Fine Particulate Matter (PM_{2.5}) and Chronic Kidney Disease

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Abstract The impact of ambient particulate matter (PM) on public health has become a great global concern, which is especially prominent in developing countries. For health purposes, PM is typically defined by size, with the smaller particles having more health impacts. Particles with a diameter <2.5 μm are called PM_{2.5}. Initial research studies have focused on the impact of PM_{2.5} on respiratory and cardiovascular diseases; nevertheless, an increasing number of data suggested that PM_{2.5} may affect every organ system in the human body, and the kidney is of no exception. The kidney is vulnerable to particulate matter because most environmental toxins are concentrated by the kidney during filtration. According to the high morbidity and mortality related to chronic kidney disease, it is necessary to

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determine the effect of $PM_{2.5}$ on kidney disease and its mechanism that needs to be identified. To understand the current status of $PM_{2.5}$ in the atmosphere and their potential harmful kidney effects in different regions of the world this review article was prepared based on peer-reviewed scientific papers, scientific reports, and database from government organizations published after the year 1998. In this review, we focus on the worldwide epidemiological evidence linking $PM_{2.5}$ with chronic kidney disease and the effect of $PM_{2.5}$ on the chronic kidney disease (CKD) progression. At the same time, we also discuss the possible mechanisms of $PM_{2.5}$ exposure leading to kidney damage, in order to emphasize the contribution of $PM_{2.5}$ to kidney damage. A global database on $PM_{2.5}$ and kidney disease should be developed to provide new ideas for the prevention and treatment of kidney disease.

Keywords Air pollution · Chronic kidney disease · Environmental health · Fine particulate matter · Kidney injury · Urbanization

Abbreviations

CI	Confidence interval
CKD	Chronic kidney disease
HR	Hazard ratio
OR	Odds ratio
$PM_{2.5}$	Fine particulate matter
US EPA	US Environmental Protection Agency
WHO	World Health Organization

1 Introduction

Air pollution is becoming an ever more serious problem due to rapid urban industrialization and modernization (Chen 2007; Power et al. 2018). The World Health Organization (WHO) reports that 90% of the world's population suffers from the polluted environment, while almost seven million deaths from air pollution every year are caused by exposure to fine particles (an annual average $PM_{2.5}$ concentration above $10 \mu g/m^3$) (World Health Organization 2018a, b, c). Air pollutants are composed of gaseous substances, volatile substances, semi-volatile substances, and particulate matter (PM) mixture (Zanobetti et al. 2009). PMs with diameters that are generally $2.5 \mu m$ and smaller (e.g., $PM_{2.5}$) have been found to have a greater impact on human health (Brunekreef and Holgate 2002; Costa et al. 2014). More than half of the global population is exposed to very low quality air ($PM_{2.5}$ concentration $> 35 \mu g/m^3$) (World Development Indicators 2017). After enrichment in $PM_{2.5}$, the above substances can be deposited in the alveoli through respiration, and can even enter the blood circulation through the gas–blood barrier, thus reaching other tissues and organs, and causing damage to many systems such as respiration,

circulation, and so on (Martinelli et al. 2013; Dominici et al. 2006; Zhu et al. 2015; World Health Organization 2018a, b, c).

Over recent years, the epidemiological studies have shown an obvious upward trend in the incidence of CKD. The global prevalence rate is about 11–13% and the incidence of adult CKD in China is around 10.8% (Zhang et al. 2012; Hill et al. 2016). Thus, the prevention and treatment of CKD are becoming vital public health problems faced by the whole world. The presence of some comorbidities such as cardiovascular disease (CVD), hypertension, and diabetes is a potential predictor of the rapid aggravation from CKD to the end-stage renal disease (ESRD). The increasing number of studies have shown that air pollution may be a new risk factor for CKD (Tonelli et al. 2012; Blum et al. 2020; Lin et al. 2020; Wu et al. 2020).

As an important organ involved in hemofiltration and toxin excretion, kidneys can be easily affected by air pollutants in blood, which is why the effect of PM_{2.5} exposure on kidney disease should not be ignored. In this review, we summarized the epidemiological evidence of kidney disease being associated with PM_{2.5} exposure, as well as the findings about the effects of PM_{2.5} on the progression of kidney disease. At the same time, we also discussed the possible mechanisms of kidney injury caused by PM_{2.5} exposure. Based on these findings, we developed a hypothesis that exposure to PM_{2.5} and CKD is interrelated and there are many biological mechanisms involved in this process.

2 Method

We searched on the World Wide Web for combinations of keywords such as fine particulate matter pollution, PM_{2.5}, source apportionment of fine PM, constituents of PM_{2.5}, PM_{2.5}, and chronic kidney disease (CKD), PM_{2.5} and end-stage renal disease, PM_{2.5} and proteinuria in PubMed, Web of Science and Google Scholar. We selected 350 peer-reviewed articles published from 1998 to 2020 containing information on fine PM and related CKD. Among the articles searched, only articles that met the following criteria were included in the review: (1) Geographical location: Journals from all over the world were considered for the literature review; (2) Sample size: Sample size was not considered in the screening process; (3) Study methodology and statistical analysis: Research methods and the associated statistical analysis were not considered during the screening process; (4) Discussion of health effect: health effects using human or animal subjects. For global and country specific variations in fine PM, databases from government organizations like the National Clean Air Program (NCAP) in India, United States Environmental Protection Agency (US EPA) in the USA, European Environment Agency (EEA) for Europe, and World Health Organization (WHO) for global database were also screened (National Clean Air Programme 2019; European Environment Agency 2019; The U.S. Environmental Protection Agency 2012; World Health Organization 2018a, b, c). This review has selected 133 papers, of which PM_{2.5} and CKD related studies were distributed in the following countries (number of papers): China (34),

Taiwan, China (5), India (3), Japan (2), South Korea (1), East Asia (1), USA (20), Canada (5), South Africa (1), United Arab Emirates (1), New Zealand (2), France (3), the UK (4), The Netherlands (2), Germany (1), Spain (1), Denmark (1), Greece (1), Europe (3), Global (8).

3 The Compositions of PM_{2.5}

PM_{2.5} is one of the main components of air pollution and a major risk factor for the global disease burden (Cohen et al. 2017; Monn and Becker 1999). PM_{2.5} is not a simple pollutant, but a mixture of many substances (Harrison et al. 2004). It often derives from different outdoor emission sources and also has different chemical compositions. Chemical components include trace heavy metals (Cd, Cr, Cu, Mn, Ni, Pb, V, and Zn), organic compounds (volatile components and polycyclic aromatic hydrocarbons), carbonaceous aerosols (elemental carbon and organic carbon), inorganic mineral dust, sea salt and water-soluble inorganic ions (NO_3^- , SO_4^{2-} , Cl^- , F^- , NO_2^- , Br^- , NH_4^+ , Na^+ , K^+ , Ca^{2+} , Mg^{2+}) (Tao et al. 2016; Feng et al. 2006; Morakinyo et al. 2016). To be specific, PM_{2.5} can also originate from indoor sources. Particles of indoor origin include components derived from biological sources. Biological components include pollen, microorganisms (fungi, bacteria, and virus) and organic compounds derived from microorganisms (endotoxin, metabolites, toxins, and other microbial fragments), many of which are known allergens (Douwes et al. 2003). The biological aerosol accounts for 5–34% of the indoor pollutants which may trigger the immune response, inflammation response, infectious disease, cancer, and other toxicity (Pollution Issues 2006; Air Quality Direct 2007; Douwes et al. 2000; Fung and Hughson 2003; Samake et al. 2017; Srikanth et al. 2008).

The wide distribution of heavy metals (metallic elements that have a relatively high density compared to water) and carbonaceous aerosols in PM_{2.5} results in severe biological problems (Zhang et al. 2016; Gadi et al. 2019). The combustion elements such as EC (elemental carbon) and combustion sources such as biomass burning (potassium, as the main trace element) have been shown to be strongly associated with mortality, compared to other components (Achilleos et al. 2017). Typical fuel oils contain Iron (Fe), Nickel (Ni), Vanadium (V), and Zinc (Zn) and they are reflected in the composition of fly ash produced from fossil-fuel combustion (Vouk and Piver 1983). The exposure to zinc may interfere with the vasoconstriction and vasodilation that increase the risk of CVD and upregulate the expression of cytokines and stress proteins (Graff et al. 2004). The exposure to vanadium and chromium potentially has a major role in inducing oxidative DNA damage (Sørensen et al. 2005). Sulfate, ammonium, and nitrate carried in PM_{2.5}, usually found in coal combustion and vehicle emissions, are the main contributors to the haze in China, which can rapidly dissolve in the well-buffered lining fluids of the respiratory system (Harrison and Yin 2000). Polycyclic aromatic hydrocarbons (PAHs) in PM_{2.5} are formed by incomplete combustion and pyrolysis of organic

substances such as coal, oil, natural gas, and wood, which can lead to carcinogenesis and gene mutation (Bandowe et al. 2014; Lundstedt et al. 2007; Yunker et al. 2002). The US Environmental Protection Agency reports that the acute exposure to PAHs may be harmful to human health (The U.S. Environmental Protection Agency 2012). However, the PAH levels in the atmosphere in China are generally higher than those in foreign countries (Farmer et al. 2003; Lee et al. 2005; Sharma et al. 2007; Wang et al. 2015).

In addition, studies from many institutions in different countries have shown that the concentration, characteristics, and toxicity of PM_{2.5} vary with time, season, location, and climate (Bell et al. 2008; Kim et al. 2019; Lee et al. 2019). Fine PM levels and exceedance of national and international standards were several times higher in Asian countries (Mukherjee and Agrawal 2017). The monitoring data of PM_{2.5} in 45 major cities around the world in 2013 showed that, as a result of the rapid expansion of cities and rapid economic growth, the highly polluted megacities were concentrated in east-central China and the Indo-Gangetic Plain, among which the most polluted areas were Delhi in India, Cairo in Egypt, and Tianjin in China with the highest annual average PM_{2.5} concentration (89 to 143 $\mu\text{g}/\text{m}^3$) (Cheng et al. 2016). The satellite data evaluation model from 2004 to 2014 showed that the estimated value of 10-year average PM_{2.5} in the Beijing-Tianjin metropolitan region (including Beijing, Tianjin, and Hebei) was generally no less than 100 $\mu\text{g}/\text{m}^3$. The 10-year average concentration of PM_{2.5} in Sichuan Basin and Yangtze River Delta is generally no less than 85 $\mu\text{g}/\text{m}^3$, and it is no less than 55 $\mu\text{g}/\text{m}^3$ in Pearl River Delta (Ma et al. 2015). PM_{2.5} levels vary greatly in different regions of the same country. It is worth noting that a recent study found that China's average annual PM_{2.5} concentrations have dropped by 30% and 50% overall (Zhai et al. 2019). PM concentrations collected by the newest air quality monitoring network of the Ministry of Environmental Protection in 190 major cities in China between April 2014 and April 2015 show that the concentration of PM_{2.5} has a significant seasonal variation, which is highest in winter and lowest in summer (Zhang and Cao 2015). Although PM_{2.5} levels in China have gradually decreased in recent years, the incidence of CKD is still very high. The reason for this is probably that PM_{2.5} levels are still higher than the WHO guidelines recommend. In addition, the damage to the kidney caused by long-term exposure to PM_{2.5} is not transient, but usually has a sequelae effect.

Mounting evidence implicates the components of PM_{2.5} can translocate from the lungs into the circulation, are filtered and excreted by the kidneys. Although currently limited, data on the link between air pollution and kidney injury or disease in humans and in animal models are also now beginning to emerge.

