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Sexually dimorphic response to tobacco in the development of chronic kidney disease: a systematic review

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Abstract

Introduction Chronic kidney disease (CKD) demonstrates a complex interaction with tobacco exposure and sex differences, where females and males may experience varying risks and outcomes. This study aims to investigate how sex differences mediate the relationship between tobacco exposure and CKD development, with a secondary focus on regional variability and social determinants of health.

Study selection and criteria Comprehensive searches on MEDLINE, EMBASE, clinicaltrials.gov, and MedRxiv until October 6, 2022, were conducted. Eligibility criteria involved any study that reported primary data on the prevalence of CKD, with information pertaining to both sex and tobacco exposure.

Data extraction Data retrieved include patient socio-demographic characteristics, general study information, diagnostic methods, social determinants of health, and the cause of CKD (e.g., tobacco-related or non-tobacco-related).

Results Studies were selected through a comprehensive search using key terms such as "chronic kidney disease," "smoking," and "sex differences," which identified 3,025 articles, of which 28 were selected for full texts after screening titles, abstracts. Among the 28 included studies, smoking was consistently identified as a significant risk factor for CKD, with notable disparities related to sex, socioeconomic status, race, and urban versus rural settings. Significant geographical variability in CKD prevalence was observed, ranging from 2.5% to 68.1%, with the highest prevalence in Asia. However, due to high heterogeneity and methodological limitations, a meta-analysis of CKD prevalence stratified by sex and tobacco exposure was not feasible.

Conclusions The findings emphasize the need for further research to comprehend the intricate relationship between, tobacco exposure, sex, and CKD management, as well as the consideration of cultural, geographical, socioeconomic, political, and structural factors when understanding the pathophysiology and management of CKD.

Keywords SDH, Health Inequities, Kidney Disease, Socioeconomic Status, Tobacco Dependency

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Introduction

Chronic Kidney Disease (CKD) affects over 800 million people with an estimated global prevalence of 13.4% [1–3]. Current guidelines identify the diagnostic criteria for CKD as (1) a glomerular filtration rate (GFR) less than 60 mL/minute/1.73 m^2, and/or (2) one or more markers suggestive of kidney damage which includes albuminuria, urinary sediment abnormalities, electrolyte abnormalities, renal tubular disorders, histological or structural changes, and a history of kidney transplant, occurring for a period of greater than three months [3, 4].

In general, females have been shown to have a superior health status than males [5]. Females have a longer life expectancy of 4.4 years as shown in 2016. They have been shown to have higher rates of survival regarding chronic heart failure and myocardial infarctions [6]. Female patients also have higher cancer-specific survivals of colorectal cancer [5]. Contrary to these previous findings, female who consume tobacco have been shown to have a greater risk of chronic diseases compared to male [5].

Individuals who consume greater than 30 packs of cigarettes per year are 2.6 times more likely to develop CKD, however difference in prevalence between females and males who consume tobacco has not been elucidated [7, 8]. Furthermore, although global tobacco smoking rates are declining in higher-income countries, little decrease is observed in lower- and middle-income countries, particularly in Asia and Africa [9–11]. It has previously been shown that sex affects the causal pathway between tobacco consumption and the development of CKD, however, the studies show ambivalent results [2, 12]. These differences may be attributed to estrogen's protective effects or testosterone's harmful effects [12]. One study examined differences in the magnitude of glomerulotubular homeostasis alteration between male and female cigarette smoke (CS)-exposed mice [13]. Both CS-exposed male and female mice experienced a significant increase in fibrosis, inflammation, and glomerulotubular damage when compared to their respective controls, but CS-exposed female mice showed a lesser effect. These observations show sex differences in inflammatory responses and cytokine production when exposed to tobacco, possibly attributed to estrogen's well-documented protective effects [13].

Projections indicate that CKD will be the fifth leading cause of death by 2040 [14, 15]. CKD burden is particularly high in lower- and middle-income countries, with India ranking eighth globally in CKD-related deaths [16, 17]. Given the potential for a sexually dimorphic response to tobacco in CKD, an improved understanding of these interactions can better help inform healthcare decision-making. Therefore, the primary objective is to investigate how sex differences mediate the causal pathway between tobacco exposure and the development of CKD. The secondary objective is to examine patterns of CKD prevalence related to regional variability and social determinants of health.

