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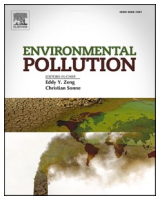

Review

The general external exposome and the development or progression of chronic kidney disease: A systematic review and meta-analyses☆

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ABSTRACT

The impact of environmental risk factors on chronic kidney disease (CKD) remains unclear. This systematic review aims to provide an overview of the literature on the association between the general external exposome and CKD development or progression. We searched MEDLINE and EMBASE for case-control or cohort studies, that investigated the association of the general external exposome with a change in eGFR or albuminuria, diagnosis or progression of CKD, or CKD-related mortality. The risk of bias of included studies was assessed using the Newcastle-Ottawa Scale. Summary effect estimates were calculated using random-effects meta-analyses. Most of the 66 included studies focused on air pollution (n = 33), e.g. particulate matter (PM) and nitric oxides (NOx), and heavy metals (n = 21) e.g. lead and cadmium. Few studies investigated chemicals (n = 7) or built environmental factors (n = 5). No articles on other environment factors such as noise, food supply, or urbanization were found. PM2.5 exposure was associated with an increased CKD and end-stage kidney disease incidence, but not with CKD-related mortality. There was mixed evidence regarding the association of NO_2 and PM10 on CKD incidence. Exposure to heavy metals might be associated with an increased risk of adverse kidney outcomes, however, evidence was inconsistent. Studies on effects of chemicals or built environment on kidney outcomes were inconclusive. In conclusion, prolonged exposure to PM2.5 is associated with an increased risk of CKD incidence and progression to kidney failure. Current studies predominantly investigate the exposure to air pollution and heavy metals, whereas chemicals and the built environment remains understudied. Substantial heterogeneity and mixed evidence were found across studies. Therefore, long-term high-quality studies are needed to elucidate the impact of exposure to chemicals or other (built) environmental factors and CKD.

1. Introduction

Chronic kidney disease (CKD) is a prevalent non-communicable condition that has a high disease burden, affecting 843 million individuals("Chapter 1: Definition and classification of CKD," 2011). Although the association between age, diabetes, and some genetic predispositions and CKD is well known(Kazancioğlu, 2013), less is understood about the association between environmental risk factors and development/progression of CKD.

In the past years, there has been growing interest in the integration of environmental components in disease etiology. The "exposome" was first described as "every exposure to which an individual is subjected from conception to death" and consists of three domains: internal exposome, specific external exposome, and general external exposome (Wild, 2012). The definition of each domain is heterogenous across literature. It is generally accepted that the internal exposome includes an individual's biological response to environmental stimuli and physiological changes for maintaining homeostasis(Buck Louis et al., 2017). Specific external exposome consists of environmental exposures on an individual level, such as diet, physical activity, tobacco use, social network, work-related exposures, and sleep. The general external exposome consists of population-level exposures, such as exposure to environmental pollutants, metals, chemicals, or the built environment.

Several factors of the exposome may play a role in the

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pathophysiology of CKD. The kidneys play a crucial role in the clearance of toxins, and due to their reabsorption function, heavy metals accumulate in the renal tubules(Sabolić, 2006). Additionally, kidneys are susceptible to the negative systemic effects of air pollution, e.g. particulate matter (PM) of various sizes(Shubham et al., 2022). Finally, unfavorable built environmental factors such as lack of green space, may induce unhealthy lifestyles, e.g. physical inactivity, which adversely affect kidney function(Mytton et al., 2012; Wilund et al., 2021).

Previous reviews have focused on certain factors in isolation, such as air pollution which reported an increased risk for kidney outcomes(M. Y. (Wu et al., 2020)) and heavy metals for which also an increased risk was found (Jalili et al., 2021). Nevertheless, so far, no other review has considered multiple domains components of the exposome. This systematic review aims to present an up-to-date comprehensive overview of factors within the general external exposome available in current literature and their effects on the development and progression of CKD. A better understanding of the link between environmental risk factors and CKD could raise awareness on environmental health and improve CKD prevention in public health strategies. This systematic review aims to provide an overview of the current literature on the association between exposure to factors of the general external exposome and development or progression of CKD.

2. Methods

This review was reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and the protocol was registered with PROSPERO #CRD42022375011(Page et al., 2021).

2.1. Data searches and sources

A search query was carried out on November 7, 2022 in MEDLINE and EMBASE using Medical Subject Headings (MeSH) terms and free-text terms (Supplementary Table S1). The search was limited to studies published from January 1, 1990 till November 7, 2022. The language restriction was set to English, and species were restricted to humans.

2.2. Inclusion and exclusion criteria

Studies with a case-control or cohort design were included. In case of case-control studies, we included those with a case group defined as "exposed to a specific environmental factor" while the control group was defined as "significantly less exposed to the same environmental factor". Other inclusion criteria were age $\geq$18 years old and studies that investigated the association between the general external exposome, i.e. community-level exposure to environmental pollutants and the built environment, and one of our outcomes of interest: change in eGFR, change in albuminuria, diagnosis of CKD, progression of CKD to kidney failure or kidney replacement therapy (KRT), and CKD-related mortality. Studies were excluded if the exposure was limited to a specific population (e.g. occupational exposure or cases of poisoning).

2.3. Study selection and data-extraction

All obtained studies obtained were independently screened for eligibility by two reviewers, first by title and abstract and subsequently by full-text. The following data were extracted from included studies: study design (i.e. case-control or cohort studies), year of publication, country, time of follow-up, population size (i.e. total, CKD and non-CKD), demographics (i.e. mean age, percentage of males), CKD risk factors including body mass index (BMI), weight status classification (i.e. percentage of overweight and obesity), diabetes, smoking status, and hypertension (i.e. total, treated and untreated), type, duration, and, dose of exposure, method of exposure assessment, confounders adjusted for in the analysis, and the outcomes of interest. The definitions of CKD and kidney failure, and formula used for eGFR calculations were extracted as well. Data were extracted independently by two reviewers. Any disagreements on selection of studies or data-extraction were resolved by discussions between the two reviewers or, when necessary, by adjudication of a third reviewer.

2.4. Risk of bias assessment

The quality of included studies was independently assessed by two reviewers using the eight-item Newcastle-Ottawa Scale (NOS) for cohort studies(Stang, 2010). The three domains evaluated were selection of cohort, comparability of cohorts, and outcome. The items assessed were representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure, demonstration that outcome of interest was not present at start of study, comparability of cohorts or analysis controlled for confounders, assessment of outcome, sufficient time of follow-up for outcomes to occur (>5 years), and adequacy of follow-up (<15% loss to follow up).

A maximum of 9 points could be awarded to each study. Each item of the NOS could be rewarded with 1 point, except for comparability: 1 point was given if age, sex, hypertension and diabetes were included in the confounding assessment, and 2 points were given if smoking and BMI or weight classification were additionally adjusted for. NOS scores were categorized into three risk of bias groups: very high risk (0–3 points), high risk (4–6 points), and low risk (7–9 points)(Lo et al., 2014).

2.5. Statistical analysis

Statistical analyses were conducted by Review Manager 5.4(The Cochrane Collaboration, 2020). In the quantitative meta-analysis, studies were included that evaluated the same exposure, outcome, outcome effect measurement (e.g. hazard ratio (HR), odds ratio (OR) or continuous) and unit of exposure (e.g. per set incremental unit or highest versus lowest quantile). A meta-analysis was performed when three or more articles determined the same exposure, outcome and outcome effect measurement. Subgroup analyses were stratified on CKD status of the included population (i.e. CKD, non-CKD or mixed/not reported).

A random effect model was used to determine the association between the exposure and incidence or progression of CKD to account for heterogeneity in study area and population, dose of exposure, time of exposure and study design. The standard I^2 statistic was used to evaluate heterogeneity between studies. A higher I^2 statistic value indicates greater heterogeneity(Higgins JPT, 2022). Results were considered statistically significant at $p < 0.05$.

3. Results

3.1. Literature search and study characteristics

In total, 8775 studies were identified from literature in the systematic search. After screening the titles and abstracts, 450 studies were selected for full-study screening. Sixty-six studies met the inclusion criteria and were included in the systematic review (Fig. 1). There were 41 included studies (62%) from Asia, 16 (24%) from North America, and 9 from (14%) Europe (Table 1). Two studies (3%) had a case-control design(Arain et al., 2015; Chen et al., 2019), whereas the other studies had a cohort design.