4 PM_{2.5} and CKD: Epidemiological Studies

A large cohort study of 100,629 non-CKD Taiwanese residents aged 20 or over found that long-term exposure to environmental PM_{2.5} was associated with an increased risk of CKD developing. For every 10 $\mu\text{g}/\text{m}^3$ increase in PM_{2.5}

concentration, the risk of CKD increased by 6% (HR:1.06, 95% CI:1.02, 1.10) (Chan et al. 2018). Of note, in this study a single measurement of eGFR <60 mL/min/ 1.73 m² was used to define CKD while it might be due to acute kidney disease or other diseases; thus, some participants might have been misclassified as having CKD based on this criterion. Currently, a large number of studies have confirmed the epidemiological evidence of the relationship between renal disease and PM_{2.5} exposure. A large cohort of 2,482,737 veterans in the USA revealed that long-term exposure to PM_{2.5} was associated with an increased risk of CKD during a median follow-up of 8.52 years. For every 10 $\mu\text{g}/\text{m}^3$ increase in PM_{2.5} concentration, the risk of developing CKD increased by 27% (HR, 1.27; 95% CI, 1.17 to 1.38) (Bowe et al. 2017, 2018). However, the study included only US veterans who were mostly older, white men. Therefore, the findings might not be generalizable to other populations. Furthermore, a median exposure to PM_{2.5} of the air quality in the USA is 10–11 $\mu\text{g}/\text{m}^3$, which is better than most countries. A study of 71,151 native biopsies from 938 hospitals in China found that higher PM_{2.5} exposure was associated with the risk of membranous nephropathy. In areas with PM_{2.5} > 70 $\mu\text{g}/\text{m}^3$, each 10 $\mu\text{g}/\text{m}^3$ increase in PM_{2.5} concentration was associated with 14% higher odds for membranous nephropathy (odds ratio, 1.14; 95% CI, 1.10 to 1.18) (Xu et al. 2016). There were some limitations of this study. First, the study included only patients from whom renal biopsy samples were taken and not the general population. Furthermore, information on patient residence were limited to the city level, where levels of PM_{2.5} were generally higher than in other regions and might have led to an underestimation of the effect of PM_{2.5}. It is of great clinical significance to studying the dose–response relationship between PM_{2.5} and the development and progression of CKD across a wide range of exposure levels. Bowe and his colleagues recently quantitated the global burden of CKD attributable to ambient air pollution in 2016 and found that more than 30% of disability-adjusted life years of CKD were related to PM_{2.5} exposure globally (Bowe et al. 2019). The study used the Global Burden of Disease study data and provided a quantitative analysis of the global burden of CKD attributable to PM_{2.5}. Although its explanations and conclusions based on a raw analysis, the results provided an intuitive way to translate from the relative risk into attributable burden of CKD due to PM pollutants. Although its explanations and conclusions were based on raw analysis, the results provided an intuitive way to translate from the relative risk into attributable burden of CKD due to PM pollutants (Table 1).

There is a strong reason to believe that PM_{2.5} may be a novel environmental risk factor for CKD. Associations between long-term PM_{2.5} exposure and death were modified by many factors, such as other air pollutants like ozone and mercury (Lelieveld et al. 2019; Stojan et al. 2019), meteorological factors like temperature, resultant wind, relative humidity and barometric pressure, epidemiological and social factors like wealth gap between rich and poor (Kioumourtzoglou et al. 2016). However, in the same environment, some people are more likely than others to develop kidney disease. This may be due to susceptibility of the population.

Previous studies suggested that elderly people and children were especially susceptible to the harmful effects of PM_{2.5} exposure (Mehta et al. 2016; Bowe et al. 2017, 2018). These studies may be influenced by the aging of the population

Table 1 Summary of epidemiological studies on the association between fine particulate matter and chronic kidney disease

Study	Type of study	Study population	Study location	Health outcome
Long-Term Exposure to Air Pollution and Increased Risk of Membranous Nephropathy in China (Xu et al. 2016)	Cohort study	General population 2004–2014	China	Long-term exposure to high-level PM _{2.5} is associated with an increased risk of membranous nephropathy (MN)
Particulate Matter Air Pollution and the Risk of Incident CKD and Progression to ESRD (Bowe et al. 2018)	Cohort study	Veterans	U.S.	There is a significant correlation between the exposure to PM _{2.5} and the risk of CKD, ESRD and the declined eGFR
Long-Term Exposure to Ambient Fine Particulate Matter and Renal Function in Older Men: The Veterans Administration Normative Aging Study (Bowe et al. 2019)	Cross-sectional study	Veterans	U.S.	PM _{2.5} exposure was associated with declined eGFR in the elderly within 1 year
Residential proximity to major roadways and renal function (Lue et al. 2013)	Cohort study	Patients with confirmed acute ischemic stroke 1999–2004	U.S.	Living near main road in patients with acute ischemic stroke is associated with declined eGFR
Associations between Long-Term Particulate Matter Exposure and Adult Renal Function in the Taipei Metropolis (Yang et al. 2017)	Cross-sectional study	General population 2007–2009	Taiwan, China	Exposure to PM ₁₀ and PM _{coarse} , instead of PM _{2.5} or PM _{2.5} Absorbance is associated with increased risk of CKD and declined eGFR in adult residents of Taipei
Long-Term Exposure to Ambient Fine Particulate Matter and Chronic Kidney Disease: A Cohort Study (Chan et al. 2018)	Cohort study	General population 2001–2014	Taiwan, China	Long-term exposure to PM _{2.5} is associated with increased risk of CKD. Every 10 µg/m ³ increase in concentration of PM _{2.5} is associated with 6% increase in the risk of CKD

(continued)

Table 1 (continued)

Study	Type of study	Study population	Study location	Health outcome
County-level air quality and the prevalence of diagnosed chronic kidney disease in the US Medicare population (Bragg-Gresham et al. 2018)	Cross-sectional study	General population	U.S.	There is a positive correlation between concentration of PM _{2.5} and diagnosis of CKD in the county-level cities. When concentration of PM _{2.5} increases by 4 µg/m ³ , the adjusted prevalence ratios of diagnosed CKD was 1.03 (95%CI:1.02–1.05; $p < 0.001$)
Effects of long-term exposure to CO and PM _{2.5} on microalbuminuria in type 2 diabetes (Chin et al. 2018)	Cohort study	Patients with type 2 diabetes 2003–2012	Taiwan	Exposure to high-level CO and PM _{2.5} can increase albuminuria in patients with type 2 diabetes mellitus (T2DM)
Associations between Ambient Fine Particulate Levels and Disease Activity in Patients with Systemic Lupus Erythematosus (SLE) (Bernatsky et al. 2010)	Cohort study	Patients (women) with SLE 2000–2007	Canada (Montreal)	Short-term changes in air pollution may affect the disease activity of autoimmune rheumatic diseases. Level of PM _{2.5} is associated with anti-dsDNA and cell tube type
Heat and PAHs Emissions in Indoor Kitchen Air and Its Impact on Kidney Dysfunctions among Kitchen Workers in Lucknow, North India (Singh et al. 2016)	Cross-sectional study	Kitchen workers	North India (Lucknow)	Exposure to PM _{2.5} , VOC, and PAH from the indoor air and presence of urinary PAHs metabolites may lead to inflammation. Thus, it may lead to microalbuminuria in kitchen workers
Association of Cigarette Smoking with Albuminuria in the United States: The Third National Health and Nutrition Examination Survey (Hogan et al. 2007)	Cross-sectional study	General population	U.S.	Current smoking and passive smoking are associated with the presence of albuminuria in the general US population with hypertension

(continued)

Table 1 (continued)

Study	Type of study	Study population	Study location	Health outcome
High particulate matter 2.5 levels and ambient temperature are associated with acute lung edema in patients with nondialysis Stage 5 chronic kidney disease (Chiu et al. 2018)	Case-crossover study	Patients with stage 5 nondialysis chronic kidney disease	Taiwan, China	A high PM _{2.5} level was associated with an increased risk of acute lung edema
Associations between long-term ambient PM _{2.5} exposure and prevalence of chronic kidney disease in China: a national cross-sectional study (Huang et al. 2019)	Cross-sectional study	General population 2007–2010	China	There is a significant association between long-term PM _{2.5} exposure with broad concentration ranges and increased prevalence of chronic kidney disease in a representative general Chinese population
Estimates of the 2016 global burden of kidney disease attributable to ambient fine particulate matter air pollution (Bowe et al. 2019)	The global burden of disease (GBD) study	194 countries and territories	Global	The 2016 global burden of incident CKD attributable to PM _{2.5} was 6,950,514 (95% uncertainty interval: 5061533–8,914,745). The global toll of CKD attributable to ambient air pollution is significant and identify several endemic geographies where air pollution may be a significant driver of CKD burden. Air pollution may need to be considered in the discussion of the global epidemiology of CKD
Particulate Matter and Albuminuria, Glomerular Filtration Rate, and Incident CKD (Blum et al. 2020)	Cohort study	Participants from the atherosclerosis risk in communities cohort 1996–1998 through 2016	U.S.	Exposure to higher annual average PM _{2.5} concentrations was associated with a higher level of albuminuria and higher risk for incident CKD in a community-based cohort

(continued)

Table 1 (continued)

Study	Type of study	Study population	Study location	Health outcome
Air pollutants and subsequent risk of chronic kidney disease and end-stage renal disease: A population-based cohort study (Lin et al. 2020)	Cohort study	General population	Taiwan, China	The concentrations of air pollutant were classified into four levels based on quartile. Compared with Q1-level PM _{2.5} , exposure to the Q4 level was at a 1.74-fold risk of CKD (95% CI = 1.53–1.98) and 1.69-fold risk of ESRD (95% CI = 1.32–2.16). Exposure to particulate was observed to be associated with an increased risk of CKD and ESRD

MN membranous nephropathy, *CKD* chronic kidney disease, *ESRD* end-stage renal disease, *eGFR* estimated glomerular filtration rate, *T2DM* type 2 diabetes mellitus, *SLE* systemic lupus erythematosus, *VOC* volatile organic compound

in Europe and the USA and the mean age of onset of CKD (Risk factor for CKD: age 60 or older) (Inker et al. 2014). In fact, vascular endothelial dysfunction worsens with age, and the vascular endothelium is more sensitive to pollutants and more vulnerable to injury in older people. Also, children and infants are susceptible to harm from inhaling PM_{2.5} because they inhale more air per pound of body weight than do adults – they breathe faster, spend more time outdoors, and have smaller body sizes. In addition, children’s immature immune systems may cause them to be more susceptible to PM_{2.5} than healthy adults. Moreover, the gender differences may exist in the effect of PM_{2.5} exposure on CKD. A study of 47,204 Chinese adults aged 18 years or older found that every 10 µg/m³ increase in PM_{2.5} was positively associated with the prevalence of chronic kidney disease (odds ratio [OR] 1.33, 95% CI 1.25–1.41, *p* < 0.001). Sex-stratified analyses showed that risk in men (OR 1.42, 95% CI 1.29–1.57) was slightly higher than in women (1.26, 1.17–1.36) (Li et al. 2020). The above-mentioned analyses cannot be generalized. Susceptibility of population is also affected by differences in age and genetic factors in various regions of the world. Therefore, more global longitudinal studies are needed in the future to directly compare the effects of PM_{2.5} on CKD.

5 PM_{2.5} and CKD: Progression and Prevention

In addition to increasing risk of kidney disease, exposure to PM_{2.5} has also been associated with an increased risk of CKD progression. A prospective cohort study of 669 veterans in the Boston area from the Veterans Affairs Normative Aging Study

Institution revealed that every 2.1 $\mu\text{g}/\text{m}^3$ increase in the concentration of PM_{2.5} results in 1.73 m^2 decreases in eGFR (95%CI:2.99 to 0.76) and 0.60 $\text{mL}/\text{min}/1.73\text{m}^2$ decrease in renal function per year (95%CI:0.79 to 0.40). It should be emphasized that the exposure level of PM_{2.5} in the study population met the environmental air quality requirements of 13.5% in the USA (Standard for 13.0 $\mu\text{g}/\text{m}^3$). Thus, it can be speculated that the higher levels of PM_{2.5} exposure can significantly increase the rate of the renal dysfunction in the exposed patients (Mehta et al. 2016). Other studies have shown that for every 10 mg/m^3 increase of PM_{2.5} concentration, the risk of eGFR decline $\leq 30\%$ increases by 28% (HR, 1.28; 95% CI:1.18 to 1.39), and the risk of ESRD increases by 26% (HR, 1.26;95% CI:1.17 to 1.35) (Bowe et al. 2017, 2018). Road traffic emissions are one of the main sources of PM_{2.5}, which has extensive cyto- and genotoxic effects, which in turn can affect the physiology, development, and mortality of a broad subset of the species that encounter roads (Pérez et al. 2010; Leonard and Hochuli 2017). A study of 1,103 patients with acute ischemic stroke in the Boston-area between 1999 and 2004 showed that eGFR levels decreased in patients living closer to major roadway, indicating a decline in renal function. The eGFR levels of patients who live 50 m away from the main road are 3.9 $\text{mL}/\text{min}/1.73\text{m}^2$ lower than in those who live 1,000 m away (95%CI: 1.0–6.7; $P = 0.007$). The decrease of renal function in patients living 50 m away from the main road is equal to the decrease of natural physiological renal function with the increase of age by 4 years (Lue et al. 2013).