Methods

This study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines, and an a priori protocol was published on PROSPERO (ID: CRD42022371292) to ensure transparency and methodological rigor [18, 19].

Search strategy

A comprehensive search, assisted by a medical librarian, was conducted in MEDLINE, EMBASE, clinicaltrials.gov, and the preprint server MedvRix, from inception until October 6th, 2022. Some keywords such as "chronic kidney disease," "smoking," "sex differences," were used. The full search strategies are available in the supplementary (Appendix S1).

Study selection

The search results were imported into Covidence, a systematic review management software. Pilot testing was conducted until Cohen's kappa inter-rater reliability value of 0.8 was achieved. Five reviewers (NV, AV, AX, EF, OH) were involved in the study selection process. Specifically, two reviewers were independently assigned to each study for title and abstract screening, followed by full-text review for eligibility. Exclusion reasons were documented, with discrepancies resolved by a third reviewer (NW) if necessary. Studies not reporting primary data (i.e., systematic reviews or post-hoc analyses), reviews, abstracts, conference posters, comments, editorials, or those not published in English were excluded.

Data extraction

Data extraction was independently performed by two reviewers for each study, involving the authors NV, AV, AX, EF, and OH. All discrepancies were resolved through discussion with a third author (NW) for full-text articles meeting the inclusion criteria. Extracted data encompassed patient characteristics (age, sex, smoking history including tobacco and other substances — exposure level and pack-years, comorbidities), general study information (country, journal, funding source), diagnostic methods (e.g., GOLD criteria), social determinants of health (race, education, study location — rural or urban communities), and the cause of CKD (e.g., tobacco-related or non-tobacco-related).

Quality assessment

The included literature's quality was assessed using the Newcastle–Ottawa Scale, a validated tool that assesses literature based on eight items across three categories: study group selection, group comparability, and establishment of exposure and outcomes [20–22].

Results

A total of 3,028 studies were identified, for which three duplicates were removed and 2,920 were excluded during the title and abstract screening. Of these, 105 studies remained for full-text screening, of which 77 were excluded for not reporting primary data stratified by both sex and tobacco exposure. Ultimately, 28 studies met the predetermined inclusion criteria (Fig. 1).

Among the 28 included studies, five focused on Japanese [32–36] populations, four on Chinese [23–26] populations, three on populations from Iran [44, 87, 92] and Norway [28, 29, 31], and two on populations from India [37, 38], Taiwan [39, 40], and the United States [41, 94]. A population from Jordan [90], Australia [91], Singapore [27], the United Kingdom [30], France [42], Uganda [43], and Russia [81] were each studied once. Race information was collected in 22 studies, with reported categories including Chinese (5) [23–27], Caucasian (4) [28–31], Japanese (5) [32–36], Indian (3) [27, 37, 38], Taiwanese (2) [39, 40], South American (1) [29], Malaysian (1) [27], non-Hispanic White (1) [33], Hispanic White (1) [33], African American (1) [33], Black Caribbean (1) [41], European (1) [42], African (1) [43], Iranian (1) [44], or other (1) [27]. Of these, 11 studies reported on education