The mean number of participants per study was 229,195, ranging between 71 and 3,083,227 participants. The mean age ranged from 27.1 to 75.3 years and the mean percentage of male participants in the studies was 53%. Eighteen studies (27%) included participants without CKD at baseline(Bo et al., 2021; Bowe et al., 2020, 2018; 2017; Chan et al., 2018; Dhingra et al., 2016; Duan et al., 2022; Grice et al., 2017; Harari et al., 2018; Hsu et al., 2017; Hwang et al., 2021; Li et al., 2021; Liu et al., 2022; Nie et al., 2021; Ran et al., 2020b; Tseng et al., 2020; Xu

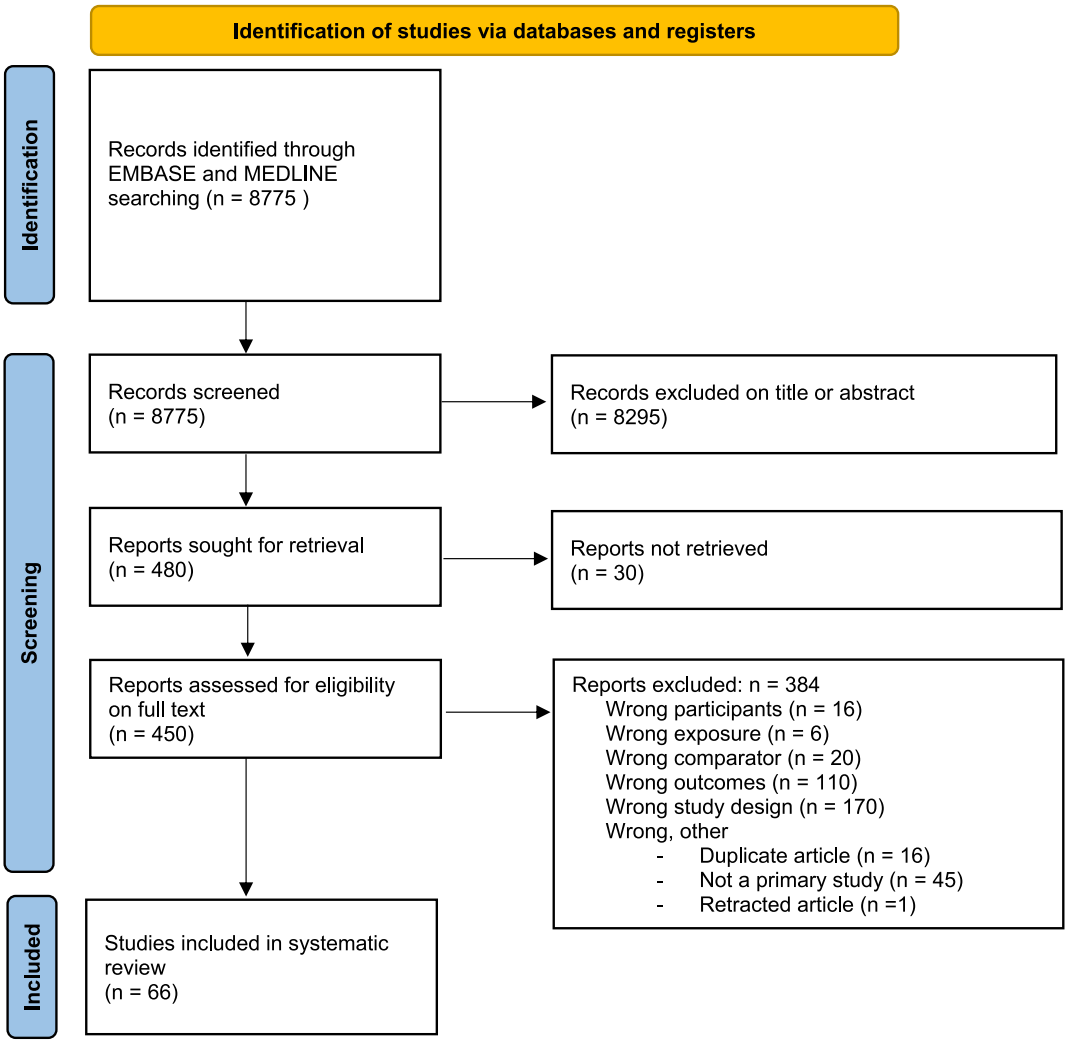

Fig. 1. Flowchart of the systematic review and meta-analysis according to PRISMA guidelines.

et al., 2022; Yang et al., 2021), 21 studies (32%) included CKD patients (Chang et al., 2022; Cheng et al., 2017; Y. Feng et al., 2021; Hsu et al., 2015; Huang et al., 2013; Jung et al., 2021a, 2021b; 2020; Kosnik et al., 2019; Lee et al., 2016; Lin et al., 2015, 2006; Y. T. Lin et al., 2020; Park et al., 2021; Ran et al., 2020a; Remigio et al., 2022; Tsai et al., 2018, 2019; Wu et al., 2022; Yoon et al., 2019; Yu et al., 2004), and ten studies (15%) had a mixed population of non-CKD and CKD participants(Arain et al., 2015; Blum et al., 2020; Chen et al., 2019; Gao et al., 2019; Ghazi et al., 2022; Lebov et al., 2015; Z. Li et al., 2022; Swaddiwudhipong et al., 2012; Wang et al., 2020, 2021). Baseline CKD stage was not reported in 17 studies (26%)(Arisawa et al., 2007; Cheng et al., 2018; Chowdhury et al., 2014; Fang et al., 2020; Y. M. Feng et al., 2021; Hellström et al., 2001; Hicken et al., 2019; Hodgson et al., 2007; Hotz et al., 1999; Jayasinghe et al., 2018; F. R. Li et al., 2022; Liang et al., 2012; S. Y. Lin et al., 2020; Mehta et al., 2016; So et al., 2022; Wang et al., 2022; C. D. Wu et al., 2020).

Time of follow-up ranged from 0.4 years to 26.8 years. Thirty-nine studies (59%) had a follow-up longer than five years(Arisawa et al., 2007; Blum et al., 2020; Bo et al., 2021; Bowe et al., 2020, 2018; 2017; Chan et al., 2018; Chowdhury et al., 2014; Ghazi et al., 2022; Grice et al., 2017; Harari et al., 2018; Hellström et al., 2001; Hicken et al., 2019; Hodgson et al., 2007; Hsu et al., 2017; Hwang et al., 2021; Jayasinghe et al., 2018; Jung et al., 2021b; Kosnik et al., 2019; Lebov et al., 2015; F. R. Li et al., 2022; Z. Li et al., 2022; Liang et al., 2012; S. Y. Lin et al., 2020; Mehta et al., 2016; Nie et al., 2021; Park et al., 2021; Ran et al., 2020a, 2020b; Remigio et al., 2022; So et al., 2022; Tsai et al., 2018, 2019; Tseng et al., 2020; Wang et al., 2022, 2021; C. D. Wu et al., 2020; Xu et al., 2022; Yang et al., 2021), 21 studies (32%) had a follow-up between one to five years(Chang et al., 2022; Cheng et al., 2017; Duan et al., 2022; Y. Feng et al., 2021; Y. M. Feng et al., 2021; Gao et al., 2019; Hotz et al., 1999; Hsu et al., 2015; Huang et al., 2013; Jung et al., 2020; Lee et al., 2016; Li et al., 2021; Lin et al., 2015, 2006; Y. T. Lin et al., 2020; Liu et al., 2022; Swaddiwudhipong et al., 2012; Wang et al., 2020; Wu et al., 2022; Yoon et al., 2019; Yu et al., 2004), and one study (1%) had a follow-up less than a year(Fang et al., 2020). For five studies (8%), the follow-up time was not reported(Arain et al., 2015; Chen et al., 2019; Cheng et al., 2018; Dhingra et al., 2016; Jung et al., 2021a).

3.2. *Risk of bias assessment*

Forty-two studies (64%)(Arain et al., 2015; Arisawa et al., 2007; Blum et al., 2020; Bo et al., 2021; Bowe et al., 2020, 2018, 2017; Chang et al., 2022; Chen et al., 2019; Cheng et al., 2017; Chowdhury et al., 2014; Dhingra et al., 2016; Duan et al., 2022; Fang et al., 2020; Y. Feng et al., 2021; Y. M. Feng et al., 2021; Gao et al., 2019; Grice et al., 2017; Hellström et al., 2001; Hodgson et al., 2007; Hsu et al., 2015; Huang et al., 2013; Jung et al., 2021a, 2021b, 2020; Kosnik et al., 2019; Lebov et al., 2015; Li et al., 2021; Liang et al., 2012; Lin et al., 2015; S. Y. Lin et al., 2020; Liu et al., 2022; Mehta et al., 2016; Park et al., 2021; Ran et al., 2020a; So et al., 2022; Tsai et al., 2018; Wang et al., 2020, 2021; C.