A cross-sectional study of 317 patients with acute pulmonary edema complicated with stage 5 nondialysis chronic nephropathy (CKD 5-ND) in Taiwan found that a high PM_{2.5} level was associated with an increased risk of acute lung edema in patients with CKD 5-ND. High ambient temperature in hot seasons and low ambient temperature in cold seasons were also associated with increased risk (Chiu et al. 2018). There is an approximate linear correlation between the relative changes of albuminuria over a one-year interval and the risk of CKD; and the presence of albuminuria may be a predictor of the CKD aggravation (Sumida et al. 2017). A study of 812 patients with T2DM in Taiwan found that the albumin-to-creatinine ratio (ACR) in patients with exposure to high-level PM_{2.5} increased 3.96 $\text{m g}/\text{g}$, while in patients with low-level it increased 3.17 mg/g , indicating that the exposure to higher levels of PM_{2.5} and CO can increase albuminuria in patients with T2DM (Chin et al. 2018). Another clinical cohort study of patients with SLE living on Montreal Island showed that the levels of PM_{2.5} exposure are associated with the anti-dsDNA and the tubular cell type, reflecting severe renal inflammation (Bernatsky et al. 2010). It has been shown that kitchen fumes contain high concentrations of PM_{2.5}. By comparing the levels of exposure to PM_{2.5}, VOC and PAH from the working environment and burden of these toxic substances on the body in 94 chefs and controls, cross-sectional study revealed that PM_{2.5} may result in the microalbuminuria in kitchen workers (Singh et al. 2016). Smoking is also an important source of indoor PM_{2.5}. A cross-sectional analysis of 15,179 participants in the third National Health and Nutrition Survey in the USA found that in passive smokers, who were grouped by a quartile of serum cotinine levels, the risk of microalbuminuria in highest group was 1.41 times higher than that in the lowest group (Hogan et al. 2007).

Although there is some evidence that CKD progression is associated with PM_{2.5} pollution, it is manifested in an increased risk of progression to ESRD, increase in albuminuria, decrease in eGFR levels, and the emergence of complications such as pulmonary edema. Current data were based on a few cohort studies and were limited to some countries, lacking globally large-scale and long-term cohort studies.

6 PM_{2.5} and CKD: Mechanisms

The toxic mechanisms underlying the relationship between PM_{2.5} and CKD still remain unclear. A large amount of researches from clinical and animal experiments have confirmed the association between exposure to PM_{2.5} and CVD (Combes and Franchineau 2019). Meanwhile, various risk factors of CVD, such as smoking, obesity, hypertension, and diabetes mellitus, are still the risk factors of CKD (Gansevoort et al. 2013; Parikh et al. 2006; Papademetriou et al. 2016). A current study shows that PM_{2.5} can easily enter the circulatory system through alveolar epithelial cells and can eventually damage the cardiovascular system, thereby causing damage to the kidneys (Milojevic et al. 2014). Therefore, we speculate that part of the pathogenic mechanism of the PM_{2.5}-related CKD may be similar to the PM_{2.5}-related CVD (Fig. 1).

Oxidative Stress Numerous studies have shown that the oxidative stress induced by PM_{2.5} has an important role in the PM_{2.5}-mediated toxicity (Li et al. 2008; Weichenthal et al. 2016; Crobeddu et al. 2017). iRHOM2(RHBDF2), a member of the rhomboid family with proteolytic activity, has been explored in the pathogenic mechanism of CKD (Liu et al. 2018; Herrlich and Kefaloyianni 2018). It has been observed that PM_{2.5} promotes the production of ROS and iRhom2 in mice exposed to PM_{2.5}, thus resulting in the blocking of Nrf2 signaling pathway, the activation of JNK MAPK signaling pathway and the damage of podocyte, and eventually in the chronic renal injury (Xu et al. 2018; Ge et al. 2018). It has also been observed that the production of ROS induced by PM_{2.5} inhibits the Nrf2 signaling pathway and the activity of downstream genes SOD1, Gclc and GSR in human embryonic stem cells. Meanwhile, N-acetylcysteine (NAC) can restore partial antioxidant stress by scavenging ROS (Jin et al. 2019). NOX4, which is a member of NADPH oxidase family, is considered as the main source of ROS production in the kidneys (Gorin et al. 2005; He et al. 2016). After the intratracheal exposure to the PM_{2.5}, the expression of NOX4 and the content of H₂O₂ in the kidneys (the mainly direct metabolite of NOX4) significantly increase while the expression of antioxidant enzyme SOD-1 significantly decreases in the BALB/c mice. Furthermore, the renin-angiotensin system (RAS) in mice can be activated by the PM_{2.5} exposure. It has been reported that Ang-II is one of the most important stimuli to promote the oxidative stress, showing that the renal damage by PM_{2.5} may be induced via activation of RAS, which in turn induces oxidative stress and inflammation (Zhang et al. 2018; Chabrashvili et al. 2003).

Fig. 1 Plausible biological pathways linking fine particulate matter exposure with chronic kidney disease (CKD). The 6 generalized intermediary pathways and the subsequent specific biological responses that could be capable of instigating CKD events are shown. *eGFR* estimated glomerular filtration rate, *PI3K* phosphatidylinositol-3-kinase, *Akt* protein kinase B, *mTOR* mammalian target of rapamycin, *FGF* fibroblast growth factor, *FGFRs* fibroblast growth factor receptors, *MAPK* mitogen-activated protein kinase, *VEGF* vascular endothelial growth factor, *JAK* Janus kinase, *STATs* spread through air spaces, *Bax* Bcl-2 associated X, *Bcl-2* B cell lymphoma-2, *LC3* light chain 3, *TNFRs* tumor necrosis factor receptors, *TACE* TNF- α converting enzyme, *NF- κ B* nuclear factor kappa-B, *I κ B* inhibitor of NF- κ B, *IL-18* Interleukin-18, *COX2* cyclooxygenase 2, *ROS* reactive oxygen species, *iRhom2* inactive rhomboid protein 2, *Ang II* angiotensin II, *SOD* seminal plasma enzymes, *GCLC* glutamate-cysteine ligase catalytic, *GSR* glutathione reductase, *TAC* total antioxidant capacity, *GSH* glutathione, *MDA* malondialdehyde, *Nrf2* nuclear factor-erythroid 2-related factor 2, *RAGE* advanced glycation end, *IFN* interferon, *PLA2R* phospholipase A2 receptor

Inflammatory Response As mentioned above, PM_{2.5} has an important role in the unhealthy effect induced by the inflammatory response (Bekki et al. 2016; Bo et al. 2016). In the type 1 DM rat model induced by STZ, the levels of the cytokines involved in the inflammatory response including IL-6 and fibrinogen significantly increase after exposure to low concentrations (close to the current air quality standards) and low-enriched PM_{2.5}. Also, the histopathologic studies show that exposure to PM_{2.5} results in glomerulosclerosis and proximal tubular injury (Yan et al. 2014). PM_{2.5} promotes the activation of inflammatory associated TNF- α invertase/TNF- α receptor (TACE/TNFRs) signaling pathway and α /nuclear factor κ B (I κ B α /NF- κ B) signaling pathways in the renal cell lines (including HEK-293, MPC5 and HK-2) from the PM_{2.5} exposed mice (Ge et al. 2018).

Vascular Injury PM_{2.5} may induce endothelial injury through systemic inflammation, oxidative stress, and atherosclerosis, resulting in glomerulosclerosis, tubular atrophy, and tubulointerstitial fibrosis, and eventually chronic kidney diseases (Rui et al. 2016; Bo et al. 2016; Liang et al. 2019). Previous studies have shown that the diesel exhaust particulate (DEP) is the main source of PM_{2.5} and ultrafine particles found in cities (Cho et al. 2004; Pérez et al. 2008). Exposure to DEP aggravates renal vascular injury in the CKD rats induced by adenine, resulting in tubular dilatation, tubular necrosis, tubular type, and decreased renal blood flow (RBF) (Nemmar et al. 2009). AngII can induce endothelial injury by activating NADPH oxidase system (Niazi et al. 2017). After intratracheal instillation of PM_{2.5}, increasing levels of circulating AngII are observed in rats, which may be due to the activation of the branches of IRE1 α /XBP1s on the unfolded protein-reactive (UPR) (Xu et al. 2017).

Immune Response Previous studies have shown that environmental pollution may break the immune balance and increase the incidence of chronic diseases (Lee and Lawrence 2018). Some of the autoimmune responses have an important role in the occurrence of a series of nephritis (Clynes et al. 1998; Chang et al. 2011; Lau et al. 2010). Idiopathic membranous nephropathy is also an autoimmune disease characterized by the formation of circulating autoantibodies against secretory phospholipase A2 receptor (PLA2R) (Beck Jr. et al. 2009). Existing studies have shown that exposure to fine particles can promote the formation of autoantibodies and immune complexes (Brown et al. 2003, 2004; Pfau et al. 2004). The deposition of IgG immune complexes has been found in the kidneys of C57Bl/6 mice after exposure to fine particles, while the presence of abnormal glomeruli and tubules suggested the occurrence of glomerulonephritis (Pfau et al. 2008).

Cell Apoptosis and Autophagy Cell apoptosis and autophagy can be induced by PM_{2.5}-exposure (Wang et al. 2017a, b; Ding et al. 2017). The activation of PI3K-Akt/mTOR signaling pathway, FGF/FGFR/MAPK/VEGF signaling pathway, and JAK-STAT signaling pathway can be promoted by PM_{2.5}, which induces the cell apoptosis and autophagy (Zheng et al. 2017; Wang et al. 2016). A recent study has revealed that the sections of renal tissue from the C57BL/6 mice and the 293 T cells exposed to the Arsenic(As) or SO₂ show severe diffuse sclerosing glomerulonephritis. Meanwhile, it has also been found the key members of Caspase family, and the expression of Bax, the indicator of Caspase Pathway, are up-regulated in the 293 T cells, while the expression of Bcl-2 is down-regulated (Ji et al. 2019). It has been reported that a large amount of Cd²⁺ accumulation is found in the kidneys of residents living near industrial areas. Cd²⁺ can significantly reduce the survival rate of renal tubular epithelial cells (HK2) and have a key role in renal injury (Kuang 2018; Thomaidis et al. 2003). The increase of LC3-II and the decrease of p62, which are both markers of cell autophagy, can be observed in the renal tubular ductal epithelial cells (NRK-52E) from the rats exposed to Cadmium for 1 h. This suggests that the short-term exposure to cadmium can rapidly activate cell autophagy and thereby counteract the damage (Lee et al. 2017).

Omics Currently, omics has been widely used in clinical research and it has become a new tool for exploration of the biomarkers in renal disease. After the intratracheal exposure to PM_{2.5}, a metabolomics test of the urine shows a significant increase in levels of cresol sulfate and p-cresol glucuronide of the uremic toxins from the exposed rats. Both of these are derivatives of p-cresol in phenylalanine metabolites. Furthermore, the levels of glucuronide acidification of acetaminophen decrease, indicating that PM_{2.5} inhibits the kidney detoxification (Zhang et al. 2017). A global analysis of the circulating miRNA genome from people exposed to traffic-related air pollutants has shown that the expression of miR-148a-3p, which is highly expressed in the kidneys, increases after the exposure to higher levels of pollution. Also, the levels of miR-148b-3p in serum have been described as one of the potential non-invasive biomarkers for the diagnosis of IgA nephropathy (Krauskopf et al. 2018).

Podocyte Injury Recent studies have revealed that exposure to PM_{2.5} can mediate the podocyte injury through a variety of mechanisms, which in turn lead to renal injury (Santana et al. 2016; Yang et al. 2018). As mentioned earlier, the PAHs in PM_{2.5} can lead to carcinogenesis and mutagenicity, and the content of PAHs in the air of China is generally higher compared to foreign countries (Bandowe et al. 2014; Lundstedt et al. 2007; Yunker et al. 2002). The highest content of PAHs of PM_{2.5} was benzo fluoranthene (BbF) observed in the atmosphere in Zhengzhou City (Wang et al. 2017a, b). Based on this, we established a mouse model of co-culture glomerular podocytes and alveolar epithelial cells, and found that the expression of Nephrit protein and Podocin protein decreased and the expression of Desmin protein increased with the increase of the concentration and exposure time to BbF ($P < 0.05$), indicating increasing of podocyte injury. Also, the number of autophagy corpuscles decreased and the expression of Beclin-1 protein and LC3B protein decreased ($P < 0.05$) with the increase of the concentration and time of the exposure, suggesting the decreased levels of autophagy in podocytes. Therefore, we speculate that the inhibition of autophagy pathway may be one of the mechanisms underlying glomerular podocyte injury induced by PAHs of PM_{2.5}, which may lead to renal disease. The specific mechanism needs to be further clarified (Zhang et al. 2020).