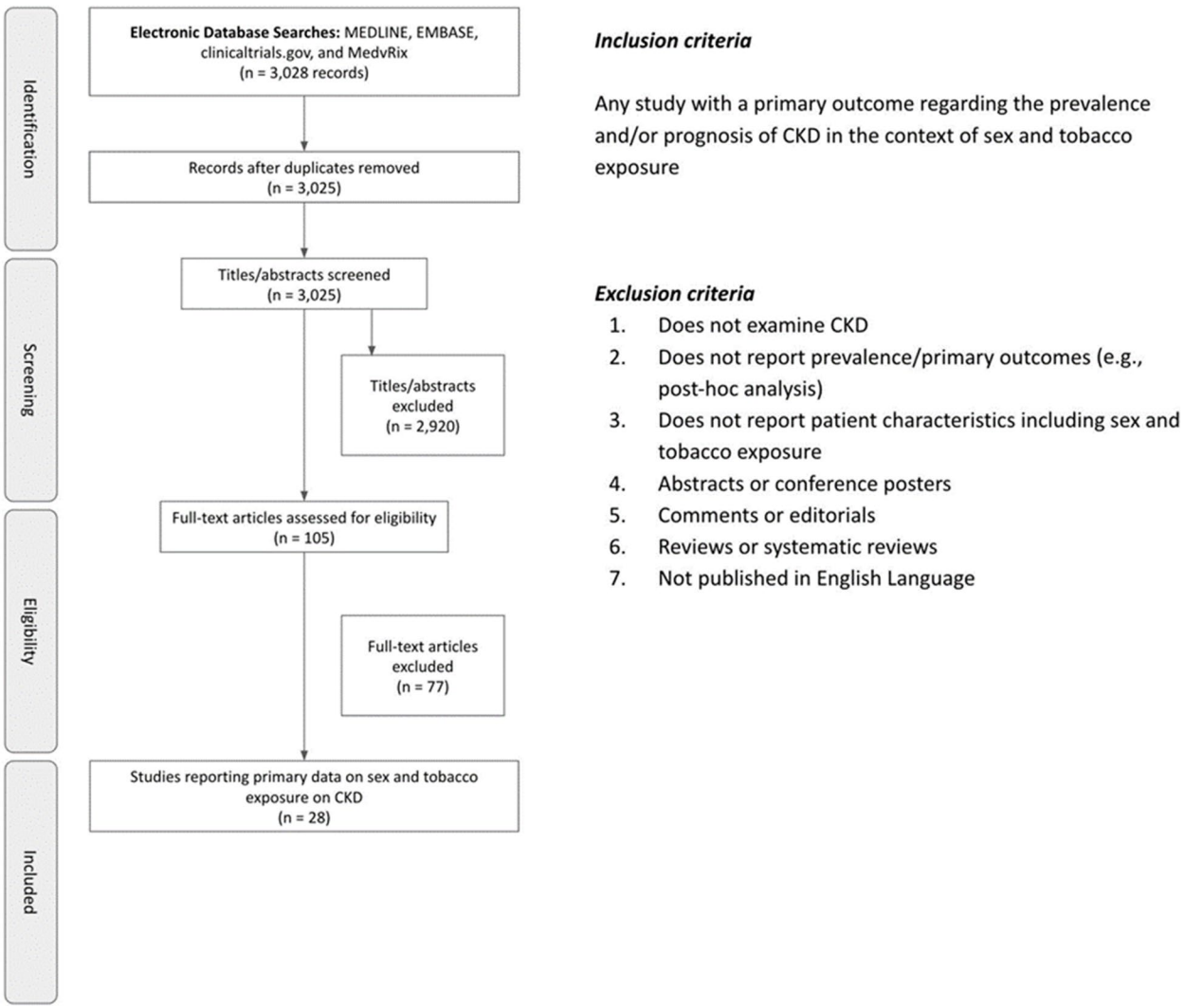

Fig. 1 Flowchart illustrating the study selection the final number of articles included ($n = 28$)

[25, 26, 28, 31, 37–39, 44, 87, 90, 92], 20 reported on comorbidities [24–27, 30, 31, 34, 35, 37–44, 81, 87, 92, 94], and 17 reported on study duration[23, 25, 27–29, 31–37, 40, 41, 44, 81, 92]. Regarding funding, 10 studies received government funding [23, 24, 27, 30, 32, 35, 36, 40, 44, 94], four had institutional funding [29, 42, 43, 92], two had industry funding [37, 38], and ten reported no funding sources [25, 28, 31, 34, 39, 41, 81, 87, 90, 91], while two did not disclose their funding sources [26, 33]. Regarding study design, 15 studies were cross-sectional, eight were prospective cohort studies, two were retrospective cohort studies, and three were case–control studies (Tables 1 and 2).

