd exposure is proteinuria, and it may precede a slowly progressive and irreversible renal tubular dysfunction [38]. Proteinuria has been ascribed to the loss of megalin and cubilin, which mediate endocytosis of filtered proteins along the proximal tubule [39–41]. The incidence of kidney stones also increases in individuals exposed chronically to or to larger Cd dose, possibly due to the increased concentration of calcium in tubular fluid and urine [11]. Last but not least, Cd exposure has been associated with the severity of diabetes [42] and hypertension [43], which themselves are risk factors for CKD.

Lead and CKD

Together with bone, kidney is a primary site of Pb accumulation as Pb is excreted by kidneys [44]. The major kidney cellular effect of exposure to Pb is the induction of mitochondrial oxidative stress [45] and inflammation [11]. This results in lipid oxidation and DNA fragmentation [46]. Low-level Pb exposure early in life causes glomerular hypertrophy, which may disrupt glomerular development [11]. Acute Pb intoxication causes proximal tubular dysfunction (Fanconi syndrome) [47], and chronic intoxication leads to progressive tubulointerstitial nephritis [48]. There is convincing preclinical and clinical evidence supporting a direct relationship between Pb exposure and development of kidney disease [49, 50]. Additionally, cross-sectional general population studies in Mexico and Korea found a correlation between serum creatinine and blood Pb levels [51, 52].

Mercury and CKD

All forms of Hg are nephrotoxic through various mechanisms. Hg is well absorbed following inhalation, and air levels correlate with exposure estimated by urinary Hg excretion. Hg has been associated with CKD progression [11, 53]. The pars recta of the proximal tubule appears to be most sensitive to the Hg toxicity [54, 55]. Acute exposure causes altered mitochondrial structure, endoplasmic reticulum dilation and nuclear pyknosis [56]. After 12 h, microvilli are lost and cell death is associated with plasma membrane rupture and cell detachment from the basement membrane [57].

Chronic exposure to mercuric compounds can lead to glomerular injury [11]. In rats, chronic exposure to methyl Hg caused glomerulosclerosis and glomerular immunoglobulin deposition. In North West England, ambient background Hg concentration (3 ng/m^3) is higher than the average background level in the UK (1.78 ng/m^3). There were significant exposure–response relations between modelled estimates of Hg exposure (low: >3 to <4; medium: 4 to 10; high: >10; or very high exposure: >20 ng/m^3) and risk of kidney disease mortality in both men and women after adjustment for age and socio-economic deprivation (test for trend: P = 0.02 for men and P = 0.03 for women) [58]. In another case–control study, occupational exposure in 272 men and women with CKD was compared with 272 controls matched for age, sex and region of residence. Hg exposure was independently associated with an increased risk of CKD [odds ratio (OR) = 5.13, 95% confidence interval (CI) 1.02–25.7] [59].

Uranium and CKD

Uranium toxicity, although relatively rare, may also cause renal damage and indeed, the kidney is the primary target for uranium toxicity following inhalation or ingestion. Approximately 40% of plasma uranium is complexed to transferrin and the remaining 60% is complexed with carbonate or bicarbonate, which are filtered by the glomerulus. In proximal tubules, the complexed uranium dissociates with decreasing pH, releasing the reactive uranyl ion, which can interact with the proximal tubule membrane. The most frequently used guideline for uranium kidney burdens is the International Commission on Radiological Protection value of 3 μg/g, a value that is based largely upon chronic animal studies [60]. A risk model equation to assess potential outcomes of acute uranium exposure was derived from 27 previously published case studies of acute exposure to soluble uranium compounds in workplace accidents. Kidney burdens of uranium for these individuals were determined from urine uranium, and correlated with health effects observed over a period of up to 38 years. Based upon the severity of health effects, each individual was assigned a score (− to 3+) and then placed into a Renal Effects Group (REG). A discriminate analysis was used to build a model equation to predict the REG based on the amount of kidney uranium [60] (Table 2).

TOBACCO AND CKD

Smoking is also an air pollutant detrimental for kidney health [61]. A recent meta-analysis investigated the relationship between cigarette smoking and CKD in the general population. Summary relative risks (SRRs) and 95% CIs were calculated using a random effects model. A total of 15 prospective cohort studies, including 65 064 incident CKD cases, were included. Compared with never-smokers, the SRRs of incident CKD were 1.34 (95% CI 1.23–1.47) for current smokers and 1.15 (95% CI 1.08–1.23) for former smokers. The SRRs for end-stage renal disease (ESRD) development were 1.91 (95% CI 1.39–2.64) for current smokers and 1.44 (95% CI 1.00–2.09) for former smokers. However, the authors noted that there was considerable heterogeneity among these studies [62]. In African Americans from the Jackson Heart Study, after adjustment for various factors, the incidence of renal function decline was higher in current smokers than in never-smokers (incidence rate ratio 1.83, 95% CI 1.31–2.56). Current smokers of 1–19 and ≥20 cigarettes daily

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Table 2. Acute renal effects and predicted outcomes of kidney uranium accumulation

REG	Kidney uranium concentration (μg/g)	Acute renal effect	Predicted outcome
0	≤2.2	None	No clinically detectable effects
1	>2.2 to ≤6.4	Possible transient indicators of renal dysfunction	Not likely to become ill
2	>6.4 to ≤18	Possible protracted indicators of renal dysfunction	May become ill
3	>18	Possible severe clinical symptoms of renal dysfunction	Likely to become ill

had an increased incidence rate ratio of residual renal function decline: 1.75 (95% CI 1.18–2.59) and 1.97 (95% CI 1.17–3.31), respectively. In addition, there was a significant progressive reduction in estimated GFR (eGFR) from Visits 1 to 3 in current and past smokers compared with never-smokers [63].