Toxic exploration of PM_{2.5} is an extremely important issue. Oxidative stress, inflammation, endothelial injury, apoptosis, autophagy, and immune response are the main potential mechanisms in PM_{2.5}-induced kidney disease progression. The research findings of in vitro cell and in vivo animal investigations have provided vital insights into the mechanisms of PM_{2.5} exposure in kidney disease progression. Better understandings of the mechanisms associated with PM_{2.5} will allow the development of new strategies to decrease the harmful effects of PM_{2.5} on the pathogenesis of various diseases. Despite all accumulating data regarding pollution and its adverse health effects, there are still gaps that have to be recognized. The pathogenesis is still not fully understood. These studies were almost based on animal models. In the future, we need to characterize which components of PM_{2.5} are primarily responsible for specific disease processes. Moreover, human subject researches need to be more developed (Table 2).

Table 2 Summary of in vivo and in vitro studies on kidney effects of PM_{2.5}

Study	Study type	Test subjects/cells	PM _{2.5} dosage	Mechanism of toxicology
<i>Oxidative stress</i>				
Activated iRhom2 drives prolonged PM _{2.5} exposure-triggered renal injury in Nrf2-defective mice (Xu et al. 2018)	In vivo and in vitro	C57BL/6 mice and HEK-293 cell and mouse podocyte	115 ± 1.5 lg/m ³ for 6 h/day, 5 times/week (mice) and 0, 50, 100, and 200 lg/mL PM _{2.5} mass for 24 h (cell)	Long-term PM _{2.5} exposure causes chronic renal injury by up-regulation of iRhom2/TACE/TNF-α axis in kidney-resident macrophages
N-acetylcysteine attenuates PM-induced apoptosis by ROS-mediated Nrf2 pathway in human embryonic stem cell (Jin et al. 2019)	In vitro	Human embryonic stem cells (hESCs)	0, 1.5, 6, and 24 µg/mL of PM _{2.5} in corresponding media	PM _{2.5} present strong toxic to hESCs, and induce cell apoptosis by ROS-mediated signaling pathway. Interestingly, NAC can decrease intracellular ROS level and protect hESCs against PM _{2.5} -induced cell apoptosis partially through activation of the Nrf2 pathway
The Kidney Injury Induced by Short-Term PM Exposure and the Prophylactic Treatment of Essential Oils in BALB/c Mice (Zhang et al. 2018)	In vivo	BALB/c mice	Intratracheal instillation of 50 µL aqueous PM _{2.5} suspensions (0.5 mg PM _{2.5} in sterile saline) on day 0 and day 2	Short-term exposure to PM _{2.5} induced acute kidney damage associated with oxidative stress and inflammatory response. The activation of RAS might be the pivotal upstream of oxidative stress and inflammatory response induced by PM _{2.5} exposure
<i>Inflammation</i>				
PM _{2.5} collected in China causes inflammatory and oxidative stress responses in macrophages through the multiple pathways (Bekki et al. 2016)	In vitro	Mouse macrophage cell line RAW264.7 and wild-type, (TLR2 ^{-/-}), (TLR4 ^{-/-}), (MyD88 ^{-/-}) mice on a BALB/c	Exposed for 3 h to PM _{2.5} at the dose of 30 g/mL	Future study will be required to investigate the role of macrophages and the contribution of the endotoxin pathway and oxidative stress on the exacerbation of the Th2 immune reaction by exposure to PM _{2.5}

(continued)

Table 2 (continued)

Study	Study type	Test subjects/cells	PM _{2.5} dosage	Mechanism of toxicology
Subchronic effects of inhaled ambient particulate matter on glucose homeostasis and target organ damage in a type 1 diabetic rat model (Yan et al. 2014)	In vivo	Sprague–Dawley (SD) rats (BioLasco Taiwan)	The average concentrations (mean [SD]) of PM _{2.5} were 13.30 [8.65]μg/m3, for 24 h/day, 7 days/week, for a total of 16 weeks (rats)	PM caused focal myocarditis, aortic medial thickness, advanced glomerulosclerosis, and accentuation of tubular damage of the kidney. PM exposure might induce the macro- and micro-vascular complications in DM through chronic hyperglycemia and systemic inflammation
iRhom2 loss alleviates renal injury in long-term PM _{2.5} -exposed mice by suppression of inflammation and oxidative stress (Ge et al. 2018)	In vivo and in vitro	C57BL/6 mice and HEK-293 cell and mouse RAW264.7 macrophages and HK-2 and MPC5 and BMDM cells	150.1 ± 2.5 μg/m3, flow rate of 65 L/min for 6 h/day, 5 times a week (mice)	iRhom2–/– mice exhibited reduced inflammatory response, as evidenced by the reduction of interleukin 1β (IL-1β), IL-6, tumor necrosis factor-α (TNF-α) and IL-18 in kidney samples, which might be, at least partly, through inactivating TNF-α converting enzyme/ TNF-α receptors (TACE/TNFRs) and inhibitor of α/ nuclear factor κ B (IκBα/NF-κB) signaling pathways
<i>Endothelial injury</i>				
PM _{2.5} -induced oxidative stress increases adhesion molecules expression in human endothelial cells through the ERK/AKT/NF-κB dependent pathway (Rui et al. 2016)	In vitro	A human umbilical vein cell line (EA.hy926) cells	25, 50, 100, or 200 μg/mL for 1, 3, 6, 12, or 24 h	PM _{2.5} -induced ROS may function as signaling molecules triggering ICAM-1 and VCAM-1 expressions through activating the ERK/AKT/NF-κB-dependent pathway, and further promoting monocyte adhesion to endothelial cells

(continued)

Table 2 (continued)

Study	Study type	Test subjects/cells	PM2.5 dosage	Mechanism of toxicology
Effect of Vitamin E and Omega-3 Fatty Acids on Protecting Ambient PM _{2.5} -Induced Inflammatory Response and Oxidative Stress in Vascular Endothelial Cells (Bo et al. 2016)	In vitro	Human umbilical vein endothelial cells (HUVECs)	50 µg/mL	Inflammation and oxidative stress might be parts of the mechanisms linking PM _{2.5} to vascular endothelial injury
Repeat dose exposure of PM triggers the disseminated intravascular coagulation (DIC) in SD rats (Liang et al. 2019).	In vivo	Specific pathogen-free (SPF) male Sprague–Dawley (SD) rats	0, 1.8, 5.4, and 16.2 mg/kg bw every 3 days for 30 days	PM _{2.5} could induce inflammatory response, vascular endothelial injury, and prothrombotic state, eventually resulted in DIC
Diesel exhaust particles in the lung aggravate experimental acute renal failure (Nemmar et al. 2009).	In vivo	Male Wistar rats	0.5 or 1 mg/kg (DEP)	The presence of DEP in the lung aggravated the renal, pulmonary, and systemic effects of CP-induced ARF
IRE1alpha/XBP1s branch of UPR links HIF1alpha activation to mediate ANGII-dependent endothelial dysfunction under particulate matter (PM) 2.5 exposure (Xu et al. 2017).	In vivo and in vitro	Male Sprague–Dawley (SD) rats and human umbilical vein endothelial cells (HUVECs)	1.5 mg/kg weight, every other day for 3 times (rats) and 6.25, 12.5, and 25 µg/mL for 24 h (cell)	PM _{2.5} exposure instigates endoplasmic reticulum instability, leading to the induction of IRE1α/XBP1s branch of UPR and links HIF1α transactivation to mediate ANGII-dependent endothelial dysfunction

(continued)

Table 2 (continued)

Study	Study type	Test subjects/cells	PM _{2.5} dosage	Mechanism of toxicology
<i>Immune response</i>				
Silica accelerated systemic autoimmune disease in lupus-prone New Zealand mixed mice (Brown et al. 2003).	In vivo	New Zealand mixed (NZM 2410) mice	30 µL saline suspensions of 1 mg crystalline silica, 2 instillations 2 weeks apart	Silica is able to exacerbate the development of autoimmune disease in a genetically susceptible mouse model. The disease acceleration involved increases in proteinuria, auto-antibody levels, circulating immune complexes, immune complex deposition, and complement C3 deposition within the kidney
Silica-exposed mice generate autoantibodies to apoptotic cells (Pfau et al. 2004)	In vivo	New Zealand mixed (NZM 2410) mice	30 µL saline suspensions of 1 mg crystalline silica, 2 instillations 2 weeks apart	Silica-induced apoptosis may exacerbate autoimmune responses by exposing antigenic epitopes to the immune system
Immunoglobulin and lymphocyte responses following silica exposure in New Zealand mixed mice (Brown et al. 2004)	In vivo	New Zealand mixed (NZM 2410) mice	30 µL saline suspensions of 1 mg crystalline silica, 2 instillations 2 weeks apart	The silica-induced alterations in immunoglobulin levels, increased TNF-α, increased B1a B cells and CD4+ T cells, with decreased regulatory T cells may provide an environment that allows for increased autoreactivity
Asbestos-induced autoimmunity in C57BL/6 mice (Pfau et al. 2008)	In vivo	C57Bl/6 mice	2 doses × 60 µg / mouse of amphibole asbestos (tremolite)	Tremolite asbestos led to the production of antinuclear antibodies, immune complex deposition in the kidneys

(continued)

Table 2 (continued)

Study	Study type	Test subjects/cells	PM2.5 dosage	Mechanism of toxicology
<i>Apoptosis and autophagy</i>				
PM _{2.5} induced apoptosis in endothelial cell through the activation of the p53-bax-caspase pathway (Wang et al. 2017b)	In vitro	Human umbilical vein endothelial cells (HUVECs)	0.2, 1, 5, 25 µg/mL for 48 or 72 h	Induction of EC apoptosis is an important mechanism by which ambient PM _{2.5} exposure poses adverse effects on the cardiovascular system
ROS-AKT-mTOR axis mediates autophagy of human umbilical vein endothelial cells induced by cooking oil fumes-derived fine particulate matters in vitro (Ding et al. 2017)	In vitro	Human umbilical vein endothelial cells (HUVECs)	0, 25, 50, 100 µg/mL of COF-derived PM _{2.5} , 100 µg/mL COF-derived PM _{2.5} + 10 mmol/L NAC, and 10 mmol/L NAC for 12, 24, and 36 h, respectively	Cooking oil fumes-derived PM _{2.5} (COFs-derived PM _{2.5}) exposure can induce oxidative stress and cytotoxic effects. ROS-AKT-mTOR axis plays a critical role in HUVECs autophagy induced by COFs-derived PM _{2.5}
Signal Transductions of BEAS-2B Cells in Response to Carcinogenic PM _{2.5} Exposure Based on a Microfluidic System (Zheng et al. 2017)	In vitro	BEAS-2B cells		The ambient fine particles could uptake into the cells by pinocytosis, mainly promoting the PI3K-Akt pathway, FGF/FGFR/ MAPK/VEGF signaling, and JAK-STAT pathway
The ER stress regulator Bip mediates cadmium-induced autophagy and neuronal senescence (Wang et al. 2016)	In vitro	The rat pheochromocytoma (PC12) cell line	0, 5, 10, and 20 µM Cd for 24 h	Autophagy regulated by Bip expression after ER stress suppressed Cd-induced neuronal senescence

(continued)

Table 2 (continued)

Study	Study type	Test subjects/cells	PM _{2.5} dosage	Mechanism of toxicology
Arsenic and sulfur dioxide co-exposure induces renal injury via activation of the NF-kappa-B and caspase signaling pathway (Ji et al. 2019)	In vivo and in vitro	Specific pathogen-free C57BL/6 mice (4 weeks; male) and 293-T cell line (human embryonic kidney cells)	Mice of group As and As+SO ₂ : 5 mg/L As for 60 days. Mice of group SO ₂ and As +SO ₂ 5 mg/m ³ SO ₂ for 6 h/day (from days 31 to 60) and the ratio of SO ₃ ²⁻ and HSO ₃ ⁻ in solution is 3:1 (mM: mM). The molecular formula of arsenic is sodium arsenite (cell)	Co-exposure caused more severe diffuse sclerosing glomerulonephritis than As and SO ₂ exposure alone. Apoptosis was aggravated by co-exposure of As and SO ₂ in 293T cells. As and SO ₂ cause cell toxicity through increasing oxidative stress, which was increased by co-exposure
Characterization of lead, cadmium, arsenic, and nickel in PM _{2.5} particles in the Athens atmosphere, Greece (Thomaidis et al. 2003)	In vitro	Pb, Cd, As, and Ni in PM _{2.5} particles		It was found that Pb, As, and Ni have common sources, which could be vehicles emissions/oil combustion and resuspended road dust. Cd and a portion of As originate from industrial activities. Pb exhibited higher values during the winter period
Initial autophagic protection switches to disruption of autophagic flux by lysosomal instability during cadmium stress accrual in renal NRK-52E cells (Lee et al. 2017)	In vitro	NRK-52E cell	5, 10, 25, and 50 µM Cd ²⁺ for a period of 0.5 h to maximally 24 h	The renal proximal tubule (PT) is the major target of cadmium (Cd ²⁺) toxicity where Cd ²⁺ causes stress and apoptosis
<i>Histology technology</i>				
Effects of the ambient fine particulate matter (PM _{2.5}) exposure on urinary metabolic profiles in rats using UPLC-Q-TOF-MS (Zhang et al. 2017)	In vivo	Male SD rats	PM _{2.5} suspension was injected into the trachea of rats, 2 times/week for 4 weeks	17 potential endogenous metabolites were identified from urinary samples in rats by UPLC-Q-TOF-MS