Additionally, seven studies reported on CKD etiology [24, 26, 37, 39, 40, 81, 87]. The reported prevalence of diabetic-related CKD ranged from 2.5% to 36.4% [24, 26, 37, 39, 81, 87], while CKD related to hypertension ranged from 3.7% to 51.1% [24, 37, 39, 81, 87]. Only one study explored IgA nephropathy as a potential cause of CKD (Table 1) [42]. A total of 22 studies identified smoking as a risk factor for CKD [23–26, 28, 30–39, 41, 42, 44, 81, 87, 91, 94]. Disparity in tobacco smoking prevalence among participants is evident, with people who currently consume tobacco, ranging from 5.6% to 55.2%, people who formerly consumed tobacco, from 4.1% to 56.1%, and people who never consumed tobacco, from 6.7% to 55.8% (Table 2) [23, 24, 26–44, 81, 87, 90–92, 94].

Regarding social determinants of health, 18 studies reported primary outcome measures [25–28, 32, 36, 38–41, 43, 87, 90, 92]. Several studies found no statistically significant impact of factors like relationship status, family structure, occupation, social class, or education on CKD prevalence [36, 38, 87]. Several studies found significant associations between CKD prevalence and socioeconomic status [39, 43].Higher education was associated with a lower likelihood of CKD in some studies but linked to kidney failure in others [25, 26, 28, 38, 87, 92]. Higher income was generally associated with lower CKD prevalence, while lower income and poverty were linked to higher CKD risk [38, 40]. Certain occupations such as security guard, farmer, or housekeeper were associated with higher rates of proteinuria compared to clerical work [32, 36, 38]. Relationship status also played a role, with widowed, divorced, separated, or never-married individuals more likely to have decreased kidney function compared to those in relationships [39, 90]. Some studies noted racial and ethnic disparities in CKD prevalence [27, 41]. Black individuals from the Caribbeans and African Americans had higher CKD rates compared to non-Black individuals [41]. Malaysian ancestries were more likely to have CKD, while individuals of Indian ancestry were less likely to have CKD compared to those of Chinese ancestry (Table 2) [27].

Four studies looked at CKD prevalence in both urban and rural populations [43, 44, 91, 92], 13 studies focused on urban setting [23–28, 31, 32, 40–42, 87, 94], and two studies focused on rural populations [37, 38]. Among the two studies, CKD prevalence in females ranged from 4.7% to 17.1%, and in males from 8.1% to 25.2% [37, 38]. Studies exclusively focused on urban populations displayed wider ranges, with CKD prevalence in females from 0.1% to 43.9%, and in males from 0.3% to 58% [23–28, 31, 32, 40–42, 87, 94]. For studies encompassing both settings, CKD prevalence in females ranged from 16.3% to 51.5%, and in males from 13.0% to 48.5%, suggesting CKD prevalence varies based on urban and rural contexts (shown in Table 1) [43, 44, 91, 92].

There was significant geographical diversity in CKD prevalence. In Asia, rates varied widely, with East Asia reporting prevalence ranging from 5.5% to 43.9% in females and 5.2% to 58.0% in males, with Taiwanese males exhibiting the highest CKD prevalence [23–26, 32–36, 39, 40]. South and Southeast Asia reported prevalence ranging from 4.7% to 24.9% in females and 8.1% to 27.1% in males [27, 37, 38]. West Asia had rates from 26.5% to 68.1% in females and 14.2% to 48.9% in males, with Jordanian females exhibiting the highest CKD prevalence [44, 87, 90, 92]. Lower rates were seen in Western and Northern Europe (0.1–16.7% in females, 0.3–16.7% in males) [28–31, 42], while Central and Western Europe showed high rates (57.4% in females, 35.0% in males) [81]. The Norwegian population had the lowest CKD prevalence for both males and females [28, 29, 31]. North America reported rates from 5.9–10.0% in females and 7.1–17.0% in males [41, 94]. One study from Africa reported prevalence of 16.2% in females and 13.0% in males, while Australia showed rates similar to Western Asia (51.5% in females, 48.5% in males) [43, 91] (Table 3).