Apart from these findings, there is also evidence linking tobacco exposure to proteinuria in those with and without kidney disease [64–67]. In 990 middle-aged men recruited from a chemical plant, proteinuria was found in 4.6% of current smokers and 1.5% of never-smokers [68]. A meta-analysis of the relationship between tobacco smoking on the development of diabetic nephropathy (DN) in type 1 diabetes mellitus (T1DM) and T2DM, identified 19 observational studies (1 case–control, 8 cross-sectional and 10 prospective cohort studies), involving more than 78 000 participants and a total of 17 832 DN cases. The relative risk (RR) (95% CI) of DN was higher in ever-smokers with T1DM (1.31, 1.06–1.62; $P = 0.006$) or T2DM (1.44, 1.24–1.67; $P < 0.001$) than in never-smokers. In T1DM ever-smokers, the RR was 1.25 (95% CI 0.86–1.83) for microalbuminuria, 1.27 (95% CI 1.10–1.48) for macroalbuminuria and 1.06 (95% CI 0.97–1.15) for ESRD. In T2DM ever-smokers, the RR was 1.46 (95% CI 0.94–2.26) for microalbuminuria, 1.72 (95% CI 1.04–2.84) for macroalbuminuria and 1.10 (95% CI 0.36–3.33) for ESRD [69]. Thus, it appears that the highest risk associated with smoking is for macroalbuminuria, likely over a basis in incipient DN.

Passive smoking has also been associated with renal damage. Assessment of the nicotine metabolite cotinine in serum and in urine has been used to quantify smoking exposure. In a cohort of 366 children with CKD aged 1–16 years, secondhand smoke exposure obtained via questionnaire and urine cotinine was associated with the prevalence odds of nephrotic range proteinuria (OR = 2.64, 95% CI 1.08–6.42) [70]. In active ($n = 24$) and passive ($n = 20$) smokers, serum cotinine levels were higher than in controls ($n = 20$), as was the urinary albumin–creatinine ratio, whereas serum creatinine was higher in active smokers [71].

This evidence suggests that smoking harms the kidneys, but how? Several mechanisms may be at play. Cigarette smoking has been associated with idiopathic nodular glomerulosclerosis and microalbuminuria or overt proteinuria in healthy individuals, and with more severe proteinuria in individuals with pre-existing renal disease such as DN [72–74]. A correlation between smoking and nephrosclerosis and glomerulonephritis was found in a nationwide population-based case–control study that included Swedish subjects, 926 cases and 998 control [75]. Smoking promoted the progression of hypertensive [67, 76] and diabetic nephropathies [77]. Cigarette smoking has been directly associated with endothelial dysfunction, intimal hyperplasia and wall thickening of myocardial and renal arterioles and arteries.

Tobacco smoke caused mesangial proliferation, glomerulosclerosis and tubulointerstitial fibrosis in experimental studies [72, 78]. Specifically, nicotine activation of nicotine receptors promotes human mesangial cell extracellular matrix production [79]. Acrolein, an aldehyde from tobacco smoke, induces renal cell reactive oxygen species (ROS) production and apoptosis [80, 81]. Smoking also increases Cd levels and this could contribute to CKD progression. Smokers have 4- to 5-fold higher Cd levels in blood and 2- to 3-fold higher kidney Cd than non-smokers [82]. Indeed, NHANES 1999–2006 data for adults without CKD showed that urine Cd levels were highest for current smokers (3- to 13-fold higher), followed by former smokers (2- to 3-fold) compared with non-smokers. Cigarette smoking greatly increases RR of exceeding renal risk-associated urine Cd levels, particularly in former smokers [28].

Passive smoking has also being associated with renal fibrosis. Glomerulosclerosis comparable to the findings in idiopathic nodular glomerulosclerosis in human beings and upregulation of interstitial fibrosis-related genes has been observed in the absence of proteinuria, suggesting that histological changes precede biochemical changes [26]. Elevated sympathetic activity, blood pressure (BP), GFR and intraglomerular capillary pressure are candidate mechanisms for smoking-induced renal damage [72]. It was also suggested that chronic environmental tobacco smoke exposure induces systemic oxidative stress, which may subsequently trigger production of profibrotic factors [83].

However, there are also contradictory findings. In healthy rats exposed to smoke soon after birth for 4 months, as a model of passive smoking, the mean number of renal vessels, glomerulosclerosis and myointimal hyperplasia did not significantly differ from control rats [84]. However, it is unclear whether the timing was appropriate to observe any effect. No differences were found in the prevalence of glomerulosclerosis between non-smokers (51 patients, 47.7%) and ever-smokers (56 patients, 52.3%) in kidney biopsy. However, the number of glomeruli obtained at biopsy may have been insufficient for assessing glomerulosclerosis [85].