(continued)

Table 2 (continued)

Study	Study type	Test subjects/cells	PM2.5 dosage	Mechanism of toxicology
The human circulating miRNome reflects multiple organ disease risks in association with short-term exposure to traffic-related air pollution (Krauskopf et al. 2018)	In vivo	Non-smoking participants, either healthy or suffering from ischemic heart disease (IHD) or chronic obstructive pulmonary disease (COPD)	Participants walked about 6 km/2 h (an exposure period), personal ambient air pollution levels of PM were assessed using a real-time condensation particle counter	54 circulating miRNAs to be dose- and pollutant species-dependently associated with PM _{2.5} already after 2 h of exposure. These circulating miRNAs actually reflect the adverse consequences of traffic pollution-induced toxicity in target tissues including the lung, heart, kidney, and brain

iRhom2 inactive rhomboid protein 2, *Nrf2* nuclear factor erythroid-2 related factor 2, *C57BL/6 mice* C57 black 6 mice, *HEK-293 cell* human embryonic kidney 293 cell, *TACE* tumor necrosis factor- α converting enzyme, *TNF- α* tumor necrosis factor- α , *ROS* reactive oxygen species, *hESCs* human embryonic stem cells, *NAC* N-Acetyl-L-cysteine, *BALB/c Mice* BALB/cByJ mice, *RAS* renin-angiotensin system, *RAW264.7* leukemia cells in mouse macrophage, *TLR* toll-like receptors, *MyD88* myeloid differentiation factor 88, *Th2* T helper 2 cell, *SD rats* Sprague-Dawley rats, *HK-2* human renal tubular epithelial cells, *MPC5* mouse podocyte clone 5, *BMDM* bone marrow derived macrophage, *IL* interleukin, *TNFRs* tumor necrosis factor receptors, *I κ B α* inhibitor of NF- κ B α , *NF- κ B* nuclear factor kappa-B, *ERK* extracellular regulated protein kinases, *AKT* protein kinase B, *ICAM-1* intercellular cell adhesion molecule-1, *VCAM-1* vascular cell adhesion molecule-1, *HUVECs* human umbilical vein endothelial cells, *DIC* disseminated intravascular coagulation, *SPF* specific pathogen free, *DEP* diesel exhaust particles, *ARF* acute renal failure, *IRE1* inositol-requiring enzyme-1, *XBP1s* spliced X-box binding protein 1, *UPR* unfolded protein response, *HIF1* hypoxic inducible factor 1, *ANGII* angiotensin II, *NZM mice* New Zealand mixed mice, *EC* endothelial cell, *mTOR* mammalian target of rapamycin, *COF* cooking oil fumes, *FGF* fibroblast growth factor, *FGFR* fibroblast growth factor receptor, *MAPK* mitogen-activated protein kinase, *VEGF* vascular endothelial growth factor, *JAK-STAT* JAK: Janus Kinase, *STAT* signal transducer and activator of transcription, *ER* endoplasmic reticulum, *PC* pheochromocytoma, *NRK-52E cells* rat renal tubular epithelial cells, *PT* proximal tubule, *IHD* ischemic heart disease, *COPD* chronic obstructive pulmonary disease, *miRNAs* microRNAs

7 Global Implication of Policies and Measurements

The reduction of PM_{2.5} in general requires concerted action by public authorities, industry, and individuals at national, regional, and even international levels. Since the harmful effect of PM_{2.5} on human health, and especially the kidneys, has been confirmed by many studies, the effective management of PM_{2.5} is necessary to reduce health risks to a minimum. In 2005, WHO announced that the recommended concentration of PM_{2.5} was less than 10 $\mu\text{g}/\text{m}^3$ for an annual average and less than 24 $\mu\text{g}/\text{m}^3$ for a 24-h average. However, these are hard to achieve. Thus, WHO gave a

three-tier interim goal (World Health Organization 2006). The Non-Communicable Diseases (NCDs) represent the largest and fastest growing threat to human health (World Health Organization 2014). Traditionally, WHO introduced the association as 4 × 4 model: four main NCDs included cardiovascular diseases, cancer, chronic respiratory diseases, and four main modifiable risk factors included tobacco use, unhealthy diet, physical inactivity, and harmful use of alcohol. The UN Political Declaration of 2018 on NCDs added air pollution as the fifth risk factor, rebranding a more comprehensive “5 × 5” model for NCDs management and control (Renshaw et al. 2019).

Many countries around the world have taken various measures to reduce PM_{2.5}. In some relatively clean countries, such as the USA, fine particulate pollution decreased 25% on average across the country between 2010 and 2016 (Clay and Muller 2019). The US administration has taken steps to weaken air quality and climate regulations for this. The US EPA strengthened the nation’s air quality standards for fine particle pollution to improve public health protection by revising the primary annual PM_{2.5} standard to 12 µg/m³ (The U.S. Environmental Protection Agency 2012). Most member states in Europe would reach PM_{2.5} levels close to or even below the WHO guideline value (of 10 µg/m³), and well below the current EU target value (which will be transformed into a limit value in 2015) of annual 25 µg/m³. In 2017, Estonia, Finland, and Norway did not report any concentrations above the WHO air quality guidelines for PM_{2.5} by EEA Report (European Environment Agency 2019). In addition to using clean energy, green technology, reduction in emissions, and lower population density, the European Environment Agency’s (EEA) European Air Quality Index provides citizens with a tool for checking the air quality in their city and supports public engagement in efforts to reduce air pollution. At the same time, India’s air quality does still not show an optimistic picture as one of the most polluted countries in the world. 11 of the 12 cities with the highest levels are located in India when looking at the database’s ranking of particulate pollution in cities from WHO (World Health Organization 2018a, b, c). The Indian government launched the National Clean Air Program (NCAP), a five-year action plan to curb air pollution, build a pan-India air quality monitoring network, and improve citizen awareness (National Clean Air Programme 2019). The programme focuses on 102 polluted Indian cities and aims to reduce PM_{2.5} levels by 20–30% over the next 5 years. By 2017, Beijing’s PM_{2.5} pollution ranking in the world’s cities dropped from the previous 40th to 187th. PM_{2.5} pollution in 62 other cities in China also fell by 30% between 2013 and 2017 (Greenstone 2018). Moreover, targeted measures should be taken to prevent the PM_{2.5} pollution, such as using air filtration devices, air anion nebulizers and wearing professional dust masks. Meanwhile, kitchen fumes should be controlled and the indoor smoking should be eliminated. Recently, some scholars have suggested taking Vitamin B as an effective way to resist the PM_{2.5} pollution. They found that Vitamin B can reduce the DNA methylation changes induced by PM_{2.5}, and that it has an important role in the inflammation and the oxidative stress (Zhong et al. 2017).

8 Conclusions

Fine particulates are important risk factors for kidney disease, especially in developing countries in which environmental pollution is prevalent. The causes of CKD and the toxic mechanisms of most environmental nephrotoxins remain to be elucidated. This paper discussed a number of large cohort studies and cross-sectional studies that associate PM_{2.5} and CKD, as well as the potential mechanisms of PM_{2.5} exposure in kidney disease progression. As mentioned earlier, CKD cases from countries such as America and Asia are estimated to be attributable to long-term exposure to PM_{2.5}, and PM_{2.5} may accelerate the progression of CKD to ESRD. In addition, studies on the pathogenic mechanisms of PM_{2.5} involve some molecular biological networks and cellular signaling pathways. In order to understand the causal relationship between PM_{2.5} exposure and CKD, it is important to study the toxic effects of various components in PM_{2.5}, as well as the effects of temperature, season and regional distribution on them. In terms of mechanisms, most studies have focused on the effects of certain specific components in PM_{2.5} in relation to oxidative stress, inflammatory response, immune response, and other general pathways. Lack of specific mechanisms of action and the pathogenesis still need to be fully elucidated. More detailed longitudinal studies and experimental designs are needed to prove which components of PM_{2.5} are responsible for CKD processes and the dose-response relationship between PM_{2.5} and the development and progression of CKD.

In short, PM_{2.5} is an important risk factor for kidney disease. A database of PM_{2.5} and chronic kidney disease should be globally developed. The data from different regions should be released every year or quarter to provide a new perspective at PM_{2.5}. This new angle might help to promote the prevention and control of chronic kidney diseases in various countries around the world. In the exploration of relevant mechanisms, from the epigenetics, genomics, proteomics, metabolomics and other levels exploring the impact of PM_{2.5} on CKD, impact mechanisms might provide experimental basis for the prevention and treatment of CKD.

We believe that via joint efforts of various countries around the world, the environmental pollution might not only be improved, but the prevention and control of CKD could also be raised to a new level.

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References

- Achilleos S, Kioumourtzoglou M-A, Wu C-D, Schwartz JD, Koutrakis P, Papatheodorou SI (2017) Acute effects of fine particulate matter constituents on mortality: a systematic review and meta-regression analysis. *Environ Int* 109:89–100. <https://doi.org/10.1016/j.envint.2017.09.010>
- Air Quality Direct (2007) Bio-aerosols. <http://www.airqualitydirect.com/bio-aerosols.htm>
- Bandowe BAM, Meusel H, R-j H, Ho K, Cao J, Hoffmann T, Wilcke W (2014) PM_{2.5}-bound oxygenated PAHs, nitro-PAHs and parent-PAHs from the atmosphere of a Chinese megacity: seasonal variation, sources and cancer risk assessment. *Sci Total Environ* 473:77–87. <https://doi.org/10.1016/j.scitotenv.2013.11.108>
- Beck LH Jr, Bonegio RG, Lambeau G, Beck DM, Powell DW, Cummins TD, Klein JB, Salant DJ (2009) M-type phospholipase A2 receptor as target antigen in idiopathic membranous nephropathy. *N Engl J Med* 361:11–21. <https://doi.org/10.1056/NEJMoa0810457>
- Bekki K, Ito T, Yoshida Y, He C, Arashidani K, He M, Sun G, Zeng Y, Sone H, Kunugita N (2016) PM_{2.5} collected in China causes inflammatory and oxidative stress responses in macrophages through the multiple pathways. *Environ Toxicol Pharmacol* 45:362–369. <https://doi.org/10.1016/j.etap.2016.06.022>
- Bell ML, Ebisu K, Peng RD, Walker J, Samet JM, Zeger SL, Dominici F (2008) Seasonal and regional short-term effects of fine particles on hospital admissions in 202 US counties, 1999–2005. *Am J Epidemiol* 168:1,301–1,310. <https://doi.org/10.1093/aje/kwn252>
- Bernatsky S, Fournier M, Pineau CA, Clarke AE, Vinet E, Smargiassi A (2010) Associations between ambient fine particulate levels and disease activity in patients with systemic lupus erythematosus (SLE). *Environ Health Perspect* 119:45–49. <https://doi.org/10.1289/ehp.1002123>
- Blum MF, Surapaneni A, Stewart JD, Liao D, Yanosky JD, Whitsel EA, Grams ME (2020) Particulate matter and albuminuria, glomerular filtration rate, and incident CKD. *Clin J Am Soc Nephrol* 15(3):311–319. <https://doi.org/10.2215/CJN.08350719>
- Bo L, Jiang S, Xie Y, Kan H, Song W, Zhao J (2016) Effect of vitamin E and omega-3 fatty acids on protecting ambient PM_{2.5}-induced inflammatory response and oxidative stress in vascular endothelial cells. *PLoS One* 11:e0152216. <https://doi.org/10.1371/journal.pone.0152216>
- Bowe B, Xie Y, Li T, Yan Y, Xian H, Al-Aly Z (2017) Associations of ambient coarse particulate matter, nitrogen dioxide, and carbon monoxide with the risk of kidney disease: a cohort study. *Lancet Planet Health* 1:e267–e276. [https://doi.org/10.1016/S2542-5196\(17\)30117-1](https://doi.org/10.1016/S2542-5196(17)30117-1)
- Bowe B, Xie Y, Li T, Yan Y, Xian H, Al-Aly Z (2018) Particulate matter air pollution and the risk of incident CKD and progression to ESRD. *J Am Soc Nephrol* 29:218–230. <https://doi.org/10.1681/ASN.2017030253>
- Bowe B, Xie Y, Li T, Yan Y, Xian H, Al-Aly Z (2019) Estimates of the 2016 global burden of kidney disease attributable to ambient fine particulate matter air pollution. *BMJ Open* 9(5):e022450. <https://doi.org/10.1136/bmjopen-2018-022450>
- Bragg-Gresham J, Morgenstern H, McClellan W, Saydah S, Pavkov M, Williams D et al (2018) County-level air quality and the prevalence of diagnosed chronic kidney disease in the US Medicare population. *PLoS One* 13(7):e0200612. <https://doi.org/10.1371/journal.pone.0200612>
- Brown J, Archer A, Pfau J, Holian A (2003) Silica accelerated systemic autoimmune disease in lupus-prone New Zealand mixed mice. *Clin Exp Immunol* 131:415–421. <https://doi.org/10.1046/j.1365-2249.2003.02094.x>
- Brown JM, Pfau JC, Holian A (2004) Immunoglobulin and lymphocyte responses following silica exposure in New Zealand mixed mice. *Inhal Toxicol* 16:133–139. <https://doi.org/10.1080/08958370490270936>
- Brunekreef B, Holgate ST (2002) Air pollution and health. *Lancet* 360:1233–1242. [https://doi.org/10.1016/S0140-6736\(02\)11274-8](https://doi.org/10.1016/S0140-6736(02)11274-8)
- Chabrashvili T, Kitiyakara C, Blau J, Karber A, Aslam S, Welch WJ, Wilcox CS (2003) Effects of ANG II type 1 and 2 receptors on oxidative stress, renal NADPH oxidase, and SOD expression.