Table 1
Baseline characteristics of included studies.[a]

Study	Country	Time of follow-up in years in mean (SD) or median [IQR]	Study sample size (% CKD)	Percentage of male	Mean age (SD)	Mean BMI (SD)	DM (%)	Current smokers (%)	Former smokers (%)	Hypertension (%)
Arain et al. (2015) (Arain et al., 2015)	Pakistan	NR	308 (40.5)	100.0	NR	NR	NR	100.0	NR	NR
Arisawa et al. (2007) (Arisawa et al., 2007)	Japan	Cohort I: 23 Cohort II: 13 [b]	Cohort I (1982–2005): 275; Cohort II (1992–2005): 329 Pooled: 604 (NR)	Cohort I: 41.5 Cohort II: 42.9 Pooled: 42.3	Cohort I: 60.6 (7.6) Cohort II: 61 (8.3)	Cohort I: 22.0 (2.6) Cohort II: NR	NR	NR	NR	NR
Blum et al. (2020) (Blum et al., 2020)	US	17.7 [NR]	10,997 (6.3)	44.0	63 (6)	28.8 (5.6)	16.5	14.7	43.5	47.5
Bo et al. (2021) (Bo et al., 2021)	Taiwan	5.1 [2.1–7.4]	163,197 (NR)	50.4	38.4 (11.6)	23.0 (3.6)	3.3	19.5	5.4	12.7
Bowe et al. (2017) (Bowe et al., 2017)	US	8.5 [8.0–8.8]	2,010,398 (0.0)	95.0	62.2 (4.4)	NR	27.8	25.7	21.7	66.8
Bowe et al. (2018) (Bowe et al., 2018)	US	8.5 [8.0–8.8]	2,482,737 (0.0)	95.2	62.5 (2.9)	NR	27.8	25.5	21.0	67.3
Bowe et al. (2020) (Bowe et al., 2020)	US	8.5 [8.0–8.8]	2,444,157 (0.0)	95.2	62.5 (2.9)	28.1 (1.1)	28.2	25.5	21.1	NR
Chan et al. (2018) (Chan et al., 2018)	Taiwan	6.5 (NR)	100,629 (NR)	52.5	38.9 (11.3)	22.9 (3.5)	3.2	20.3	5.4	12.5
Chang et al. (2022) (Chang et al., 2022)	Taiwan	2.54 (1.25)	5301 (100.0)	58.5	62.6 (14.0)	NR	39.7	25.6	NR	73.3
Chen et al. (2019) (Chen et al., 2019)	China	NR	331 (5.4)	33.5	57.4 (9.1)	23.5 (4.4)	NR	34.1	NR	NR
Cheng et al. (2018) (Cheng et al., 2018)	Taiwan	NR	339,330 (NR)	51.5	54.12 (12.9)	NR	22.1	NR	NR	43.7
Cheng et al. (2017) (Cheng et al., 2017)	Taiwan	1–2 [b]	8854 (100.0)	62.3	47.5 (13.0)	NR	10.3	27.2	NR	26.8
Chowdhury et al. (2014) (Chowdhury et al., 2014)	US	12.2 [NR]	58,307 (NR)	100.0	39.0 (11.7)	NR	NR	NR	NR	NR
Dhingra et al. (2016) (Dhingra et al., 2016)	US	NR	28,240 (0.0)	48.7	51.8 (15.2)	NR	85.5	20.1	31.1	42.7
Duan et al. (2022) (Duan et al., 2022)	China	3.8 [2.0–5.5]	72,425 (0.0)	58.3	38 (3.0)	23.4 (0.8)	6.8	NR	NR	27.9
Fang et al. (2020) (Fang et al., 2020)	China	0.42 [b]	71 (NR)	49.3	65.1 (2.8)	25.0 (2.4)	NR	NR	NR	NR
Feng et al. (2021) (Y. Feng et al., 2021)	US	1.8 [0.8–3.3]	384,276 (100.0)	55.6	74.5 (1.9)	27.3 (1.5)	NR	3.9	NR	NR
Feng et al. (2021) (Y. M. Feng et al., 2021)	Belgium	4.7 (NR)	820 (NR)	49.3	51.2 (15.7)	26.5 (4.3)	3.9	20.5	NR	41.6
Gao et al. (2019) (Gao et al., 2019)	US	3–5 [b]	809 (22.0)	100.0	72.3 (6.7)	NR	13.6	4.5	65.2	71.0
Ghazi et al. (2022) (Ghazi et al., 2022)	US	8.5 [NR]	113,725 (11.3)	45.0	50 (18)	NR	11.0	NR	NR	35.0
Grice et al. (2017) (Grice et al., 2017)	US	26.8 [16.0–32.4]	149 (0.0)	34.0	37.9 (3.7)	33.1 (1.3)	100.0	NR	NR	NR
Harari et al. (2018) (Harari et al., 2018)	Sweden	16 (NR)	2567 (0.0)	39.8	57 (5.9)	26 (3.9)	7.8	26.1	33.8	63.1
Hellström et al. (2001) (Hellström et al., 2001)	Sweden	17 [b]	NR	NR	NR	NR	NR	NR	NR	NR
Hicken et al. (2019) (Hicken et al., 2019)	US	9.2 [8.4–9.6]	5892 (NR)	48.0	62 (10)	28 (5)	12.0	13.0	37.0	44.0
Hodgson et al. (2007) (Hodgson et al., 2007)	UK	20 [b]	NR	NR	NR	NR	NR	NR	NR	NR
Hotz et al. (1999) (Hotz et al., 1999)	Belgium	5 [b]	593 (NR)	35.1	45.2 (14.5)	25.9 (4.6)	2.3	31.8	20.2	30.9
Hsu et al. (2015) (Hsu et al., 2015)	Taiwan	3 [b]	937 (100.0)	50.7	56.0 (13.6)	22.2 (3.2)	22.0	18.2	NR	17.0
Hsu et al. (2017) (Hsu et al., 2017)	Taiwan	14 [b]	6093 (0.0)	49.6	62.2 (9.7)	24.3 (3.6)	NR	40.1	NR	NR
Huang et al. (2013) (Huang et al., 2013)	Taiwan	2 [b]	89 (100.0)	65.2	60.1 (9.5)	24.9 (3.3)	100.0	15.7	NR	95.5
Hwang et al. (2021) (Hwang et al., 2021)	Korea	8 [b]	164,093 (0.0)	47.8	NR	NR	NR	23.0	5.3	NR
Jayasinghe et al. (2018) (Jayasinghe et al., 2018)	Sweden	10 [b]	1016 (NR)	50	70 (0.0)	27 (4.3)	NR	NR	NR	NR

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Table 1 (*continued*)