TRAFFIC AND NEARBY INDUSTRIAL POLLUTION AND CKD

Traffic air pollution is another kind of air pollution. Among 8497 Taipei city residents, regression models were used to estimate the participants' 1-year exposures to PM of different sizes and traffic-related exhaust, $PM_{2.5}$ absorbance, NO_2 and nitrogen oxidases (NO_x). Interquartile range (IQR) increments of $PM_{2.5}$ absorbance (0.4×10^{-5}/m) and NO_2 (7.0 mg/m^3) were associated with 1.07 and 0.84% lower eGFR, respectively. Similar associations were also observed for PM_{10} and $PM_{2.5–10}$. Two-pollutant models showed that PM_{10} and $PM_{2.5}$ absorbances were associated with lower eGFR. Authors conclude that 1-year exposures to traffic-related air pollution were associated with lower eGFR, higher CKD prevalence and increased risk of CKD progression among the elderly. Of note, there were no significant findings with regard to proteinuria, but albuminuria was not assessed [5]. Among 1103 consecutive Boston-area patients hospitalized with acute ischaemic stroke between 1999 and 2004, linear regression

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was used to evaluate the association between eGFR and categories of residential distance to major roadway (0 to ≤50, 50 to ≤100, 100 to ≤200, 200 to ≤400, 400 to ≤1000 and >1000 m) adjusting for age, sex, race, smoking, comorbid conditions, treatment with angiotensin-converting enzyme inhibitor and neighbourhood-level socioeconomic characteristics. Patients living closer to a major roadway had lower eGFR than patients living farther away (P_{trend} = 0.01). Comparing patients living 50 m versus 1000 m from a major roadway, patients living within 50 m had 3.9 mL/min/1.73 m^2 lower eGFR (95% CI 1.0–6.7; P = 0.007), a difference comparable in magnitude to the reduction in eGFR observed for a 4-year increase in age in population-based studies. The magnitude of this association did not differ significantly across categories of age, sex, race, history of hypertension, diabetes or socioeconomic status. However, as this study involved patients who were hospitalized with acute ischaemic stroke, the generalizability of the results to the general population is questionable. Proteinuria was not studied [86]. Excess kidney disease mortality was found in persons living within 2 km of industrial plants potentially releasing renal toxicants in Runcorn, UK: the standardized mortality ratio in males was 131 (95% CI 90–185) and in females 161 (95% CI 118–214) compared with a reference population living at 2.01–7.5 km [87].

PM AND CKD: EPIDEMIOLOGIC STUDIES

There are many studies showing association with various PM and CKD. A weak acceleration in the progression of albuminuria was observed during chronic exposure to PM_{10} in Multi-Ethnic Study of Atherosclerosis cohort [88]. In China, long-term exposure to $PM_{2.5}$ was associated with an increased risk of membranous nephropathy in a nonlinear pattern in 71 151 native kidney biopsy samples from 938 hospitals in 282 cities. During the study period, $PM_{2.5}$ exposure varied from 6 to 114 μg/m^3 (mean 52.6 μg/m^3) among the 282 cities. Each 10 μg/m^3 increase in $PM_{2.5}$ concentration was associated with 14% higher odds of a patient developing membranous nephropathy (OR = 1.14, 95% CI 1.10–1.18) in regions with $PM_{2.5}$ levels >70 μg/m^3, but the effect size in regions with $PM_{2.5}$ <60 μg/m^3 was greatly attenuated [89].

Another longitudinal observational cohort study that enrolled 2 482 487 US veterans demonstrated the association of $PM_{2.5}$ concentrations with higher risk of incident CKD and progression to ESRD [90]. One-year $PM_{2.5}$ exposure was associated with a lower eGFR among older men [91]. Among 21 656 Taiwanese adults, individual exposures to PM_{10}, coarse particles (PM_{coarse}) or $PM_{2.5}$ were related to renal function. An IQR increase in PM_{10} (5.83 μg/m^3) was negatively associated with eGFR by –0.69 (95% CI –0.89 to –0.48) mL/min/1.73 m^2 and positively associated with the prevalence of CKD with adjusted OR = 1.15 (95% CI 1.07–1.23). An IQR increase in PM_{coarse} (6.59 μg/m^3) was significantly associated with lower eGFR by –1.07 (95% CI –1.32 to –0.81) mL/min/1.73 m^2 and with CKD with OR = 1.26 (95% CI 1.15–1.38). In contrast, neither outcome was significantly associated with $PM_{2.5}$. Stratified analyses indicated that associations of CKD with both PM_{10} and PM_{coarse} were limited to participants <65 years of age and were stronger in (for PM_{10}) or limited to (PM_{coarse}) women. Associations also appeared to be stronger in those without hypertension than in those with hypertension, and in normal versus overweight participants [19].

In a recent cohort study, Bowe *et al.* [92] investigated the associations regarding coarse PM, NO_2 and CO with the risk of kidney disease. The authors evaluated the association between PM_{10}, NO_2 and CO concentrations and risk of incident eGFR of <60 mL/min/1.73 m^2, incident CKD, eGFR decline of ≥30% and ESRD. Participants were followed-up over a median of 8.52 years (IQR: 8.05–8.80). This study is one of the biggest, involving 2 010 398 participants. Among those individuals, the median concentration for PM_{10} was 20.45 μg/m^3 (IQR: 14.64–24.81), NO_2 was 14.54 parts per billion (9.69–17.91) and CO was 0.51 parts per million (0.40–0.64). An increased risk of eGFR <60 mL/min/1.73 m^2 was associated with an IQR increase in concentrations of PM_{10} [hazard ratio (HR) = 1.07, 95% CI 1.06–1.08], NO_2 (HR = 1.09, 95% CI 1.08–1.10) and CO (HR = 1.09, 95% CI 1.08–1.10). An increased risk of incident CKD was associated with an IQR increase in concentrations of PM_{10} (HR = 1.07, 95% CI 1.05–1.08), NO_2 (HR = 1.09, 95% CI 1.08–1.11) and CO (HR = 1.10, 95% CI 1.08–1.11). An increased risk of an eGFR decline of ≥30% was associated with an IQR increase in concentrations of PM_{10} (1.08, 95% CI 1.07–1.09), NO_2 (1.12, 95% CI 1.10–1.13) and CO (1.09, 95% CI 1.08–1.10). An increased risk of ESRD was associated with an IQR increase in concentrations of PM_{10} (1.09, 95% CI 1.06–1.12) and NO_2 (1.09, 95% CI 1.06–1.12). This study, which has a high statistical power, showed that higher concentrations of PM_{10}, NO_2 and CO are associated with increased risk of incident CKD, eGFR decline and ESRD [92].