- Am J Physiol Regul Integr Compar Physiol 285:R117–R124. <https://doi.org/10.1152/ajpregu.00476.2002>
- Chan T-C, Zhang Z, Lin B-C, Lin C, Deng H-B, Chuang YC, Chan JW, Jiang WK, Tam T, Chang L-y (2018) Long-term exposure to ambient fine particulate matter and chronic kidney disease: a cohort study. *Environ Health Perspect* 126:107002. <https://doi.org/10.1289/EHP3304>
- Chang A, Henderson SG, Brandt D, Liu N, Guttikonda R, Hsieh C, Kaverina N, TO Utset, Meehan SM, Quigg RJ (2011) In situ B cell-mediated immune responses and tubulointerstitial inflammation in human lupus nephritis. *J Immunol* 186:1849–1860. <https://doi.org/10.4049/jimmunol.1001983>
- Chen J (2007) Rapid urbanization in China: a real challenge to soil protection and food security. *Catena* 69:1–15. <https://doi.org/10.1016/j.catena.2006.04.019>
- Cheng Z, Luo L, Wang S, Wang Y, Sharma S, Shimadera H, Wang X, Bressi M, de Miranda RM, Jiang J (2016) Status and characteristics of ambient PM_{2.5} pollution in global megacities. *Environ Int* 89:212–221. <https://doi.org/10.1016/j.envint.2016.02.003>
- Chin W-S, Chang Y-K, Huang L-F, Tsui H-C, Hsu C-C, Guo Y-LL (2018) Effects of long-term exposure to CO and PM_{2.5} on microalbuminuria in type 2 diabetes. *Int J Hyg Environ Health* 221:602–608. <https://doi.org/10.1016/j.ijheh.2018.04.009>
- Chiu P-F, Chang C-H, Wu C-L, Chang T-H, Tsai C-C, Kor C-T, Li J-R, Kuo C-L, Huang C-S, Chu CC (2018) High particulate matter 2.5 levels and ambient temperature are associated with acute lung edema in patients with nondialysis Stage 5 chronic kidney disease. *Nephrol Dial Transplant*. <https://doi.org/10.1093/ndt/gfy144>
- Cho AK, Di Stefano E, You Y, Rodriguez CE, Schmitz DA, Kumagai Y, Miguel AH, Eiguren-Fernandez A, Kobayashi T, Avol E (2004) Determination of four quinones in diesel exhaust particles, SRM 1649a, and atmospheric PM_{2.5} special issue of aerosol science and technology on findings from the fine particulate matter supersites program. *Aerosol Sci Tech* 38:68–81. <https://doi.org/10.1080/02786820390229471>
- Clay K, Muller NZ (2019) Recent increases in air pollution: evidence and implications for mortality. National Bureau of Economic Research. <https://doi.org/10.3386/w26381>
- Clynes R, Dumitru C, Ravetch JV (1998) Uncoupling of immune complex formation and kidney damage in autoimmune glomerulonephritis. *Science* 279:1052–1054. <https://doi.org/10.1126/science.279.5353.1052>
- Cohen AJ, Brauer M, Burnett R, Anderson HR, Frostad J, Estep K, Balakrishnan K, Brunekreef B, Dandona L, Dandona R (2017) Estimates and 25-year trends of the global burden of disease attributable to ambient air pollution: an analysis of data from the Global Burden of Diseases Study 2015. *Lancet* 389:1907–1918. [https://doi.org/10.1016/S0140-6736\(17\)30505-6](https://doi.org/10.1016/S0140-6736(17)30505-6)
- Combes A, Franchineau G (2019) Fine particle environmental pollution and cardiovascular diseases. *Metabolism* 100:153944. <https://doi.org/10.1016/j.metabol.2019.07.008>
- Costa S, Ferreira J, Silveira C, Costa C, Lopes D, Relvas H, Borrego C, Roebeling P, Miranda AI, Paulo Teixeira J (2014) Integrating health on air quality assessment – review report on health risks of two major European outdoor air pollutants: PM and NO₂. *J Toxicol Environ Health Part B* 17:307–340. <https://doi.org/10.1080/10937404.2014.946164>
- Crobeddu B, Aragao-Santiago L, Bui L-C, Boland S, Squiban AB (2017) Oxidative potential of particulate matter 2.5 as predictive indicator of cellular stress. *Environ Pollut* 230:125–133. <https://doi.org/10.1016/j.envpol.2017.06.051>
- Ding R, Zhang C, Zhu X, Cheng H, Zhu F, Xu Y, Liu Y, Wen L, Cao J (2017) ROS-AKT-mTOR axis mediates autophagy of human umbilical vein endothelial cells induced by cooking oil fumes-derived fine particulate matters in vitro. *Free Radic Biol Med* 113:452–460. <https://doi.org/10.1016/j.freeradbiomed.2017.10.386>
- Dominici F, Peng RD, Bell ML, Pham L, McDermott A, Zeger SL, Samet JM (2006) Fine particulate air pollution and hospital admission for cardiovascular and respiratory diseases. *JAMA* 295:1127–1134. <https://doi.org/10.1001/jama.295.10.1127>
- Douwes J, Wouters I, Dubbeld H, van Zwieten L, Steerenberg P, Doekes G, Heederik D (2000) Upper airway inflammation assessed by nasal lavage in compost workers: a relation with

- bio-aerosol exposure. *Am J Ind Med* 37:459–468. [https://doi.org/10.1002/\(SICI\)1097-0274\(200005\)37:5<459::AID-AJIM2>3.0.CO;2-J](https://doi.org/10.1002/(SICI)1097-0274(200005)37:5<459::AID-AJIM2>3.0.CO;2-J)
- Douwes J, Thorne P, Pearce N, Heederik D (2003) Bioaerosol health effects and exposure assessment: progress and prospects. *Ann Occup Hyg* 47:187–200. <https://doi.org/10.1093/annhyg/meg032>
- European Environment Agency (2019) Air quality in Europe – 2019 report. <https://www.eea.europa.eu/publications/air-quality-in-europe-2019>
- Farmer PB, Singh R, Kaur B, Sram RJ, Binkova B, Kalina I, Popov TA, Garte S, Taioli E, Gabelova A (2003) Molecular epidemiology studies of carcinogenic environmental pollutants: effects of polycyclic aromatic hydrocarbons (PAHs) in environmental pollution on exogenous and oxidative DNA damage. *Mut Res Rev Mut Res* 544:397–402. <https://doi.org/10.1016/j.mrrev.2003.09.002>
- Feng J, Chan CK, Fang M, Hu M, He L, Tang X (2006) Characteristics of organic matter in PM_{2.5} in Shanghai. *Chemosphere* 64:1393–1400. <https://doi.org/10.1016/j.chemosphere.2005.12.026>
- Fung F, Hughson WG (2003) Health effects of indoor fungal bioaerosol exposure. *Appl Occup Environ Hyg* 18:535–544. <https://doi.org/10.1080/10473220301451>
- Gadi R, Sharma SK, Mandal TK (2019) Seasonal variation, source apportionment and source attributed health risk of fine carbonaceous aerosols over National Capital Region, India. *Chemosphere* 237:124500. <https://doi.org/10.1016/j.chemosphere.2019.124500>
- Gansevoort RT, Correa-Rotter R, Hemmelgarn BR, Jafar TH, Heerspink HJL, Mann JF, Matsushita K, Wen CP (2013) Chronic kidney disease and cardiovascular risk: epidemiology, mechanisms, and prevention. *Lancet* 382:339–352. [https://doi.org/10.1016/S0140-6736\(13\)60595-4](https://doi.org/10.1016/S0140-6736(13)60595-4)
- Ge CX, Xu MX, Qin YT, Gu TT, Lv JX, Wang MX, Wang SJ, Ma YJ, Lou DS, Li Q, Hu LF, Tan J (2018) iRhoms2 loss alleviates renal injury in long-term PM_{2.5}-exposed mice by suppression of inflammation and oxidative stress. *Redox Biol* 19:147–157. <https://doi.org/10.1016/j.redox.2018.08.009>
- Gorin Y, Block K, Hernandez J, Bhandari B, Wagner B, Barnes JL, Abboud HE (2005) Nox4 NAD(P)H oxidase mediates hypertrophy and fibronectin expression in the diabetic kidney. *J Biol Chem* 280:39616–39626. <https://doi.org/10.1074/jbc.M502412200>
- Graff DW, Cascio WE, Brackhan JA, Devlin RB (2004) Metal particulate matter components affect gene expression and beat frequency of neonatal rat ventricular myocytes. *Environ Health Perspect* 112:792–798. <https://doi.org/10.1289/ehp.112-1241994>
- Greenstone M (2018) Four years after declaring war on pollution, China is winning *New York Times*, A8.
- Harrison RM, Yin J (2000) Particulate matter in the atmosphere: which particle properties are important for its effects on health? *Sci Total Environ* 249:85–101. [https://doi.org/10.1016/S0048-9697\(99\)00513-6](https://doi.org/10.1016/S0048-9697(99)00513-6)
- Harrison RM, Jones AM, Lawrence RG (2004) Major component composition of PM₁₀ and PM_{2.5} from roadside and urban background sites. *Atmos Environ* 38:4531–4538. <https://doi.org/10.2147/IJNRD.S39739>
- He T, Xiong J, Nie L, Yu Y, Guan X, Xu X, Xiao T, Yang K, Liu L, Zhang D (2016) Resveratrol inhibits renal interstitial fibrosis in diabetic nephropathy by regulating AMPK/NOX4/ROS pathway. *J Mol Med* 94:1359–1371. <https://doi.org/10.1007/s00109-016-1451-y>
- Herrlich A, Kefaloyianni E (2018) iRhoms: a potential path to more specific therapeutic targeting of lupus nephritis. <https://doi.org/10.1053/j.ajkd.2018.04.010>
- Hill NR, Fatoba ST, Oke JL, Hirst JA, O’Callaghan CA, Lasserson DS, Hobbs FR (2016) Global prevalence of chronic kidney disease—a systematic review and meta-analysis. *PLoS One* 11: e0158765. <https://doi.org/10.1371/journal.pone.0158765>
- Hogan SL, Hogan SL, Vupputuri S, Guo X, Cai J, Colindres RE, Heiss G, Coresh J (2007) Association of cigarette smoking with albuminuria in the United States: the third National Health and Nutrition Examination Survey. *Ren Fail* 29:133–142. <https://doi.org/10.1080/08860220601098888>