The quality of included literature was assessed as Good and Poor, as per the Newcastle–Ottawa Scale (Table 4). Ten studies demonstrated high methodological rigor and were rated as Good [28, 30, 32–36, 41, 44, 93], while 18 were rated as Poor due to a risk of bias [23–27, 29, 31, 37, 39, 40, 42, 43, 81, 87, 90–92, 94]. Participant selection scores ranged from two to four, indicating moderate to low risk of bias. Participant comparability scores ranged from zero to two, indicating high to low risk of bias. Outcome determination scores ranged from one to three, indicating high to low risk of bias. Regarding funding, 10 studies received government funding [23, 24, 27, 30, 32, 35, 36, 40, 44, 94], four had institutional funding [29, 42, 43, 92], two had industry funding [37, 38], and ten reported no funding sources [25, 28, 31, 34, 39, 41, 81, 87, 90, 91], while two did not disclose their funding sources [26, 33]. Regarding study design, 15 studies were cross-sectional [24–27, 29–31, 37, 39, 43, 81, 87, 90, 91,

Table 1 Publication characteristics of the included studies and associated risk factors of chronic kidney disease

Author (Year)	Source of Funding	Country	Study Location (Rural/Urban)	Study Design	Study Duration	Comorbidities	Race	Risk factors for CKD
Dehghani (2022) [87]	None	Iran	Urban	Cross-sectional	Not reported	Obesity; Diabetes Mellitus; Cardiovascular disease; Hypertension; Hypertriglyceridemia; Hypercholesterolemia	Not reported	BMI ≥ 30 (n = 1024/9781; 10.5%) diabetes (n = 735/9781; 7.5%) hypertriglyceridemia (n = 1424/9781; 14.6%) history of cardiovascular disease (n = 349/9781; 3.6%) hypertension (n = 898/9781; 9.2%) LDL ≥ 130 (n = 1528/9781; 15.6%) history of kidney stone (n = 518/9781; 5.3%) hypercholesterolemia (n = 1167/9781; 11.9%)
Alramly (2013) [90]	None	Jordan	Not reported	Descriptive; Cross-sectional; Correlational	Not reported	Not reported	Not reported	Not reported
Briganti (2002) [91]	None	Australia	Urban; Rural	Cross-sectional	Not reported	Not reported	Not reported	Not reported
Dong (2021) [23]	Government	China	Urban	Observational Cohort	10 years	Not reported	Chinese	Not reported
Hallan (2011) [28]	None	Norway	Urban	Prospective Cohort	10.3 years	Not reported	Caucasian	Not reported
Huang (2016) [24]	Government	China	Urban	Cross-sectional	Not reported	Hyperuricemia; Hypertension; Diabetes; Cardiovascular disease	Chinese	30 > BMI ≥ 25 (kg/m2) (n = 1003/24886; 4.0%) BMI ≥ 30 (kg/m2) (n = 134/24886; 0.5%) high triglyceride (n = 740/24886; 3.0%) high cholesterolemia (n = 1021/24886; 4.1%) Hyperuricemia (n = 1207/24886; 4.9%) Low HDL-C (n = 1110/24886; 4.5%) High LDL-C (n = 130/24886; 0.5%) High fasting plasma glucose (n = 351/24886; 1.4%) Drinking (n = 79/24886; 0.3%) Hypertension (n = 1841/24886; 7.4%) Diabetes (n = 629/24886; 2.5%) Cardiovascular disease (n = 945/24886; 3.8%)
Noborisaka (2013) [32]	Government	Japan	Urban	Retrospective Cohort	6 years	Not reported	Japanese	Not reported
Sepanlou (2017) [92]	Institutional	Iran	Urban; Rural	Observational cohort	2 years	Cardiovascular disease; Hypertension; Diabetes	Not reported	Not reported
Umesawa (2018) [33]	Not reported	Japan	Not reported	Observational cohort	10 years	Not reported	Japanese Non-Hispanic White Hispanic White African American	Not reported
Xue (2014) [25]	None	China	Urban	Cross-sectional	4 months	Cardiovascular disease; Diabetes mellitus; Hyperlipidemia; Hypercholesterolemia; Hyperuricemia	Chinese	Not reported

Table 1 (continued)