AIR POLLUTION AND BP

Air pollution has been associated with increased cardiovascular morbidity and mortality in numerous epidemiological studies. One of the proposed mechanisms involves increased BP, which is a risk factor for the development of CKD [93]. Large population studies showed that higher PM levels are associated with higher BP levels, even based on one BP measurement [94–99]. Data from the Nurses' Health Study revealed that exposure to PM_{10} was associated with a slight increased risk of incident self-reported hypertension (PM_{10}, HR 1.02, 95% CI 1.00–1.04) [100]. Similar findings were also observed in a Taiwanese study, which found that long-term exposure to $PM_{2.5}$ was associated with increased risk of hypertension [101]. In another study, among 24 845 adults in Northeastern China, long-term exposure to air pollution was associated with increased odds of hypertension and more strongly with prehypertension [102]. Additionally, a recent systematic review and meta-analysis reported a positive association between ambient air pollution and elevated odds of hypertension [95, 103–108].

Apart from these studies, a very recent meta-analysis searched for the global association between ambient air pollution and BP. Seven international and Chinese databases encompassing 0.7 million participants from 16 countries were searched for studies examining the associations of $PM_{2.5}$, $PM_{2.5–10}$ or PM_{10} and gaseous (SO_2, NO_2, NO_x, O_3, CO) air pollutants with hypertension or BP. The overall meta-analysis showed significant associations of long-term exposures to $PM_{2.5}$ with hypertension (OR = 1.05), and of PM_{10}, $PM_{2.5}$ and NO_2 with diastolic BP (b-values: 0.47–0.86 mmHg). In addition, short-term exposures to four (PM_{10}, $PM_{2.5}$, SO_2, NO_2), two ($PM_{2.5}$ and SO_2) and four air pollutants (PM_{10}, $PM_{2.5}$, SO_2 and NO_2) were significantly associated with hypertension (ORs = 1.05–1.10), systolic BP (b-values: 0.53–0.75 mmHg) and diastolic BP (b-values: 0.15–0.64 mmHg), respectively. Stratified analyses showed a generally stronger relationship among men, Asians, North Americans and areas with higher air pollutant levels [103]. Additional studies have observed that not only single BP measurements but repeated BP measurements are also related to PM levels [106, 109–111].

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An analysis of the association of exposure to PM_{10} (average concentration $23.5 \pm 13.6 \mu g/m^3$) with ambulatory BP and with sodium excretion in 359 adults disclosed that after controlling for potential confounders, a 10 $\mu g/m^3$ increase in PM_{10} levels was positively associated with nighttime systolic BP, nighttime diastolic BP and negatively associated with nocturnal systolic BP dipping and daytime urinary sodium excretion, but not with nighttime sodium excretion. The effect sizes per 10 $\mu g/m^3$ of PM_{10} were in the order of 1.0 mmHg for nighttime systolic BP and 0.5 mmHg for nighttime diastolic BP. The associations of short-term increase in PM_{10} with higher nighttime BP and blunted systolic BP dipping were preceded by associations with reduced ability of the kidney to excrete sodium during daytime. The authors suggested that the underlying mechanism linking air pollution to increased cardiovascular risk may include disturbed circadian rhythms of renal sodium handling and BP [112]. Smaller studies (48 healthy vehicular traffic controllers and 10 patients with impaired lung function) did not find any association between air pollution and ambulatory BP [113, 114].

Air pollution has also been associated with BP in children. A study of Chinese children aged 5–17 years found a positive association between short-term (2 years) exposure to ambient air pollution and elevated BP [115]. The interaction between exposure to pet ownership and air pollutants on hypertension was studied in 9354 Chinese children (aged 5–17 years) from 24 elementary and middle schools during 2012–13. Four-year average concentrations of PM_{10}, SO_2, NO_2 and O_3 were collected from 2009 to 2012. Hypertension was defined as average diastolic or systolic BP (three measurements) in the 95th percentile or higher based on height, age and sex. Children not exposed to pets exhibited consistently stronger effects of air pollution than those exposed to pets. The highest ORs per 30.6 mg/m^3 increase in PM_{10} were 1.79 (95% CI 1.29–2.50) in children without current pet exposure compared with 1.24 (95% CI 0.85–1.82) in children with current pet exposure. As for BP, only O_3 had an interaction for all exposure to pet ownership and showed lower BP in children exposed to pets. The increases in mean diastolic BP per 46.3 mg/m^3 increase in O_3 were 0.60 mmHg (95% CI 0.21–0.48) in children without pet exposure *in utero* compared with 0.34 mmHg (95% CI 0.21–0.48) in their counterparts. When stratified by age, pet exposure was more protective among younger children. This suggests that pet ownership reduces susceptibility to the health effects of pollutants [17].