- Huang J, Li G, Wang J, Wu S, Guo X, Zhang L (2019) Associations between long-term ambient PM_{2.5} exposure and prevalence of chronic kidney disease in China: a national cross-sectional study. *Lancet* 394:S93. [https://doi.org/10.1016/S0140-6736\(19\)32429-8](https://doi.org/10.1016/S0140-6736(19)32429-8)
- Inker LA, Astor BC, Fox CH, Isakova T, Lash JP, Peralta CA, Tamura MK, Feldman HI (2014) KDOQI US commentary on the 2012 KDIGO clinical practice guideline for the evaluation and management of CKD. *Am J Kidney Dis* 63:713–735. <https://doi.org/10.1053/j.ajkd.2014.01.416>
- Ji P-y, Z-y L, Wang H, Dong J-t, Li X-j, Yi H-l (2019) Arsenic and sulfur dioxide co-exposure induce renal injury via activation of the NF- κ B and caspase signaling pathway. *Chemosphere* 224:280–288. <https://doi.org/10.1016/j.chemosphere.2019.02.111>
- Jin L, Ni J, Tao Y, Weng X, Zhu Y, Yan J, Hu B (2019) N-acetylcysteine attenuates PM_{2.5}-induced apoptosis by ROS-mediated Nrf2 pathway in human embryonic stem cells. *Sci Total Environ* 666:713–720. <https://doi.org/10.1016/j.scitotenv.2019.02.307>
- Kim H, Kim H, Lee J-T (2019) Spatial variation in lag structure in the short-term effects of air pollution on mortality in seven major South Korean cities, 2006–2013. *Environ Int* 125:595–605. <https://doi.org/10.1016/j.envint.2018.09.004>
- Kioumourtoglou MA, Schwartz J, James P, Dominici F, Zanobetti A (2016) PM_{2.5} and mortality in 207 US cities: modification by temperature and city characteristics. *Epidemiology (Cambridge, Mass)* 27(2):221. <https://doi.org/10.1097/EDE.0000000000000422>
- Krauskopf J, Caiment F, van Veldhoven K, Chadeau-Hyam M, Sinharay R, Chung KF, Cullinan P, Collins P, Barratt B, Kelly FJ (2018) The human circulating miRNome reflects multiple organ disease risks in association with short-term exposure to traffic-related air pollution. *Environ Int* 113:26–34. <https://doi.org/10.1016/j.envint.2018.01.014>
- Kuang X (2018) A study on the key role of cadmium accumulation induced by PM_{2.5} Exposure in renal injury. In: ISEE conference abstracts
- Lau KK, Suzuki H, Novak J, Wyatt RJ (2010) Pathogenesis of Henoch-Schönlein purpura nephritis. *Pediatr Nephrol* 25:19. <https://doi.org/10.1007/s00467-009-1230-x>
- Lee F, Lawrence DA (2018) From infections to anthropogenic inflicted pathologies: Involvement of immune balance. *J Toxicol Environ Health Part B* 21:24–46. <https://doi.org/10.1080/10937404.2017.1412212>
- Lee RG, Coleman P, Jones JL, Jones KC, Lohmann R (2005) Emission factors and importance of PCDD/Fs, PCBs, PCNs, PAHs and PM₁₀ from the domestic burning of coal and wood in the UK. *Environ Sci Technol* 39:1436–1447. <https://doi.org/10.1021/es048745i>
- Lee W-K, Probst S, Santoyo-Sánchez M, Al-Hamdani W, Diebels I, von Sivers J-K, Kerek E, Prenner E, Thévenod F (2017) Initial autophagic protection switches to disruption of autophagic flux by lysosomal instability during cadmium stress accrual in renal NRK-52E cells. *Arch Toxicol* 91:3225–3245. <https://doi.org/10.1007/s00204-017-1942-9>
- Lee CS, Chou C-K, Cheung H, Tsai C-Y, Huang W-R, Huang S-H, Chen M-J, Liao H-T, Wu C-F, Tsao T-M (2019) Seasonal variation of chemical characteristics of fine particulate matter at a high-elevation subtropical forest in East Asia. *Environ Pollut* 246:668–677. <https://doi.org/10.1016/j.envpol.2018.11.033>
- Lelieveld J, Klingmüller K, Pozzer A, Burnett R, Haines A, Ramanathan V (2019) Effects of fossil fuel and total anthropogenic emission removal on public health and climate. *Proc Natl Acad Sci* 116:7192–7197. <https://doi.org/10.1073/pnas.1819989116>
- Leonard RJ, Hochuli DF (2017) Exhausting all avenues: why impacts of air pollution should be part of road ecology. *Front Ecol Environ* 15:443–449. <https://doi.org/10.1002/fee.1521>
- Li N, Xia T, Nel AE (2008) The role of oxidative stress in ambient particulate matter-induced lung diseases and its implications in the toxicity of engineered nanoparticles. *Free Radic Biol Med* 44:1689–1699. <https://doi.org/10.1016/j.freeradbiomed.2008.01.028>
- Li GX, Huang J, Wang JW, Zhao MH, Liu Y, Guo XB, Wu SW, Zhang LX (2020) Long-Term Exposure to Ambient PM_{2.5} and Increased Risk of CKD Prevalence in China. *Journal of the American Society of Nephrology*. ASN.2020040517. <https://doi.org/10.1681/ASN.2020040517>

- Liang S, Zhao T, Hu H, Shi Y, Xu Q, Miller MR, Duan J, Sun Z (2019) Repeat dose exposure of PM_{2.5} triggers the disseminated intravascular coagulation (DIC) in SD rats. *Sci Total Environ* 663:245–253. <https://doi.org/10.1016/j.scitotenv.2019.01.346>
- Lin SY, Ju SW, Lin CL, Hsu WH, Lin CC, Ting IW, Kao CH (2020) Air pollutants and subsequent risk of chronic kidney disease and end-stage renal disease: a population-based cohort study. *Environ Pollut* 261:114154. <https://doi.org/10.1016/j.envpol.2020.114154>
- Liu S, Ye L, Tao J, Ge C, Huang L, Yu J (2018) Total flavones of *Abelmoschus manihot* improve diabetic nephropathy by inhibiting the iRhom2/TACE signalling pathway activity in rats. *Pharm Biol* 56:1–11. <https://doi.org/10.1080/13880209.2017.1412467>
- Lue S-H, Wellenius GA, Wilker EH, Mostofsky E, Mittleman MA (2013) Residential proximity to major roadways and renal function. *J Epidemiol Community Health* 67:629–634. <https://doi.org/10.1136/jech-2012-202307>
- Lundstedt S, White PA, Lemieux CL, Lynes KD, Lambert IB, Öberg L, Haglund P, Tysklind M (2007) Sources, fate, and toxic hazards of oxygenated polycyclic aromatic hydrocarbons (PAHs) at PAH-contaminated sites. *AMBIO J Hum Environ* 36:475–486. [https://doi.org/10.1579/0044-7447\(2007\)36\[475:SFATHO\]2.0.CO;2](https://doi.org/10.1579/0044-7447(2007)36[475:SFATHO]2.0.CO;2)
- Ma Z, Hu X, Sayer AM, Levy R, Zhang Q, Xue Y, Tong S, Bi J, Huang L, Liu Y (2015) Satellite-based spatiotemporal trends in PM_{2.5} concentrations: China, 2004–2013. *Environ Health Perspect* 124:184–192. <https://doi.org/10.1289/ehp.1409481>
- Martinelli N, Olivieri O, Girelli D (2013) Air particulate matter and cardiovascular disease: a narrative review. *Eur J Intern Med* 24:295–302. <https://doi.org/10.1016/j.ejim.2013.04.001>
- Mehta AJ, Zanobetti A, Bind M-AC, Kloog I, Koutrakis P, Sparrow D, Vokonas PS, Schwartz JD (2016) Long-term exposure to ambient fine particulate matter and renal function in older men: the veterans administration normative aging study. *Environ Health Perspect* 124:1353–1360. <https://doi.org/10.1289/ehp.1510269>
- Milojevic A, Wilkinson P, Armstrong B, Bhaskaran K, Smeeth L, Hajat S (2014) Short-term effects of air pollution on a range of cardiovascular events in England and Wales: case-crossover analysis of the MINAP database, hospital admissions and mortality. *Heart* 100:1093–1098. <https://doi.org/10.1136/heartjnl-2013-304963>
- Monn C, Becker S (1999) Cytotoxicity and induction of proinflammatory cytokines from human monocytes exposed to fine (PM_{2.5}) and coarse particles (PM_{10–2.5}) in outdoor and indoor air. *Toxicol Appl Pharmacol* 155:245–252. <https://doi.org/10.1006/taap.1998.8591>
- Morakinyo OM, Mokgobu MI, Mukhola MS, Hunter RP (2016) Health outcomes of exposure to biological and chemical components of inhalable and respirable particulate matter. *Int J Environ Res Public Health* 13:592. <https://doi.org/10.3390/ijerph13060592>
- Mukherjee A, Agrawal M (2017) A global perspective of fine particulate matter pollution and its health effects. In: *Reviews of environmental contamination and toxicology*. Springer, Berlin, pp 5–51. https://doi.org/10.1007/398_2017_3
- National Clean Air Programme (2019) Extensive consultation with all the relevant stakeholders foundation for formulation of NCAP: Dr. Harsh Vardhan. <https://pib.gov.in/PressReleasePage.aspx?PRID=1559384>
- Nemmar A, Al-Salam S, Zia S, Yasin J, Al Husseni I, Ali BH (2009) Diesel exhaust particles in the lung aggravate experimental acute renal failure. *Toxicol Sci* 113:267–277. <https://doi.org/10.1093/toxsci/kfp222>
- Niaz ZR, Silva GC, Ribeiro TP, León-González AJ, Kassem M, Mirajkar A, Alvi A, Abbas M, Zgheel F, Schini-Kerth VB (2017) EPA: DHA 6: 1 prevents angiotensin II-induced hypertension and endothelial dysfunction in rats: role of NADPH oxidase-and COX-derived oxidative stress. *Hypertens Res* 40:966. <https://doi.org/10.1038/hr.2017.72>
- Papademetriou V, Zaheer M, Doumas M, Lovato L, Applegate WB, Tsioufis C, Mottle A, Punthakee Z, Cushman WC, AS Group (2016) Cardiovascular outcomes in action to control cardiovascular risk in diabetes: Impact of blood pressure level and presence of kidney disease. *Am J Nephrol* 43:271–280. <https://doi.org/10.1159/000446122>

- Parikh NI, Hwang S-J, Larson MG, Meigs JB, Levy D, Fox CS (2006) Cardiovascular disease risk factors in chronic kidney disease: overall burden and rates of treatment and control. *Arch Intern Med* 166:1884–1891. <https://doi.org/10.1001/archinte.166.17.1884>
- Pérez N, Pey J, Querol X, Alastuey A, López J, Viana M (2008) Partitioning of major and trace components in PM10–PM2. 5–PM1 at an urban site in Southern Europe. *Atmos Environ* 42:1677–1691. <https://doi.org/10.1016/j.atmosenv.2007.11.034>
- Pérez N, Pey J, Cusack M, Reche C, Querol X, Alastuey A, Viana M (2010) Variability of particle number, black carbon, and PM10, PM2. 5, and PM1 levels and speciation: influence of road traffic emissions on urban air quality. *Aerosol Sci Tech* 44:487–499. <https://doi.org/10.1080/02786821003758286>
- Pfau JC, Brown JM, Holian A (2004) Silica-exposed mice generate autoantibodies to apoptotic cells. *Toxicology* 195:167–176. <https://doi.org/10.1016/j.tox.2003.09.011>
- Pfau JC, Sentissi JJ, Sa L, Calderon-Garcidueñas L, Brown JM, Blake DJ (2008) Asbestos-induced autoimmunity in C57BL/6 mice. *J Immunotoxicol* 5:129–137. <https://doi.org/10.1080/15476910802085756>
- Pollution Issues (2006) Indoor Air Pollution. <http://www.pollutionissues.com/Ho-Li/Indoor-Air-Pollution.html>
- Power AL, Tennant RK, Jones RT, Tang Y, Du J, Worsley AT, Love J (2018) Monitoring impacts of urbanisation and industrialisation on air quality in the Anthropocene using urban pond sediments. *Frontiers in Earth Science* 6:131. <https://doi.org/10.3389/feart.2018.00131>
- Renshaw N, Dissard R, Beagley J (2019) NCD alliance annual report 2018. https://ncdalliance.org/sites/default/files/resource_files/NCDA_AnnualReport%202018_FV_LowRes.pdf
- Rui W, Guan L, Zhang F, Zhang W, Ding W (2016) PM2. 5-induced oxidative stress increases adhesion molecules expression in human endothelial cells through the ERK/AKT/NF- κ B-dependent pathway. *J Appl Toxicol* 36:48–59. <https://doi.org/10.1002/jat.3143>
- Samake A, Uzu G, Martins J, Calas A, Vince E, Parat S, Jaffrezou J (2017) The unexpected role of bioaerosols in the oxidative potential of PM. *Sci Rep* 7:10978. <https://doi.org/10.1038/s41598-017-11178-0>
- Santana PT, Martel J, Lai H-C, Perfettini J-L, Kanellopoulos JM, Young JD, Coutinho-Silva R, Ojcius DM (2016) Is the inflammasome relevant for epithelial cell function? *Microbes Infect* 18:93–101. <https://doi.org/10.1016/j.micinf.2015.10.007>
- Sharma H, Jain V, Khan ZH (2007) Characterization and source identification of polycyclic aromatic hydrocarbons (PAHs) in the urban environment of Delhi. *Chemosphere* 66:302–310. <https://doi.org/10.1016/j.chemosphere.2006.05.003>
- Singh A, Kamal R, Mudiam MKR, Gupta MK, Satyanarayana GNV, Bihari V, Shukla N, Khan AH, Kesavachandran CN (2016) Heat and PAHs emissions in indoor kitchen air and its impact on kidney dysfunctions among kitchen workers in Lucknow, North India. *PLoS One* 11: e0148641. <https://doi.org/10.1371/journal.pone.0148641>
- Sørensen M, Schins RP, Hertel O, Loft S (2005) Transition metals in personal samples of PM2. 5 and oxidative stress in human volunteers. *Cancer Epidemiol Prev Biomark* 14:1340–1343. <https://doi.org/10.1158/1055-9965>
- Srikanth P, Sudharsanam S, Steinberg R (2008) Bio-aerosols in indoor environment: composition, health effects and analysis. *Indian J Med Microbiol* 26:302. <https://doi.org/10.4103/0255-0857.43555>
- Stojan G, Curriero F, Kvit A, Petri MA (2019) Environmental and atmospheric factors in systemic lupus erythematosus: a regression analysis. *Ann Rheum Dis* 78(Suppl 2). <https://doi.org/10.1136/annrheumdis-2019-eular.5962>
- Sumida K, Molnar MZ, Potukuchi PK, George K, Thomas F, Lu JL, Yamagata K, Kalantar-Zadeh K, Kovesdy CP (2017) Changes in albuminuria and subsequent risk of incident kidney disease. *Clin J Am Soc Nephrol* 12:1941–1949. <https://doi.org/10.2215/CJN.02720317>
- Tao J, Wang Y, Wei J, Zhang R, Li T (2016) Characteristics of organic and elemental carbon in the indoor/outdoor air PM_{2.5} in Beijing. *Wei sheng yan jiu J Hyg Res* 45:795–806