Study	Country	Time of follow-up in years in mean (SD) or median [IQR]	Study sample size (% CKD)	Percentage of male	Mean age (SD)	Mean BMI (SD)	DM (%)	Current smokers (%)	Former smokers (%)	Hypertension (%)
Jung et al. (2021a) (Jung et al., 2021a)	Korea	13 [b]	29,602 (100.0)	47.0	55.3 (17.0)	NR	21.0	NR	NR	33.0
Jung et al. (2020) (Jung et al., 2020)	Korea	4.2 (1.8)	5041 (100.0)	59.0	60.5 (13.5)	22.9 (3.4)	10.0	10.0	30.0	NR
Jung et al. (2021b) (Jung et al., 2021b)	Korea	Participants from 2002: 6.1 (4.0); participants from 2008: 4.1 (2.5)	48,319 (100.0)	48.6	57.6 (17.0)	NR	21.0	NR	NR	34.2
Kosnik et al. (2019) (Kosnik et al., 2019)	US	14 [b]	1,092,281 (100.0)	55.8	NR	NR	NR	5.9	NR	NR
Lebov et al. (2015) (Lebov et al., 2015)	US	15.4 [b]	13,717 (0.5)	0.0	NR	NR	4.0	NR	NR	16.4
Lee et al. (2016) (Lee et al., 2016)	Taiwan	3 [b]	306 (100.0)	36.9	49.3 (13.5)	NR	12.1	22.2	NR	87.3
Li et al. (2021) (Li et al., 2021)	China	1–3 [b]	169 (0.0)	36.7	64.0 (8.7)	24.9 (3.6)	14.8	11.8	10.1	54.4
Li et al. (2022) (F. R. Li et al., 2022)	UK	11.7 [NR]	381,678 (NR)	44.0	55.7 (8.1)	27.1 (4.6)	3.7	9.9	NR	NR
Li et al. (2022) Z. (Li et al., 2022)	China	10 [b]	967 (27.6)	50.4	63.9 (6.2)	25.1 (3.3)	100.0	15.8	12.7	64.5
Liang et al. (2012) (Liang et al., 2012)	China	8 [b]	412 (0.0)	34.0	NR	NR	NR	NR	NR	NR
Lin et al. (2015) (Lin et al., 2015)	Taiwan	2 [b]	160 (100.0)	23.8	50.5 (10.5)	NR	11.9	0.0	NR	45.6
Lin et al. (2006) (Lin et al., 2006)	Taiwan	2 [b]	108 (100.0)	NR	56.2 (12.7)	25.6 (3.6)	NR	5.6	NR	NR
Lin et al. (2020) (S. Y. Lin et al., 2020)	Taiwan	11.9 [11.8–12.0]	161,970 (0.0)	43.8	37.9 (3.4)	NR	10.1	NR	NR	29.1
Lin et al. (2020) (Y. T. (Lin et al., 2020))	Taiwan	1–12 [b]	6628 (100.0)	57.6	67.8 (3.2)	24.4 (0.8)	35.8	9.9	7.9	56.4
Liu et al. (2022) (Liu et al., 2022)	China	1.5 [NR]	90,032 (NR)	48.4	68.4 (6.3)	25.1 (3.6)	15.0	19.6	NR	40.5
Mehta et al. (2016) (Mehta et al., 2016)	US	11 [b]	669 (NR)	100.0	73.5 (6.8)	28.2 (4.1)	17.0	5.0	67.0	71.0
Nie et al. (2021) (Nie et al., 2021)	China	10 [b]	1370 (0.0)	41.2	61.7 (6.6)	24.6 (3.3)	NR	18.2	9.1	43.3
Park et al. (2021) (Park et al., 2021)	Korea	6.8 (4.6)	64,565 (100.0)	49.0	54.0 (17.0)	NR	22.1	5.1	NR	32.0
Ran et al. (2020a) (Ran et al., 2020a)	China	9–12 [b]	902 (100.0)	42.1	72.8 (6.0)	NR	67.0	NR	NR	34.9
Ran et al. (2020b) (Ran et al., 2020b)	China	10–12 [b]	61,447 (0.0)	34.1	72.0 (5.6)	NR	12.3	9.6	19.3	36.0
Remigio et al. (2022) (Remigio et al., 2022)	US	15 [b]	48,338 (100.0)	57.5	NR	NR	59.9	NR	NR	NR
So et al. (2022) (So et al., 2022)	Denmark	17 [b]	3,083,227 (NR)	48.3	53.0 (15.2)	NR	NR	NR	NR	NR
Swaddiwudhipong et al. (2012) (Swaddiwudhipong et al., 2012)	Thailand	5 [b]	436 (17.7)	34.2	51.9 (12.4)	22.0 (4.0)	6.9	57.3	NR	32.8
Tsai et al. (2018) (Tsai et al., 2018)	Taiwan	12 [b]	2343 (100.0)	57.3	66,4 (13.2)	25.1 (4.2)	43.3	8.7	NR	71.7
Tsai et al. (2019) (Tsai et al., 2019)	Taiwan	7.0 [4.3–8.2]	293 (100.0)	54.0	57 (14)	25.8 (4.1)	38.0	22.0	NR	84.0
Tseng et al. (2020) (Tseng et al., 2020)	Taiwan	13 [b]	4075 (0.0)	82.09	43.1 (18.4)	NR	13.3	NR	NR	9.6
Wang et al. (2020) (Wang et al., 2020)	China	1 [b]	7071 (0.6)	0.0	46.0 (2.3)	NR	NR	NR	NR	NR
Wang et al. (2022) (Wang et al., 2022)	UK	11.7 [NR]	458,968 (0.0)	45.6	55.6 (8.1)	NR	NR	10.4	NR	NR
Wang et al. (2021) (Wang et al., 2021)	China	8 [b]	467 (3.2)	34.9	51.2 (11.0)	22.9 (3.1)	NR	16.3	NR	NR
Wu et al. (2020) (C. D. Wu et al., 2020)	Taiwan	10 [b]	623,894 (NR)	48.7	42.3 (16.2)	NR	NR	NR	NR	18.0
Wu et al. (2022) (Wu et al., 2022)	Taiwan	2.3 (2.9)	6480 (100.0)	61.5	75.3 (14.8)	NR	42.3	9.9	26.2	74.5
Xu et al. (2022) (Xu et al., 2022)	Sweden	19.5 (SD)	30,396 (0.0)	40.0	58 (8)	25.8 (4.1)	5.0	28.0	34.0	28.0
Yang et al. (2021) (Yang et al., 2021)	US	24 (SD)	3768 (0.0)	47.2	27.1 (3.6)	27.4 (5.9)	14.0	18.5	NR	59.6
Yoon et al. (2019) (Yoon et al., 2019)	Korea	4.7 (4.4)	31,291 (100.0)	59.0	65.6 (12.3)	21.2 (3.1)	53.6	NR	NR	40.5
Yu et al. (2004) (Yu et al., 2004)	Taiwan	4 [b]	121 (100.0)	76.8	57.0 (13.0)	25.9 (3.6)	0.0	NR	10.0	76.0

[a] Abbreviations: BMI= Body Mass Index, DM = Diabetes Mellitus, CKD= Chronic Kidney Disease, IQR=Interquartile range, NR= Not reported, SD = standard deviation, UK = United Kingdom, US= United States.

[b] The reported follow-up time was not specifically mentioned as mean or median follow-up time in the article.

D. Wu et al., 2020; Wu et al., 2022; Yu et al., 2004)were rated as having a high risk of bias, 23 studies (35%)(Chan et al., 2018; Cheng et al., 2018; Ghazi et al., 2022; Harari et al., 2018; Hicken et al., 2019; Hotz et al., 1999; Hsu et al., 2017; Hwang et al., 2021; Jayasinghe et al., 2018; Lee et al., 2016; F. R. Li et al., 2022; Z. Li et al., 2022; Lin et al., 2006; Y. T. (Lin et al., 2020); Nie et al., 2021; Ran et al., 2020b; Remigio et al., 2022; Swaddiwudhipong et al., 2012; Tsai et al., 2019; Tseng et al., 2020; Wang et al., 2022; Xu et al., 2022; Yang et al., 2021) were rated as having low risk of bias, and one study (1%) was rated as having very high risk of bias in overall performance(Yoon et al., 2019) (Supplementary Table S2). The worst scoring NOS items were ascertainment of exposure (mean = 0.42 out of 1 max), comparability of cohorts (mean = 1.05 out of 2 max) and adequacy of follow-up of cohorts (mean = 0.18 out of 1 max).

3.3. General external exposures and outcomes

The overview of exposure and outcomes per study is presented in Supplementary Table S3. The majority of studies investigated air pollution (n = 33; 48%, PM2.5, PM10, nitric oxides (NO_x), NO_2, NO, sulfur dioxide (SO_2), ozone (O_3), carbon monoxide (CO), and black carbon (BC))(Blum et al., 2020; Bo et al., 2021; Bowe et al., 2020, 2018; 2017; Chan et al., 2018; Chang et al., 2022; Duan et al., 2022; Fang et al., 2020; Y. Feng et al., 2021; Y. M. Feng et al., 2021; Gao et al., 2019; Ghazi et al., 2022; Hwang et al., 2021; Jung et al., 2021a, 2021b; 2020; Li et al., 2021; F. R. Li et al., 2022; Lin et al., 2015; S. Y. Lin et al., 2020; Y. T. Lin et al., 2020; Liu et al., 2022; Mehta et al., 2016; Ran et al., 2020a, 2020b; Remigio et al., 2022; So et al., 2022; Wang et al., 2020, 2022; C. D. Wu et al., 2020; Wu et al., 2022; Xu et al., 2022) or heavy metals (n = 21; 30%, cadmium, lead, arsenic, and mercury)(Arain et al., 2015; Arisawa et al., 2007; Chen et al., 2019; Cheng et al., 2018, 2017; Chowdhury et al., 2014; Harari et al., 2018; Hellström et al., 2001; Hodgson et al., 2007; Hotz et al., 1999; Hsu et al., 2015, 2017; Huang et al., 2013; Lee et al., 2016; Liang et al., 2012; Lin et al., 2006; Swaddiwudhipong et al., 2012; Tsai et al., 2018; Wang et al., 2021; Yang et al., 2021; Yu et al., 2004) on the incidence or progression of CKD. Chemicals were investigated in seven studies (10%), which included three studies about pesticides(Grice et al., 2017; Jayasinghe et al., 2018; Lebov et al., 2015), two studies about perfluorooctanoic acid (PFOA) and perfluorooctanesulfonic acid (PFOS)(Dhingra et al., 2016; Z. Li et al., 2022), one study about melamine(Tsai et al., 2019) and one study about bisphenol A(Nie et al., 2021). Five studies (7%) focused on the association between built environmental factors on incidence and progression of CKD, of which three focused on greenness(Jung et al., 2021a; Park et al., 2021; C. D. Wu et al., 2020) and the remaining two focused on neighborhood social context(Hicken et al., 2019) and access to healthcare/environmental quality index(Kosnik et al., 2019). Lastly, two studies (3%) determined the association between heat injury/heat stress(Remigio et al., 2022; Tseng et al., 2020) and one study (1%) determined the association between sunlight on CKD incidence or progression(Yoon et al., 2019).