However, there are also conflicting findings. For instance, a meta-analysis that examined the association between long-term exposure to air pollution and arterial BP in the European Study of Cohorts for Air Pollution Effects ($n = 164\,484$) revealed that NO_2 exposure was associated with a weak inverse relationship with systolic BP (0.29; 95% CI −0.70 to 0.12) among individuals not taking BP-lowering medication [116]. There are also some studies that found either no association [113, 117] or a negative association [118] of PM with BP. It should be noted that these negative studies are smaller in number and a large body of evidence still suggests a positive correlation between air pollution and hypertension.

AIR POLLUTION AND DIABETES

Diabetes is an ever-increasing worldwide health problem. Systematic reviews, meta-analyses and epidemiological studies confirm that exposure to air pollution may be associated with the incidence or prevalence of DM [119–124]. Several cohort studies also showed greater T2DM risk with exposure to higher levels of NO [125, 126] and $PM_{2.5}$ [127, 128].

The effect of long-term exposure to ambient PM on the prevalence of T2DM and hypertension was explored in Iranian adults grouped by PM_{10} concentration $<100\,\mu g/m^3$ (5-year average $83.95 \pm 7.81\,\mu g/m^3$) or $>100\,\mu g/m^3$ (5-year average $120.15 \pm 6.81\,\mu g/m^3$). The prevalence of T2DM (13.8% versus 10.7%, $P = 0.01$; OR = 1.32, 95% CI 1.03–1.69) and hypertension (15.7 versus 11.9%, $P = 0.005$; OR = 1.55, 95% CI 1.20–1.99) was higher in the city with higher PM_{10} exposure [129]. The association between long-term exposure to PM, NO_x and O_3 and baseline prevalence and incidence of T2DM was also studied in a large administrative cohort in Rome, Italy. A total of 1 425 580 subjects aged 35+ years in January 2008 were assessed and followed for 6 years. A positive association was found between NO_x exposures and prevalence of diabetes with ORs up to 1.010 (95% CI 1.002–1.017) and 1.015 (95% CI 1.009–1.021) for NO_2 and NO_x, respectively, per 10 $\mu g/m^3$ and 20 $\mu g/m^3$. They also found some evidence of an association between NO_x and O_3 and incidence of diabetes with HRs of 1.011 (95% CI 1.003–1.019) and 1.015 (95% CI 1.002–1.027) per 20 and 10 $\mu g/m^3$ increases, respectively. The association with O_3 with incident diabetes was stronger in women than in men and among those aged <50 years [6]. However, no association was found between PM_{10}, $PM_{2.5}$ or $PM_{2.5–10}$, and diabetes. In the Netherlands, long-term exposure to NO_2 was associated with prevalence of diabetes (OR = 1.07, 95% CI 1.05–1.09 per IQR increases) after adjustment for individual confounders such as body mass index (BMI) and physical activity [130].

In a very large-scale prospective study involving 1 729 108 participants who were followed-up for a median of 8.5 years, the relationship between $PM_{2.5}$ and the risk of incident diabetes was investigated. All models were adjusted for age, race, sex, eGFR, systolic BP, hyperlipidaemia, chronic lung disease, CVD, cancer, BMI, smoking status, use of an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker and other covariates. In adjusted models, a 10 $\mu g/m^3$ increase in $PM_{2.5}$ was associated with increased risk of diabetes (HR = 1.15, 95% CI 1.08–1.22). The authors concluded that there is a significant association between increased $PM_{2.5}$ exposure and the risk of diabetes with variable geographical distribution. More importantly, the risk is significant at concentrations below those recommended by regulatory agencies. This suggests that even a low concentration of air pollution might be unsafe, and adverse effects of air pollution become obvious at relatively low concentrations below those currently considered as safe by regulatory agencies [131]. In 429 overweight and obese African American and Latino Los Angeles children, both NO_2 and $PM_{2.5}$ were associated with higher fasting glycaemia and insulin, lower insulin sensitivity and higher insulin secretion. Specifically, each SD increase in NO_2 and $PM_{2.5}$ exposure was associated with 22.8% ($P < 0.001$) and 24.7% ($P < 0.001$) higher fasting insulin, respectively. At the same time, each SD increase in NO_2 and $PM_{2.5}$ exposure was associated with a 1.6% ($P < 0.001$) and 1.6% ($P < 0.001$) higher fasting glucose, respectively. HOMA-IR was 25.1% ($P < 0.001$) and 26.9% ($P < 0.001$) higher and insulin sensitivity 8.5% ($P = 0.03$) and 11.2% ($P = 0.003$) lower for each SD increase in NO_2 and $PM_{2.5}$ exposure. Regarding adiposity estimates, only elevated annual exposure to $PM_{2.5}$ was associated with a higher BMI z-score ($\beta = 0.05$; $P = 0.04$). Each SD increase in non-freeway NO_x exposure was related to a 12.1% higher fasting insulin ($P < 0.001$), 0.7% higher fasting glucose ($P = 0.047$), 12.9% higher HOMA-IR ($P < 0.001$) and 6.9% lower insulin sensitivity ($P = 0.02$) [132]. In a large American cohort (Cancer Prevention Study-II participants), a strong effect of ozone on diabetes-related mortality was found (HR = 1.16, 95%