- The U.S. Environmental Protection Agency (2012) Revised air quality standards for particle pollution and updates to the air quality index (AQI). https://www.epa.gov/sites/production/files/2016-04/documents/2012_aqi_factsheet.pdf
- Thomaidis NS, Bakeas EB, Siskos PA (2003) Characterization of lead, cadmium, arsenic and nickel in PM_{2.5} particles in the Athens atmosphere, Greece. *Chemosphere* 52:959–966. [https://doi.org/10.1016/S0045-6535\(03\)00295-9](https://doi.org/10.1016/S0045-6535(03)00295-9)
- Tonelli M, Muntner P, Lloyd A, Manns BJ, Klarenbach S, Pannu N, James MT, Hemmelgarn BR, AKD Network (2012) Risk of coronary events in people with chronic kidney disease compared with those with diabetes: a population-level cohort study. *Lancet* 380:807–814. [https://doi.org/10.1016/S0140-6736\(12\)60572-8](https://doi.org/10.1016/S0140-6736(12)60572-8)
- Vouk VB, Piver WT (1983) Metallic elements in fossil fuel combustion products: amounts and form of emi Zhang, Y., Ji, X., Ku, T., Li, G., & Sang, N. (2016). Heavy metals bound to fine particulate matter from northern China induce season-dependent health risks: a study based on myocardial toxicity. *Environ Pollut* 216:380–390. <https://doi.org/10.1016/j.envpol.2016.05.072>
- Wang J, Li X, Jiang N, Zhang W, Zhang R, Tang X (2015) Long term observations of PM_{2.5}-associated PAHs: Comparisons between normal and episode days. *Atmos Environ* 104:228–236. <https://doi.org/10.1016/j.atmosenv.2015.01.026>
- Wang T, Yuan Y, Zou H, Yang J, Zhao S, Ma Y, Wang Y, Bian J, Liu X, Gu J (2016) The ER stress regulator Bip mediates cadmium-induced autophagy and neuronal senescence. *Sci Rep* 6:38091. <https://doi.org/10.1038/srep38091>
- Wang Q, Jiang N, Yin S, Li X, Yu F, Guo Y, Zhang R (2017a) Carbonaceous species in PM_{2.5} and PM₁₀ in urban area of Zhengzhou in China: seasonal variations and source apportionment. *Atmos Res* 191:1–11. <https://doi.org/10.1016/j.atmosres.2017.02.003>
- Wang W, Deng Z, Feng Y, Liao F, Zhou F, Feng S, Wang X (2017b) PM_{2.5} induced apoptosis in endothelial cell through the activation of the p53-bax-caspase pathway. *Chemosphere* 177:135–143. <https://doi.org/10.1016/j.chemosphere.2017.02.144>
- Weichenthal SA, Lavigne E, Evans GJ, Godri Pollitt KJ, Burnett RT (2016) Fine particulate matter and emergency room visits for respiratory illness. Effect modification by oxidative potential. *Am J Respiratory Crit Care Med* 194:577–586. <https://doi.org/10.1164/rccm.201512-2434OC>
- World Development Indicators (2017) EN.ATM.PM25.MC.T1.ZS, SP.POP.TOTL. <https://databank.worldbank.org/WHO-Interim-Target-1/id/8030eb3e>
- World Health Organization (2006) WHO Air quality guidelines for particulate matter, ozone, nitrogen dioxide and sulfur dioxide. https://apps.who.int/iris/bitstream/handle/10665/69477/WHO_SDE_PHE_OEH_06.02_eng.pdf;jsessionid=07757F4EC9D55DE3904B89AFE1D9D155?sequence=1
- World Health Organization (2014) WHO global status report on NCDs, 2014. http://apps.who.int/iris/bitstream/10665/148114/1/9789241564854_eng.pdf
- World Health Organization (2018a) 9 out of 10 people worldwide breathe polluted air, but more countries are taking action. <https://www.who.int/zh/news-room/detail/02-05-2018-9-out-of-10-people-worldwide-breathe-polluted-air-but-more-countries-are-taking-action>
- World Health Organization (2018b) Ambient (outdoor) air quality and health. [https://www.who.int/news-room/fact-sheets/detail/ambient-\(outdoor\)-air-quality-and-health](https://www.who.int/news-room/fact-sheets/detail/ambient-(outdoor)-air-quality-and-health)
- World Health Organization (2018c) WHO Global Ambient Air Quality Database (update 2018). <https://www.who.int/airpollution/data/cities/en/>
- Wu MY, Lo WC, Chao CT, Wu MS, Chiang CK (2020) Association between air pollutants and development of chronic kidney disease: a systematic review and meta-analysis. *Sci Total Environ* 706:135522. <https://doi.org/10.1016/j.envpol.2020.114154>
- Xu X, Wang G, Chen N, Lu T, Nie S, Xu G, Zhang P, Luo Y, Wang Y, Wang X (2016) Long-term exposure to air pollution and increased risk of membranous nephropathy in China. *J Am Soc Nephrol* 27:3739–3746. <https://doi.org/10.1681/ASN.2016010093>
- Xu X, Wang H, Xing C, Gu Y, Liu S, Xu H, Hu M, Song L (2017) IRE1α/XBP1s branch of UPR links HIF1α activation to mediate ANGII-dependent endothelial dysfunction under particulate matter (PM) 2.5 exposure. *Sci Rep* 7:13507. <https://doi.org/10.1038/s41598-017-13156-y>

- Xu M-X, Qin Y-T, Ge C-X, Gu T-T, Lou D-S, Li Q, Hu L-F, Li Y-Y, Yang W-W, Tan J (2018) Activated iRhom2 drives prolonged PM_{2.5} exposure-triggered renal injury in Nrf2-defective mice. *Nanotoxicology* 12:1045–1067. <https://doi.org/10.1080/17435390.2018.1513093>
- Yan Y-H, Chou CC-K, Wang J-S, Tung C-L, Li Y-R, Lo K, Cheng T-J (2014) Subchronic effects of inhaled ambient particulate matter on glucose homeostasis and target organ damage in a type 1 diabetic rat model. *Toxicol Appl Pharmacol* 281:211–220. <https://doi.org/10.1016/j.taap.2014.10.005>
- Yang YR, Chen YM, Chen SY, Chan CC (2017) Associations between long-term particulate matter exposure and adult renal function in the Taipei metropolis. *Environ Health Perspect* 125 (4):602–607. <https://doi.org/10.1289/EHP302>
- Yang S, Li R, Shu X, Li Q (2018) Environmental pollutants and diabetic kidney disease (DKD). *Med Res Arch* 6. <https://doi.org/10.18103/mra.v6i4.1770>
- Yunker MB, Macdonald RW, Vingarzan R, Mitchell RH, Goyette D, Sylvestre S (2002) PAHs in the Fraser River basin: a critical appraisal of PAH ratios as indicators of PAH source and composition. *Org Geochem* 33:489–515. [https://doi.org/10.1016/S0146-6380\(02\)00002-5](https://doi.org/10.1016/S0146-6380(02)00002-5)
- Zanobetti A, Franklin M, Koutrakis P, Schwartz J (2009) Fine particulate air pollution and its components in association with cause-specific emergency admissions. *Environ Health* 8:58. <https://doi.org/10.1186/1476-069X-8-58>
- Zhai S, Jacob DJ, Wang X, Shen L, Li K, Zhang Y, Gui K, Zhao T, Liao H (2019) Fine particulate matter (PM_{2.5}) trends in China, 2013–2018: separating contributions from anthropogenic emissions and meteorology. *Atmos Chem Phys* 19:11031–11041. <https://doi.org/10.5194/acp-19-11031-2019>
- Zhang Y-L, Cao F (2015) Fine particulate matter (PM_{2.5}) in China at a city level. *Sci Rep* 5:14884. <https://doi.org/10.1038/srep14884>
- Zhang L, Wang F, Wang L, Wang W, Liu B, Liu J, Chen M, He Q, Liao Y, Yu X (2012) Prevalence of chronic kidney disease in China: a cross-sectional survey. *Lancet* 379:815–822. [https://doi.org/10.1016/S0140-6736\(12\)60033-6](https://doi.org/10.1016/S0140-6736(12)60033-6)
- Zhang Y, Ji X, Ku T, Li G, Sang N (2016) Heavy metals bound to fine particulate matter from northern China induce season-dependent health risks: a study based on myocardial toxicity. *Environ Pollut* 216:380–390. <https://doi.org/10.1016/j.envpol.2016.05.072>
- Zhang L, Xu T, Pi Z, Zheng M, Song F, Liu Z (2017) Effects of the ambient fine particulate matter (PM_{2.5}) exposure on urinary metabolic profiles in rats using UPLC-Q-TOF-MS. *Chin Chem Lett.* <https://doi.org/10.1016/j.cclet.2017.11.019>
- Zhang Y, Li Q, Fang M, Ma Y, Liu N, Yan X, Zhou J, Li F (2018) The kidney injury induced by short-term PM_{2.5} exposure and the prophylactic treatment of essential oils in BALB/c Mice. *Oxidat Med Cell Longevity* 2018. <https://doi.org/10.1155/2018/9098627>
- Zhang Y, Liu D, Liu Z (2020) The benzo [b] fluoranthene in the atmospheric fine particulate matter induces mouse glomerular podocytes injury via inhibition of autophagy. *Ecotoxicol Environ Saf* 195:110403. <https://doi.org/10.1016/j.ecoenv.2020.110403>
- Zheng L, Liu S, Zhuang G, Xu J, Liu Q, Zhang X, Deng C, Guo Z, Zhao W, Liu T (2017) Signal transductions of BEAS-2B cells in response to carcinogenic PM_{2.5} exposure based on a microfluidic system. *Anal Chem* 89:5413–5421. <https://doi.org/10.1021/acs.analchem.7b00218>
- Zhong J, Karlsson O, Wang G, Li J, Guo Y, Lin X, Zemplenyi M, Sanchez-Guerra M, Trevisi L, Urch B (2017) B vitamins attenuate the epigenetic effects of ambient fine particles in a pilot human intervention trial. *Proc Natl Acad Sci* 114:3503–3508. <https://doi.org/10.1073/pnas.1618545114>
- Zhu X, Liu Y, Chen Y, Yao C, Che Z, Cao J (2015) Maternal exposure to fine particulate matter (PM_{2.5}) and pregnancy outcomes: a meta-analysis. *Environ Sci Pollut Res* 22:3383–3396. <https://doi.org/10.1007/s11356-014-3458-7>

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