Author (Year)	Source of Funding	Country	Study Location (Rural/Urban)	Study Design	Study Duration	Comorbidities	Race	Risk factors for CKD
Yamagata (2007) [34]	None	Japan	Not reported	Prospective Cohort	10 years	Proteinuria; Hematuria; Hypertension; Diabetes; Obesity; Hypercholesterolemia; Hypertriglyceridemia	Japanese	Not reported
Yang (2018) [26]	Not reported	China	Urban	Cross-sectional	Not reported	Diabetes; Stroke; Coronary heart disease; Peripheral Arterial Disease; Hypertension;	Chinese	BMI category (n, %) Underweight (*n* = 113/31574; 0.4%) Normal (*n* = 1659/31574; 5.3%) Overweight (n = 1867/31574; 5.9%) Obese (*n* = 5718/31574; 18.1%) Alcohol status (n, %) Non-drinker (*n* = 6319/31574; 20.0%) Current drinker (*n* = 1299/31574; 4.1%) Ex-drinker (*n* = 1761/31574; 5.6%) CHD (*n* = 315/31574; 1.0%) Stroke (*n* = 608/31574; 1.9%) PAD (*n*, %) Yes (*n* = 143/31574; 0.5%) Suspected (n = 48/31574; 0.2%) DR Status (n,%) No DR (*n* = 5041/31574; 16.0%) Non-sight threatening (*n* = 1990/31574; 6.3%) Sight threatening (*n* = 1575/31574; 5.0%) Ungradable (*n* = 31/31574; 0.1%)
Anupama (2014) [37]	Industry	India	Rural	Cross-sectional	11 months	Diabetes mellitus; Hypertension; Ischemic heart disease; Stroke	Indian	BMI < 18 (*n* = 31/2091; 1.5%) 18–22.9 (*n* = 65/2091; 3.1%) 23–24.9 (*n* = 16/2091; 0.8%) > 25 (*n* = 19/2091; 0.9%) Hypertension (*n* = 78/2091; 3.7%) Diabetes (*n* = 80/2091; 3.82%)

Table 1 (continued)

Author (Year)	Source of Funding	Country	Study Location (Rural/Urban)	Study Design	Study Duration	Comorbidities	Race	Risk factors for CKD
Chang (2020) [39]	None	Taiwan	Not reported	Cross-sectional	Not reported	Hypertension; Diabetes; Dyslipidemia; Hyperuricemia/gout; Urinary tract stones; Cardiovascular disease; Cancer	Taiwanese	BMI Underweight (*n* = 2762/297603; 0.9%) Normal (*n* = 36,575/297603; 12.3%) Overweight (*n* = 29,309/297603; 9.8%) Obese (*n* = 18,568/297603; 6.2%) Missing value (*n* = 1005/297603; 0.3%) Exercise habit No (*n* = 12,212/297603; 4.1%) Occasional (*n* = 28,282/297603; 9.5%) Regular (*n* = 41,105/297603; 13.8%) Missing value (*n* = 6620/297603; 2.2%) Alcohol drinking No (*n* = 86,177/297603; 29.0%) Yes (*n* = 1727/297603; 0.58%) Missing value (*n* = 315/297603; 0.1%) Hypertension (*n* = 47,553/297603; 16.0%) Diabetes (*n* = 19,802/297603; 6.7%) Dyslipidemia (*n* = 60,389/297603; 20.3%) Hyperuricemia/gout (*n* = 32,220/297603; 10.8%) Urinary tract stones (*n* = 1887/297603; 0.6%) Cardiovascular disease (*n* = 24,101/297603; 8.1%) Cancer (*n* = 478/297603; 0.2%)
Gjerde (2012) [29]	Institutional	Norway	Not reported	Cross-sectional	1.5 years	Not reported	Caucasian South American	Not reported
Gummidi (2020) [38]	Industry	India	Rural	Prospective Cohort	Not reported	Hypertension; Diabetes; Heart disease; Obesity	Indian	Not reported
Lew (2017) [27]	Government	Singapore	Urban	Cross-sectional	4 years	Hypertension; Diabetes mellitus; Cardiovascular disease; Stroke	Chinese Indian Malaysian Other	Not reported
Miguez-Burbano (2009) [41]	None	United States	Urban	Case–control	1 year	Hypertension; Diabetes; Cancer; Hepatitis C; Hepatitis B	Black Caribbean	Not reported
Nakamura (2015) [35]	Government	Japan	Not reported	Observational cohort	14.8 years	Diabetes; Proteinuria	Japanese	Not reported
Nitsch (2006) [30]	Government	United Kingdom	Not reported	Cross-sectional	Not reported	Obesity; Hypertriglyceridemia; Diabetes;	Caucasian	Not reported
Noborisaka (2013) [36]	Government	Japan	Not reported	Retrospective observational	6 years	Not reported	Japanese	Not reported