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CI 1.07–1.26 per fixed increment of 10 parts per billion, equal to 20 μg/m^3 O_3) [133]. Rats exposed to realistic concentrations of ozone (0.8 parts per million = 1.69 μg/m^3) developed insulin resistance induced by c-Jun N-terminal kinase activation that disrupted insulin signalling in skeletal muscles, suggesting a cause-and-effect relationship between ozone and insulin resistance [134]. The association of long-term residential exposure to $PM_{2.5}$ with the prevalence and incidence of T2DM was studied in 61 447 elderly Hong Kong residents enrolled in 1998–2001, following participants without DM at baseline to 31 December 2010 to ascertain the first hospital admissions for T2DM. Over a mean follow-up of 9.8 years, 806 incident cases of T2DM occurred. After adjusting for potential confounders, the OR for every IQR (3.2 μg/m^3) increase of $PM_{2.5}$ concentration was 1.06 (95% CI 1.01–1.11) for prevalent DM, while the corresponding HR was 1.15 (95% CI 1.05–1.25) for incident T2DM [135]. These findings were in accordance with prior finding regarding $PM_{2.5}$ and DM [136, 137] and with prospective cohort studies that examined the effect of long-term $PM_{2.5}$ exposure on T2DM incidence [125, 127, 128].

Although all these findings suggest a strong relationship between air pollution and DM, some conflicting findings exist. Exposure to SO_2 and PM_{10} was significantly related to the prevalence of T2DM in women, but not in men, suggesting gender differences [122]. Other prospective cohort studies also low in numbers failed to observe statistically significant associations between long-term $PM_{2.5}$ exposure and incident DM [126, 138]. In the Framingham Offspring cohort, participants living 64 m (25th percentile) from a major roadway had 0.28% (95% CI 0.05–0.51%) higher fasting plasma glucose than participants living 413 m (75th percentile) away, and the association appeared to be driven by participants who lived within 50 m from a major roadway. Higher exposures to 3- to 7-day moving averages of black carbon and NO_x were associated with higher plasma glucose, whereas the associations for ozone were negative, but there was no association with insulin resistance as evaluated by the HOMA-index [139].

Generally, in short-term exposure studies, exposure to air pollution was associated with higher levels of glucose, insulin or HOMA-IR [140, 141], whereas in longer term exposure, most of the positive associations were found with glucose but not with insulin or HOMA-IR [142, 143].

MESOAMERICAN NEPHROPATHY

MesoAmerican nephropathy (MeN) is another recently recognized endemic form of CKD. MeN can be considered as an environmental disease since it mostly affects people working in agricultural areas and with a tendency to be found in specific geographical locations, such as Nicaragua and El Salvador and other Central American countries. Additionally, global warming is thought to contribute to the increased incidence of MeN. Patients with MeN present with elevated creatinine levels, no hypertension and urine albumin levels are normal or of non-nephrotic range. The cause and pathogenesis of MeN are still not fully known; however, the repeated dehydration hypothesis is thought to play a role in the development of kidney disease. In this scenario, occupational heat exposure with repeated episodes of volume and salt depletion occurs during the disease process. Potential mechanisms include the development of hyperosmolarity with the activation of the aldose reductase–fructokinase pathway in the proximal tubule leading to local injury and inflammation, and the possibility that renal injury may be the consequence of repeated uricosuria and urate crystal formation as a consequence of both increased generation and urinary concentration, similar to a chronic tumour lysis syndrome. The epidemic is postulated to be increasing due to the effects of global warming. The renal morphology shows glomerulosclerosis of varying degrees, glomerular hypertrophy and signs of chronic glomerular ischaemia, together with mild to moderate chronic tubulointerstitial damage [131, 144, 145]. As MeN is considered as an environmental disease due to global warming, interventional studies to reduce heat stress may be of great importance. Indeed, a recent Phase 1 study showed that after an intervention with sugarcane workers, self-reported water consumption increased 25% and symptoms associated with heat stress and dehydration decreased [146]. It is now evident that new health problems with environmental and climate changes such as MeN will be of more interest in the near future, and preventive measures will be of the utmost importance for the prevention of a MeN epidemic.

BALKAN ENDEMIC NEPHROPATHY AND CHINESE HERB NEPHROPATHY

Balkan endemic nephropathy (BEN) is a kind of endemic nephropathy associated with upper urethelial cancer with specific geographical distribution along tributaries of the Danube River in Bosnia–Herzegovina, Croatia, Macedonia, Serbia, Bulgaria and Romania. Several hypotheses on the cause of BEN have been suggested such as mycotoxins, heavy metals, viruses and trace element insufficiencies. However, recent evidence suggests that chronic dietary exposure to aristolochic acid (AA)—a principal component of *Aristolochia clematitis*—which grows as a weed in the wheat fields of the endemic regions—is the cause of BEN [147].

BEN is described as a familial clustering and a slowly progressive kidney disease. The clinical signs and symptoms of BEN are non-specific and often remain latent for years and even decades. After an initial asymptomatic stage, patients suffer from weakness and lassitude, mild lumbar pain and pallor of the skin. At a later stage, anaemia is associated with a significant loss of renal function. Proteinuria of tubular type and specifically, β_2-microglobulinuria is observed. Histologically, BEN is characterized by tubular atrophy with extensive hypocellular fibrosis decreasing from the outer to the inner cortex of the kidney [148, 149]. Nowadays, BEN is considered as an environmental disease since environmental exposure to AA by BEN patients has been confirmed [150, 151]. Other evidence of BEN being an environmental disease comes from the fact that in the last few decades, exposure to AA has decreased due to the significant improvement in farming and milling practices, disabling and preventing the contamination of flour [152].