Time of exposure was not reported in 38 (58%) studies(Arain et al., 2015; Arisawa et al., 2007; Blum et al., 2020; Bo et al., 2021; Bowe et al., 2020, 2018, 2017; Chan et al., 2018; Chen et al., 2019; Cheng et al., 2018, 2017; Chowdhury et al., 2014; Y. Feng et al., 2021; Y. M. Feng et al., 2021 ; Grice et al., 2017; Harari et al., 2018; Hellström et al., 2001; Hicken et al., 2019; Hodgson et al., 2007; Hotz et al., 1999; Hsu et al., 2015, 2017; Huang et al., 2013; Jayasinghe et al., 2018; Jung et al., 2021b; Lee et al., 2016; Z. Li et al., 2022; Lin et al., 2006; S. Y. Lin et al., 2020; Nie et al., 2021; Park et al., 2021; Tsai et al., 2018, 2019; Tseng et al., 2020; Wu et al., 2022; Yang et al., 2021; Yoon et al., 2019; Yu et al., 2004), longer than five years in ten (15%) studies(Jung et al., 2021a; Liang et al., 2012; Y. T. Lin et al., 2020; Mehta et al., 2016; Ran et al., 2020a, 2020b; Remigio et al., 2022; So et al., 2022; Wang et al., 2020, 2021), between 1 and 5 years in 11 (17%) studies(Chang et al., 2022; Dhingra et al., 2016; Duan et al., 2022; Fang et al., 2020; Ghazi et al., 2022; Hwang et al., 2021; F. R. Li et al., 2022; Lin et al., 2015; Liu et al., 2022; Swaddiwudhipong et al., 2012; Wang et al., 2022), less than one year in three (5%) studies(Gao et al., 2019; Kosnik et al., 2019; Li et al., 2021) and variable in four (6%) studies(Jung et al., 2020; Lebov et al., 2015; C. D. Wu et al., 2020; Xu et al., 2022). Exposure to air pollution was mainly estimated from a database based on residential addresses, whereas exposure to metals and chemicals was usually measured by analytical sampling in urine or blood. Change in eGFR was the most often reported outcome (n = 27; 41%), followed by diagnosis of CKD (n = 23; 35%), CKD-related mortality (n = 19; 29%), and progression to kidney failure or KRT (n = 15; 23%). Albuminuria was the least often reported outcome (n = 4; 6%).

The studies were heterogeneous in aspects such as definition used for incidence and progression of CKD or kidney failure (Supplementary Table S4), formula used to calculate eGFR, reporting of effect measure, unit of exposure, and estimated dose of exposure (Supplementary Table S3).

4. Metals

No meta-analyses were performed for the studies on metals due to heterogeneity in effect measurement, unit of exposure, or study population. Heavy metal exposure was associated with an increased risk of adverse kidney outcomes in most studies. Specifically, the majority of studies found an association between exposure to cadmium/lead/arsenic and decrease of eGFR. However, the evidence across these studies remains inconsistent and uncertain.

Four studies reported that exposure of cadmium was associated with a decrease in eGFR (Arain et al., 2015; Liang et al., 2012; Swaddiwudhipong et al., 2012; Wang et al., 2021), whereas two studies did not find this association(Chen et al., 2019; Hotz et al., 1999). One study found an association between increased cadmium exposure and presence of albuminuria(Liang et al., 2012). Two studies found an increased risk of CKD incidence(Swaddiwudhipong et al., 2012; Wang et al., 2021). One study found that moderate, but not high exposure to cadmium was associated with increased risk of KRT(Swaddiwudhipong et al., 2012). Increased cadmium exposure was also associated with an increased CKD-related mortality in two studies (Hsu et al., 2015; Lee et al., 2016), whereas one study did not observe this association(Arisawa et al., 2007).

Exposure to lead was associated with a decrease in eGFR in four studies(Harari et al., 2018; Huang et al., 2013; Lin et al., 2006; Yu et al., 2004), whereas one study did not find this association(Chen et al., 2019). One study found that exposure to lead in the highest quantile compared to the reference was associated with increased incidence of CKD(Harari et al., 2018). Exposure to lead was not associated with incidence of kidney failure in one study(Chowdhury et al., 2014).

Exposure to arsenic was associated with a decreased eGFR in two studies(Arain et al., 2015; Cheng et al., 2017), whereas one study did not find this association(Yang et al., 2021). One study(Hsu et al., 2017) found that increased exposure to arsenic was associated with an increased incidence of CKD but this was not replicated in another study (Yang et al., 2021). Higher exposure to arsenic was associated with an increased risk of incidence of kidney failure in one study(Cheng et al., 2018).

4.1. Chemicals

No meta-analyses were performed for the studies on chemicals due to heterogeneity in chemical of exposure. No conclusive results can be drawn due to the limited studies on classes of chemical toxicants such as pesticides, per- and polyfluoroalkyl substances and organic compounds. Exposure to some pesticides, e.g. alachlor, butylate and paraquat and some low chlorine polychlorinated biphenyls, was associated with progression of CKD to kidney failure(Grice et al., 2017; Lebov et al., 2015). Other pesticides, such as dichlorvos, chlorpyrifos, diazinon, parathion, permethrin, lindane, and persistent pesticides were not associated with incidence of kidney failure. One study showed that increased baseline serum dichlorodiphenyldichloroethylene levels were associated with greater eGFR decline over time(Jayasinghe et al., 2018). No association was found between PFOA exposure and incidence of CKD(Dhingra et al., 2016; Z. Li et al., 2022). Exposure to increased levels of PFOS was associated with decreased CKD incidence in patients with type II diabetes (Z. Li et al., 2022). Exposure to high level melamine was associated with a decrease in eGFR, but not incidence of kidney failure(Tsai et al., 2019). Increased exposure to bisphenol A was associated with decrease in annual eGFR decline and incidence of CKD(Nie et al., 2021).

4.2. Built environment

No meta-analyses were performed for the studies on built environment due to heterogeneity in effect measurement, unit of exposure or study population. Three studies focused on the association of greenness, as measured by the Normalized Difference Vegetation Index(Jung et al., 2021a; Park et al., 2021) or measured using the percentage of green space in the residential environment(C. D. Wu et al., 2020), with CKD outcomes. Jung et al. found an association between increased exposure to greenness and increased mortality in CKD patients, whereas Park et al., did not. Wu et al. found an association between increased exposure to greenness and decreased incidence of kidney failure, whereas Park et al. did not (Park et al., 2021; C. D. Wu et al., 2020). The neighborhood problem score and neighborhood social cohesion score were not associated with increased decline of eGFR from baseline (Hicken et al., 2019). The difference in environmental quality index categories was not associated with CKD-related mortality(Kosnik et al., 2019). The same study reported that survival of kidney failure was increased in patients living over 10 miles from the nearest hospital compared to under 10 miles.

4.3. Other exposures

Patients with a history of heat injury were more likely to develop CKD and kidney failure, compared to patients without a history of heat injury(Tseng et al., 2020). However, exposure to extreme heat events were not associated with increased CKD mortality(Remigio et al., 2022). Increased exposure to sunlight was associated with an increased risk of CKD-related mortality in kidney failure patients(Yoon et al., 2019).