Table 1 (continued)

Author (Year)	Source of Funding	Country	Study Location (Rural/Urban)	Study Design	Study Duration	Comorbidities	Race	Risk factors for CKD
Roseman (2017) [94]	Government	United States	Urban	Cross-sectional	Not reported	Hypertension; Diabetes; Albuminuria; Cardiovascular disease	Not reported	Not reported
Stengel (2000) [42]	Institutional	France	Urban	Case–control	Not reported	Hypertension	European	Not reported
Hallan (2006) [31]	None	Norway	Urban	Cross-sectional	2 years	Diabetes mellitus; Cardiovascular disease; Hypertension; Obesity	Caucasian	Not reported
Kalyesubula (2017) [43]	Institutional	Uganda	Urban; Rural	Cross-sectional	Not reported	HIV-Infection; Diabetes; Hypertension; Proteinuria	African	Not reported
Korbut (2019) [81]	None	Russia	Not reported	Cross-sectional	10 years	Diabetes; Diabetic retinopathy; Arterial hypertension; Coronary artery disease; Myocardial infarction in anamnesis; Chronic heart failure; Carotid atherosclerosis; Cerebrovascular event in anamnesis; Peripheral artery disease	Not reported	Diabetic retinopathy ($n=131/360$; 36.4%) Arterial hypertension ($n=184/360$; 51.1%) Coronary artery disease ($n=99/360$; 27.5%) Myocardial infarction in anamnesis ($n=36/360$; 10.0%) Chronic heart failure ($n=11/360$; 3.1%) Carotid atherosclerosis ($n=91/360$; 25.3%) Cerebrovascular event in anamnesis ($n=24/360$; 6.7%) Peripheral artery disease ($n=141/360$; 39.2%)
Su (2015) [40]	Government	Taiwan	Urban	Case–control	2 years	Obesity; Hepatitis B; Hepatitis C; Hyperuricemia; Anemia; Hyperlipidemia;	Taiwanese	Obesity ($n=592/9138$; 6.5%) Hyperuricemia ($n=1291/9138$; 14.1%) Anemia ($n=863/9138$; 9.4%) Hyperlipidemia ($n=1495/9138$; 16.4%) Alcohol intake (ever) ($n=767/9138$; 8.4%) Exercise habits (ever) ($n=3338/9138$; 36.5%) Groundwater using (ever) ($n=293/9138$; 3.2%)
Tohidi (2012) [44]	Government	Iran	Urban; Rural	Prospective Observational	9.9 years	Diabetes mellitus; Hypertension; Cardiovascular disease	Iranian	Not reported

Table 2 Main findings on tobacco exposure, social determinants of health and chronic kidney disease

Author (Year)	Total Sample Size	Sample Size (female)	Sample Size (male)	Mean (SD) or Range of Age Male in years	Mean (SD) or Range of Age Female in years	Diagnostic Method	CKD in females	CKD in males	Current/ Former/ Never Smoking History (n and %)	Mean (SD) or Range of Pack Year Smoking History	Identified Risk Factors for CKD	Social Determinants of Health
Dehghani (2022) [87]	9,781	4,860	4,921	Not reported	Not reported	CKD (serum creatinine and eGFR < 60 ml/ min/1.73m2)	1499	1186	Smoked (*n* = 2210; 22.6%) Never Smoked (*n* = 7571; 77.4%)	Not reported	Smoking; Female sex	Statistically significant protective factors against CKD: Higher education Not statistically significant association with CKD: Marital status
Alramly (2013) [90]	161	69	92	Not reported	Not reported	CKD (interview and medical files)	47	45	Smoked (*n* = 75; 47%) Never Smoked (*n* = 86; 53%)	Not reported	Male sex	Those with ESRD were significantly more likely to have a marital status of being single/divorced/ widowed compared to married than those with CKD
Briganti (2002) [91]	11,247	5,910	5,337	Not reported	Not reported	Renal impairment (eGFR < 60 mL/ min/1.73 m2)	3044	2588	Current Smokers (*n* = 2621; 23.3%) Non-Smokers (*n* = 8626; 76.7%)	GFR ≥ 60: 18.1 ± 0.8 GFR < 60: 33.0 ± 5.7	Smoking; Male sex	None
Dong (2021) [23]	141,516	78,078	63,438	63.07 ± 11.45	65.71 ± 11.78	ESRD (ICD-9-CM or eGFR < 15 ml/ min/1.73m2)	5794	3315	Smoked (*n* = 5137; 10.87%) Never Smoked (*n* = 42,129; 89.13%)	Not reported	Smoking; Male sex	None