Chinese herb nephropathy (CHN) is another nephropathy that is also related to AA. This nephropathy appeared to be the dramatic consequence of a substitution of *Stephania tetrandra* by *Aristolochia fangchi*, which is rich in AA, because both herbs share the same common name and one can be used instead of the other in traditional Chinese medicine irrespective of their botanical classification. The true incidence of aristolochic acid nephropathy (AAN) is largely unknown and probably underestimated, as numerous ingredients known or suspected to contain AA are used in traditional medicine in China, Japan and India. CHN is characterized by a rapidly progressive interstitial nephritis, leading to ESRD and urothelial malignancy [153]. In most of the cases, urinary sediment was unremarkable, and dipstick analysis for albuminuria was negative. Macroscopically, the

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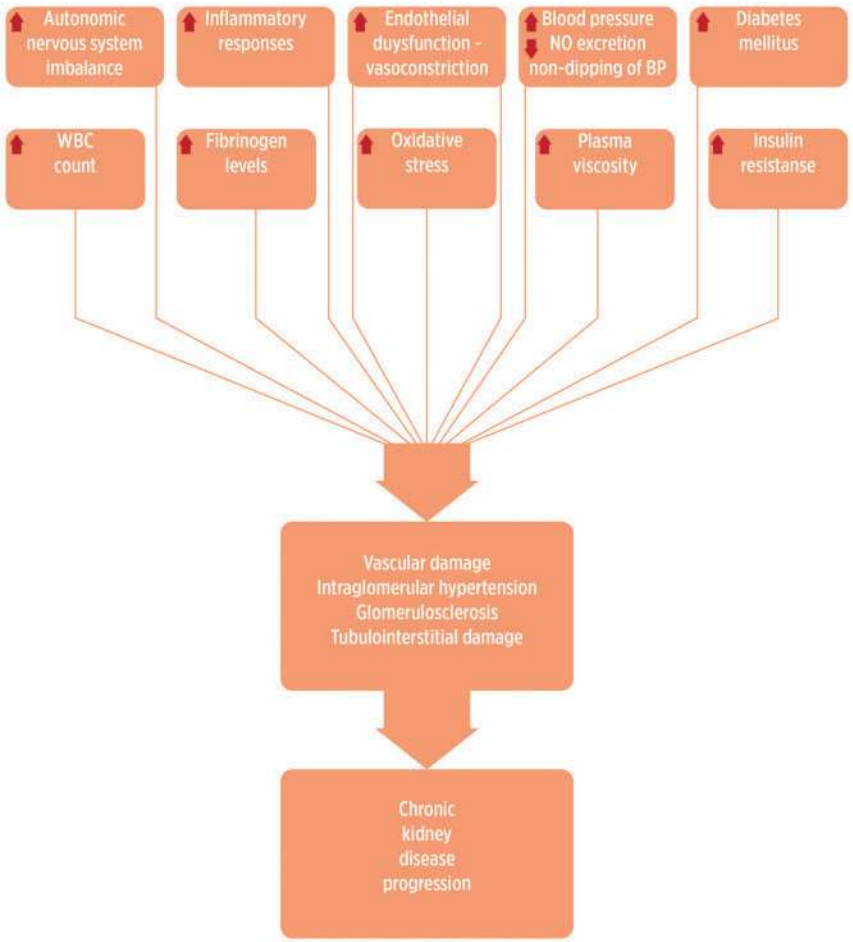


FIGURE 2: Pathogenic mechanisms of environmental pollutants leading to kidney damage. WBC, white blood cell.

kidneys were shrunk, asymmetric in about half of the cases with irregular outlines in one-third [154].

Microscopically, an extensive interstitial fibrosis with atrophy and loss of proximal tubules was the predominant lesion, which was mainly located in the superficial cortex and progressed towards the deep cortex. The glomeruli were relatively spared, although, in the later stage of the disease, they displayed a mild collapse of the capillaries and a wrinkling of the basement membrane [155]. Some suggest that BEN and CHN can be considered as two faces of Janus; however, recent evidence suggests that except in specific cases of acute tubular necrosis, no similarity could be found in the tubulointerstitial compartment with histological lesions observed in BEN and CHN [153]. However, as discussed above, both BEN and CHN can be considered as specific forms of nephropathy with specific geographical distribution.

PATHOGENESIS

Several mechanisms have been proposed to link exposure to air pollution with BP and kidney damage (Figure 2). Inhaled PM can trigger acute autonomic nervous system imbalance and systemic proinflammatory responses and can activate vascular endothelial dysfunction and arterial vasoconstriction [156, 157]. Impaired sodium excretion associated with PM [112] may also increase BP since an impaired capacity to excrete sodium during daytime would lead to a non-dipping pattern [158]. Long-term exposure to traffic pollution leads to vascular endothelial injury, systemic inflammation, atherosclerosis and microvascular changes [13, 159]. Evidence from Apo-E knockout mice and hyperlipidaemic rabbits indicates that long-term exposure to urban air pollution causes increased atherosclerosis with inflammatory characteristics [160, 161]. Moreover, in community-dwelling adults, traffic-related pollution is positively associated with carotid intima–media thickness [162, 163]. Mice chronically and continuously exposed to ambient levels of air pollution for 4 months developed significant more thickening (decreased lumen/wall ratios) in pulmonary and coronary arteries than mice exposed to filtered air in which PM_{10} and NO_2 were reduced by 50 and 75%, respectively. However, no evidence of influence of air pollution was detected in intra parenchymal renal arteries, which are well-known targets of systemic hypertension. One possibility is that pulmonary and cardiac effects were promoted by highly reactive substances present in the air, which may not reach sufficiently high levels in the renal circulation [164]. A recent experimental study reported that 16 weeks of exposure to concentrated ambient PM (average 13.3 $\mu g/m^3$) versus filtered air was positively associated with glomerulosclerosis in rat T1DM [165]. Air pollution has been associated with objective markers of cardiovascular risk, such as circulating white cell counts, plasma fibrinogen levels and decreased heart rate variability

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[166, 167]. PM has been reported to be associated with increased plasma viscosity [168], changes in blood characteristics [169] and indicators of abnormal autonomic function of the heart, including increased heart rate, decreased heart rate variability and increased cardiac arrhythmias [170].