5. Air pollution

5.1. PM2.5 and incidence of CKD

Nine studies (follow-up time ranged from 1.53 to 11.9 years) were included in the meta-analysis of PM2.5 and incidence of CKD(Bowe et al., 2020, 2018; Chan et al., 2018; Duan et al., 2022; Ghazi et al., 2022; F. R. Li et al., 2022; S. Y. Lin et al., 2020; Liu et al., 2022; Wang et al., 2022)(Fig. 2). PM2.5 was consistently associated with an increased risk of CKD regardless of study population (without CKD or mixed population) or whether studies compared the risk per 10 $\mu g/m^3$, or quantiles of exposure.

5.2. PM2.5 and incidence of kidney failure

Five studies (follow-up time ranged from 8.52 to 12 years) included in the meta-analysis of PM2.5 and progression to kidney failure(Bowe et al., 2020, 2018; S. Y. Lin et al., 2020; Y. T. Lin et al., 2020; C. D. Wu

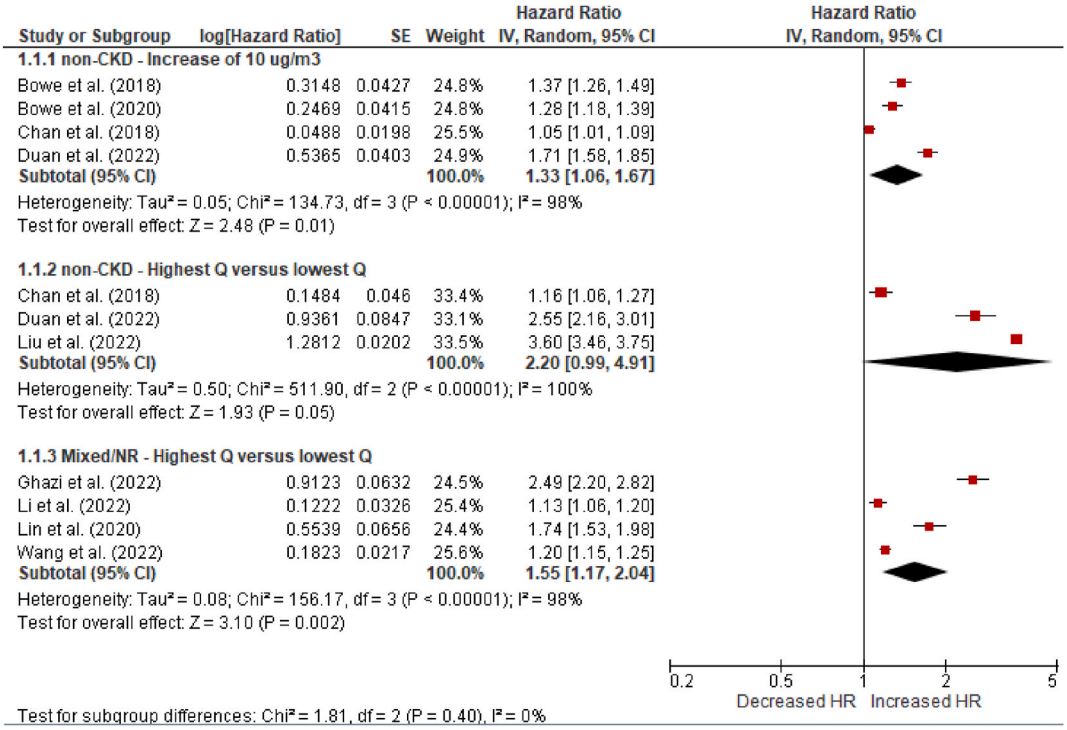

Fig. 2. Forest plot demonstrating HR and 95% CI of pooled results from the random effects models to evaluate the association between PM2.5 and incidence of CKD. Abbreviations: CKD = chronic kidney disease; CI = confidence interval; HR = hazard ratio; PM = particulate matter; NR = not reported, Q = quantile.

et al., 2020) (Fig. 3). PM2.5 was consistently associated with an increased risk of kidney failure regardless of study population (without CKD, with CKD or mixed population) or whether studies compared the risk per 10 μg/m^3, or quantiles of exposure.

5.3. PM2.5 and CKD-related mortality

Three studies (follow-up time ranged from 1.84 to 17 years) were included in the meta-analysis of PM2.5 and CKD-related mortality(Y. Feng et al., 2021; Y. T. Lin et al., 2020; So et al., 2022)(Fig. 4). There was mixed evidence regarding the association of exposure of PM2.5 and CKD-related mortality when comparing the risk per 10 μg/m^3 in a mixed population and population with CKD and the quantiles of exposure in a population with CKD. All but one study observed no association between PM2.5 and CKD-related mortality(Y. Feng et al., 2021).

5.4. NO_2 and incidence of CKD

Five studies (follow-up time ranged from 1.57 to 11.9 years) were included in the meta-analysis of PM2.5 and incidence of CKD(Hwang et al., 2021; F. R. Li et al., 2022; S. Y. Lin et al., 2020; Liu et al., 2022; Wang et al., 2022)(Fig. 5). There was mixed evidence regarding the association of exposure of NO_2 on increased risk of CKD when comparing the highest quantile to the lowest quantile in non-CKD and mixed population, as all but one study showed no association of NO_2 exposure and incidence of CKD(Hwang et al., 2021).

5.5. PM10 and incidence of CKD

Four studies (follow-up time ranged from 1.57 to 11.7 years) were included in the meta-analysis of PM10 and incidence of CKD(Hwang et al., 2021; F. R. Li et al., 2022; Liu et al., 2022; Wang et al., 2022) (Fig. 6). There was mixed evidence regarding the association of exposure of PM10 on increased risk of CKD when comparing the highest quantile to the lowest quantile in non-CKD and mixed population, as all but one study showed no association of PM10 exposure and incidence of CKD (Hwang et al., 2021).

5.6. Subgroup analysis

No differences were found in the subgroup analysis of the association between PM2.5 and incidence of CKD, progression to kidney failure and CKD-related mortality (i.e. p-values for interaction were 0.40, 0.75 and 0.31, respectively) (Figs. 2–4). Additionally, no differences were found in the subgroup analysis regarding the association of NO_2 (Fig. 5) and PM10 (Fig. 6) with incidence of CKD (i.e. p-values for interaction were 0.54 and 0.40, respectively).

6. Discussion

6.1. Main findings

This systematic review provides a comprehensive, up-to-date overview of the general external exposome and its association with the development and progression of CKD. Current literature reports mostly on air pollution and heavy metals. Little is published on chemicals or built environmental factors. Built environment remains limited to green space, and no articles were found that evaluated the association between climate change, noise, food supply or urbanization and kidney disease. These built environmental factors may influence mental health and lifestyle factors such as physical activity and diet which are implicated in the pathophysiology of CKD (Dixon et al., 2021; Renalds et al., 2010; Smith et al., 2017).

Due to the large heterogeneity in the included articles, the determination of one environmental factor instead of co-exposure on development or progression of CKD and the lack of quality in an considerable number of environmental exposure articles, the results should be interpreted tentatively.

Long-term exposure to certain air pollutants likely increases the susceptibility to development and progression of CKD. This meta-analysis shows an association between PM2.5 exposure with increased incidence of CKD, in accordance with two other meta-analyses (Liu