Smoking is an independent risk factor for CKD and might result in intraglomerular hypertension, vascular damage or glomerulosclerosis via multiple complex interactions of non-haemodynamic (angiotensin II, transforming growth factor-β1, endothelin-1) and haemodynamic factors [171], and occupational exposures to Cd and Pb may affect the magnitude of kidney damage conferred by smoking [172].

An interaction with obesity has also been described. Concentrated PM and ozone exposures induced inflammation and oxidative stress in peri-renal adipose tissue in rats [173]. Ambient fine PM matter may exaggerate adipose inflammation, induce insulin resistance and oxidative stress, mitochondrial functions and gene expression in adipose tissue [174–176]. Furthermore, diabetes and obesity may enhance the associations between $PM_{2.5}$ and biomarkers of systemic inflammation [177], which in turn would lead to diminished insulin action [178]. Air pollution may also be associated with dysregulated release of peptides or proteins (adipokines) secreted by adipose tissue that regulates carbohydrate metabolism [174, 175, 179]. Mice exposed to $PM_{2.5}$ developed a non-alcoholic steatohepatitis-like phenotype of impaired hepatic glycogen storage, glucose intolerance and insulin resistance. Moreover, exposure to $PM_{2.5}$ activated inflammatory response pathways mediated through cJun N-terminal kinase, nuclear factor kappa B and toll-like receptor 4, and suppressed the insulin receptor substrate 1-mediated signalling [180].

RESEARCH NEEDS

The detrimental effects of air pollution on the kidney have just begun to be acknowledged. Various pollutants (toxic metals, PM, cigarette smoke and gases) may harm the kidney. However, it is not exactly known which pollutant by itself specifically causes damage or what type of damage.

Despite all accumulating data regarding pollution and its adverse health effects, there are still gaps that have to be recognized. This issue is very important since pollution is a global health threat that was responsible for an estimated 9 million premature deaths as well as for 268 million disability-adjusted life-years in 2015, which means great economic losses. The majority—71%—of the deaths attributed to pollution are caused by non-communicable diseases. To end neglect of pollution and advance prevention of pollution-related disease, commissions have been formed such as the Lancet Commission on Pollution and Health. The Commission identified substantial gaps in knowledge about pollution and noted that these gaps result in underestimation of pollution's contribution to the global burden of disease. To close these gaps and guide prevention, the Commission made research recommendations and proposed creation of a Global Observatory on Pollution and Health. It is of no doubt that successful pollution research needs transdisciplinary collaborations among exposure science, epidemiology, data science, engineering, health policy and economics. Studies must be stimulated regarding the burden of disease due to pollution in cities and countries that include options for pollution control and disease prevention, source apportionment studies that analyse the amounts of pollution, country-level analyses of the burden of disease and loss of human capital attributable to various pollutants and all pollution in specific countries. These studies are essential for identifying the pollution sources with the most significant effects on human health and for prioritizing interventions [181].

Besides these issues, specific mechanisms of kidney injury are not known. PM is a complex mixture of chemical compounds, the behaviour of which strongly depends on the atmospheric conditions. Furthermore, it is not clear regarding the mechanisms that lead to development of CKD. For example, $PM_{2.5}$ is associated both with DM and hypertension. However, it is not clear how much of the association of $PM_{2.5}$ to CKD development is attributed to DM and hypertension separately. These issues are important to plan preferential preventive measures according to dominant-associated mechanisms. Last but not the least, more needs to be known about the causal relationship between exposure to levels of environmental pollution and ultimately cause-specific mortality. Further studies are needed to explore which compound(s) within PM might be responsible for the observed associations and what manoeuvres may prevent or treat these adverse effects.

Prospective studies should explore whether improving air pollution, setting preventive measures for clean air and using green energy have beneficial effects on hard endpoints, such as reduction in the incidence of diabetes, hypertension and CKD. Additionally, more longitudinal studies in different parts of the world with different pollution levels are needed to directly compare the effects of air pollution on human health. Recent initiatives to restrict the use of diesel fuels for urban transportation in Europe offer the opportunity to design and fund such studies.

CONCLUSION

The classic view that air pollution is a risk factor for upper and lower respiratory airways is now challenged by evidence that air pollution may also impact other organs such as heart, vessels and kidneys. The inflammatory mediators induced by PM 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 [13]. However, there is also evidence of direct harm to the kidneys. The pathogenesis is still not fully understood. Studies are needed to characterize which type of air pollutant is primarily responsible for specific disease processes. It is necessary to raise awareness and recruit into action policy-makers, industry representatives establishing air quality standards, emissions controls and promoting the use of greener energy. More detailed longitudinal studies and also experimental designs are needed to demonstrate cause-and-effect relationships between specific air pollutants and kidney damage as well as the impact of manoeuvres that decrease air pollution.

CONFLICT OF INTEREST STATEMENT

None declared.

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