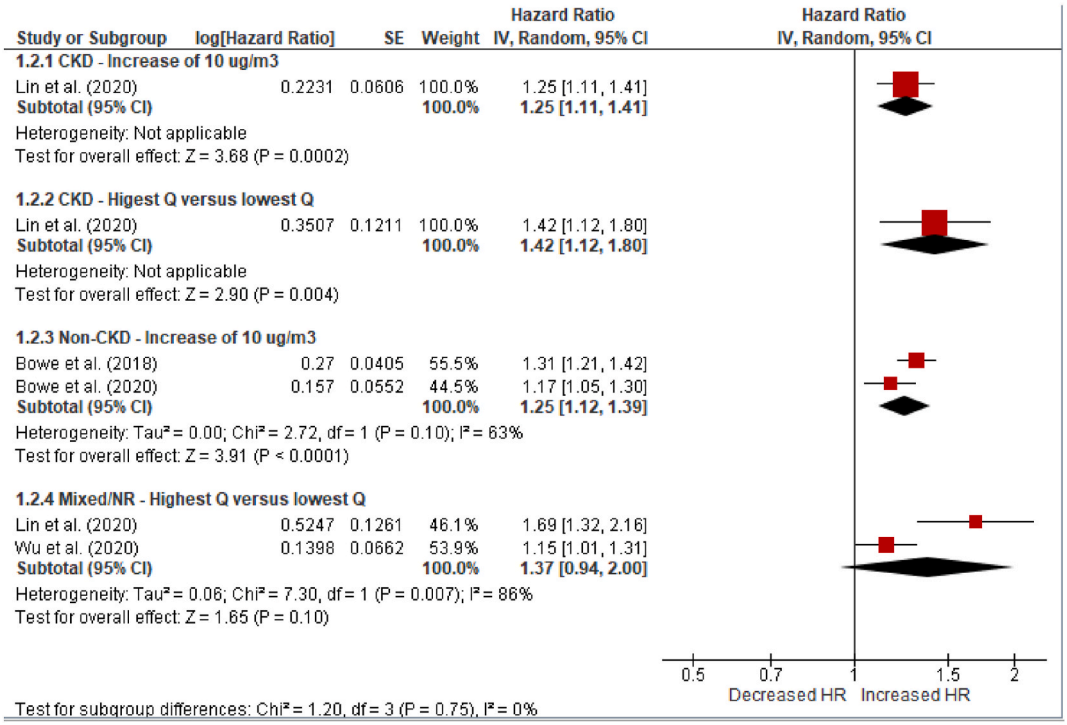

Fig. 3. Forest plot demonstrating HR and 95% CI of pooled results from the random effects models to evaluate the association between PM2.5 and progression to kidney failure. Abbreviations: CI = confidence interval; HR = hazard ratio; PM = particulate matter; NR = not reported, Q = quantile.

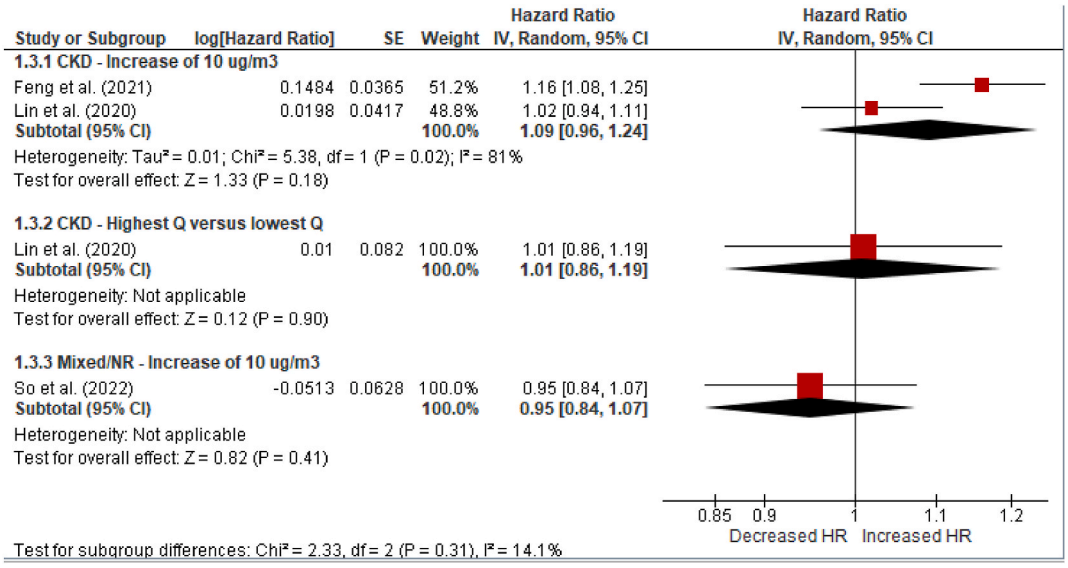

Fig. 4. Forest plot demonstrating HR and 95% CI of pooled results from the random effects models to evaluate the association between PM2.5 and CKD-related mortality. Abbreviations: CKD = chronic kidney disease; CI = confidence interval; HR = hazard ratio; PM = particulate matter; NR = not reported, Q = quantile.

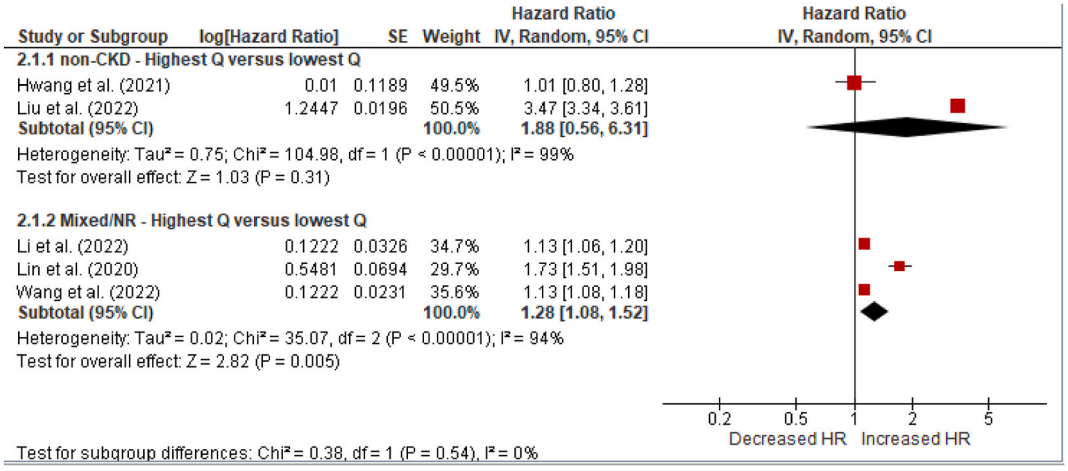

Fig. 5. Forest plot demonstrating HR and 95% CI of pooled results from the random effects models to evaluate the association between NO_2 and incidence of CKD. Abbreviations: CKD = chronic kidney disease; CI = confidence interval; HR = hazard ratio; NO_2 = nitric dioxide, NR = not reported, Q = quantile.

et al., 2020; M. Y. Wu et al., 2020). Interestingly, to our knowledge, our meta-analysis is the first to determine an association between PM2.5 exposure with progression to kidney failure, but not with CKD-related mortality. Moreover, our meta-analysis showed mixed evidence regarding the association of exposure to NO_2 and PM10 on increased incidence of CKD. The meta-analysis by Wu et al. did report an association between NO_2 and PM10 and the incidence of CKD (M. Y. Wu et al., 2020). The difference could be explained by the inclusion of different articles in the meta-analyses: we included more studies, which were published between 2020 and 2022, whereas Wu et al. included studies between 2017 and 2018.

6.2. Certainty of evidence

Large heterogeneity was found in the reporting of effect measurement, the unit of exposure and the estimated dose of exposure. For example, variation in exposure to cadmium and lead in different countries is dependent on factors such as diet, informal acid battery recycling, and electronic waste(Ericson et al., 2021; Satarug et al., 2020). Exposure to air pollutants is high in many cities worldwide, but generally higher in Asia(Kumar et al., 2018;New WHO global air quality guidelines: more pressure on nations to reduce air pollution levels, 2021; WHO, 2022). As an example, the air quality guidelines of the World Health Organization state that the recommended annually maximum exposure levels of PM2.5 and PM10 are 5 $\mu g/m^3$ and 15 $\mu g/m^3$(WHO, 2022). The reported average PM2.5 and PM10 exposure exceeded this limit in all but one study(F. R. Li et al., 2022) included in this systematic review(Chang et al., 2022; Jung et al., 2021b; Liu et al., 2022; Wang et al., 2020; Xu et al., 2022), with even exposures higher than 50 $\mu g/m^3$ (PM2.5) and 90 $\mu g/m^3$ (PM10)(Liu et al., 2022). Moreover, the included studies often determine the association of one environmental factor on development or progression of CKD, whereas environmental factors cannot be considered in isolation and co-exposures/interaction certainly apply in real time.

The quality of research in general external exposome and its association with the development and progression of CKD is low in several aspects. Firstly, almost all studies regarding air pollution, except one (Fang et al., 2020), did not measure personalized air pollution exposures

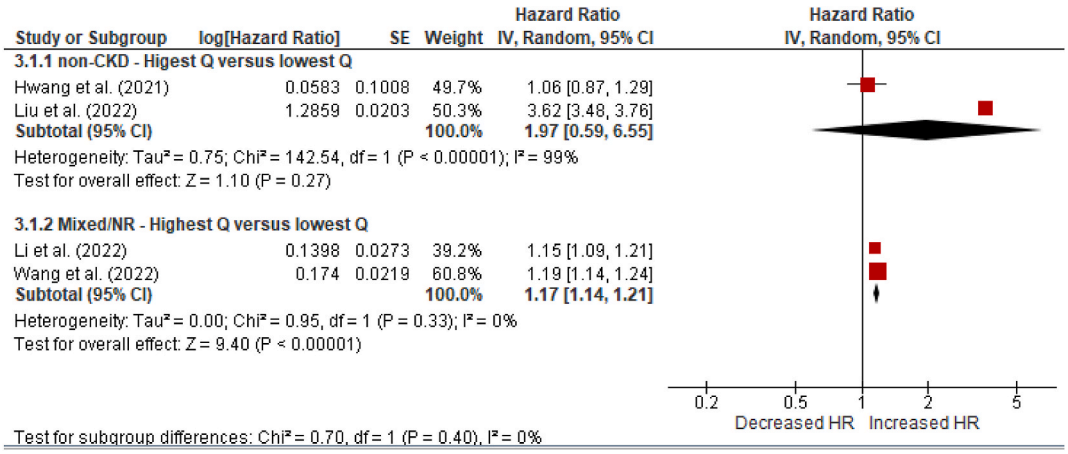

Fig. 6. Forest plot demonstrating HR and 95% CI of pooled results from the random effects models to evaluate the association between PM10 and incidence of CKD. Abbreviations: CKD = chronic kidney disease; CI = confidence interval; HR = hazard ratio; PM = particulate matter; NR = not reported, Q = quantile.

but relied on residential exposure levels. People within a same geographical location can have vastly different exposure levels (e.g. indoor vs. outdoor exposure), and therefore it is valuable to monitor personalized exposure to improve estimation of exposure levels. Secondly, the CKD patients in the included studies are often poorly defined. Including the CKD stage of the research population would be of important value, as declined kidney function leads to accumulation of toxic substances(Lim et al., 2021). Patients in advanced CKD stages might therefore be more susceptible to harmful effects of environmental exposures. Thirdly, time of exposure was also poorly reported. Toxicity is dependent on dose and duration of exposure, and consequently reporting of time of exposure is essential(Rozman and Doull, 2000). Fourthly, the adequacy of follow-up was insufficient, as indicated by our risk of bias assessment. Lastly, the comparability of cohorts was insufficient in the majority of articles. The comparability of cohort could be improved by adjustment of important variables related to susceptibility to CKD, e.g. age, hypertension, diabetes, history of smoking and BMI.

6.3. Potential biological mechanisms

The biological mechanism underlying the association of air pollution and kidney health can be direct or indirect(Shubham et al., 2022). Air pollutants are pro-inflammatory and cause direct kidney injury by inducing multiple interconnected metabolic pathways, which is described in-depth in the review by Shubham et al. (2022). Repeated cycles of inflammation, hypercoagulation, and hypoxia cause vascular injury and immune complex deposition. This chronic injury leads to glomerular sclerosis, tubular damage and atrophy, eventually resulting in reduced filtration and tubular function in the kidney. Air pollution can also indirectly affect kidney health by increasing the risk of CKD risk factors like diabetes, hypertension, and cardiovascular diseases, which in turn accelerate the development or progression of kidney disease (Brook, 2007; Rajagopalan and Brook, 2012).

The direct nephrotoxic mechanism of heavy metals has been described extensively(Madden and Fowler, 2000; Sabolić, 2006). In short, accumulation of heavy metals leads to depletion of antioxidants superoxide dismutase and glutathione and increase of reactive oxygen species, resulting in oxidative stress and lipid peroxidation. The increase in free radicals damage the permeability of intracellular organelles, leading to accumulation of Ca^{2+} in the organelles and release of cytochrome *c* in the cytoplasm. Cytochrome *c* promotes transformation of procaspase into caspase, which induces apoptosis and necrosis. Increased cell death eventually leads to loss of kidney function and development of CKD. Some of the heavy metals could amplify individual risk factors, such as development of cardiovascular diseases, and exacerbate kidney injury(Mishra et al., 2022). For example, cadmium desensitizes atrial natriuretic peptide receptors and may decrease the physiological regulation of blood pressure(Giridhar et al., 1992).

Future research should examine the interaction between environmental exposures and individual risk factors risk on CKD.

6.4. Strengths and limitations

This review provides an up-to-date, comprehensive overview of the current literature on the association between the general external exposome, including metals, chemicals, air pollution and built environment, and the development and progression of CKD, determined on multiple outcomes instead of one single outcome. By solely including cohort or case-control studies and excluding other study designs such as cross-sectional study designs, the association between exposure and outcome can be determined prospectively. Furthermore, excluding studies performed in a specific population, such as workers or participants in a contaminated area ensures that the results can be extrapolated to the general population in the researched region. Subgroup analyses allowed evaluation of the heterogeneity in effects.

One limitation of this review is that, although we attempted to group the most comparable studies, high statistical and clinical heterogeneity was identified, mainly due to large differences in dose of exposure measurements. Moreover, a potential overlap of included patients across studies cannot be completely excluded given the multiple analyses on large datasets. Lastly, we could not perform a meta-analysis of the continuous change in eGFR and exposure to components of the general external exposome due to lack of a control group.

6.5. Implications

It is likely that environmental risk factors can (indirectly) exacerbate the effect of individual risk factors and vice versa. For example, patients with hypertension may exhibit heightened vulnerability to the adverse effects of air pollution, as exposure to air pollution may exacerbate the pre-existing hypertension, resulting in increased susceptibility to renal damage(Tavera Busso et al., 2018). Therefore, it is important to take environmental as well as individual risk factors into account when assessing susceptibility to development or progression of CKD.

Potential measures could be taken by policymakers regarding environmental exposure and CKD. New measures would differ per region, as large differences can be found in quantity of environmental exposure as well as resources for mitigation strategies. This review emphasizes the importance of reducing air pollution. Mitigation strategies for air pollution include the promotion of active transport and sharing

mobility, the reduction of energy use in the household environment, energy production from renewable sources, and the use of electric vehicles(Sofia et al., 2020). People who are more vulnerable to air pollution, such as older adults and people who are active outdoors, might benefit most from these mitigation strategies(Carlisle and Sharp, 2001; Probst-Hensch, 2010). Improving air quality could reduce incidence of CKD among other health implications, such as respiratory and cardiovascular diseases(Al-Kindi et al., 2020; Jiang et al., 2016).

Moreover, the source of lead, cadmium and arsenic exposure is mainly food, air, cigarettes, and drinking water(Järup, 2003), and therefore anti-smoking campaigns and reduction of heavy metals in soil and plants are important. Strategies for reducing heavy metals accumulation include phytoremediation, avoiding the usage of phosphate fertilizers and using proper soil amendments(Narayanan and Ma, 2023; Schaefer et al., 2020). On an individual level, promotion of a high-antioxidant diet might reduce the toxic effects of heavy metals (Schaefer et al., 2020). Identification of populations that are vulnerable to heavy metal exposure, such as factory workers, would be of value to explore in future research(Sirinara et al., 2023).

7. Conclusion

The components of the general external exposome thpossat are mostly researched are air pollution and heavy metals. Long-term exposure to certain air pollutants and heavy metals likely increase the susceptibility to development and progression of CKD. Future exposome studies should focus on the effect of chemicals or built environments factors as these are currently underexplored. Large heterogeneity and mixed evidence were found across included studies and therefore more research is needed to draw conclusions on the effect of components of the general external exposome on development and progression of CKD. Studies should improve in quality by better reporting of time of exposure, loss of follow-up and CKD stage of the included population as well as the presence of comorbidities that enhance susceptibility to CKD such as hypertension, diabetes, and obesity.

Disclosure statement

The authors declares that they have no relevant or material financial interests that relate to the research described in this paper.

CRediT authorship contribution statement

Kate H. Liang: Conceptualization, Formal analysis, Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing. **Julia M.T. Colombijn:** Investigation, Writing – review & editing. **Marianne C. Verhaar:** Conceptualization, Writing – review & editing. **Marc Ghannoum:** Methodology, Writing – review & editing. **Erik J. Timmermans:** Conceptualization, Investigation, Methodology, Supervision, Writing – review & editing. **Robin W.M. Vernooij:** Conceptualization, Investigation, Methodology, Supervision, Writing – review & editing.

Declaration of competing interest

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

Data availability

No data was used for the research described in the article.

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Appendix A. Supplementary data

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