Table 2 (continued)

Author (Year)	Total Sample Size	Sample Size (female)	Sample Size (male)	Mean (SD) or Range of Age Male in years	Mean (SD) or Range of Age Female in years	Diagnostic Method	CKD in females	CKD in males	Current/ Former/ Never Smoking History (n and %)	Mean (SD) or Range of Pack Year Smoking History	Identified Risk Factors for CKD	Social Determinants of Health
Hallan (2011) [28]	65,589	34,911	30,678	Not reported	Not reported	decrease of eGFR to 15 ml/min/1.73 m^2	46	78	Current (n = 18,168; 27.7%) Former (n = 17,119; 26.1%) Never (n = 29,515; (45.0%) Unknown (n = 787; (1.2%)	Former smoker: 11.4 ± 12.8 Current smoker: 14.5 ± 11.1	Smoking; Male sex	Statistically significant risk factor for kidney failure: Higher education
Huang (2016) [24]	24,886	13,670	11,216	Not reported	Not reported	CKD (NKF K/DOQI Guidelines)	2409	1669	Smoked (n = 2455; 9.86%) Never Smoked (n = 22,431, 90.14%)	Not reported	Smoking; Female sex	None
Noborisaka (2013) [32]	6,662	2,698	3,964	49.4 ± 7.8	50.2 ± 7.2	CKD (GFR and proteinuria levels as per the new JSN criteria)	418	559	Current (n = 2384; 35.8%) Former (n = 979; 14.7%) Never (n = 3299; 49.5%)	Not reported	Smoking	Statistically significant risk factor for development of moderate to severe CKD: Miscellaneous job category
Sepanlou (2017) [92]	11,409	5,996	5,413	57.0 ± 8.3	55.5 ± 7.6	CKD (eGFR < 60 ml/min/1.73m2)	1588	1112	Smoked (n = 1871; 16.4%) Never Smoked (n = 9538; 83.6%)	Not reported	Female sex	Statistically significant protective factors against CKD: Literacy, rural residence

Table 2 (continued)

Author (Year)	Total Sample Size	Sample Size (female)	Sample Size (male)	Mean (SD) or Range of Age Male in years	Mean (SD) or Range of Age Female in years	Diagnostic Method	CKD in females	CKD in males	Current/ Former/ Never Smoking History (n and %)	Mean (SD) or Range of Pack Year Smoking History	Identified Risk Factors for CKD	Social Determinants of Health
Umesawa (2018) [33]	135,007	94,005	41,002	57.5	54.6	eGFR < 45 mL/min/1.73 m^2 and/or proteinuria by dipstick)	10,358	6,106	Current (*n* = 23,541; 17.4%) Former (*n* = 12,233; 9.1%) Never (*n* = 99,233; 73.5%)	Not reported	Smoking	None
Xue (2014) [25]	14,399	5,838	8,561	49.64 ± 16.65	48.13 ± 18.01	eGFR < 60 mL/min/1.73 m^2	619	747	Not reported	Not reported	Smoking; Female sex	Statistically significant protective factors against CKD: Higher education
Yamagata (2007) [34]	123,764	82,752	41,012	61.8 ± 10.2	58.3 ± 10.0	eGFR < 60 mL/min/1.73 m^2	17,413	6,305	Current (*n* = 22,809; 18.4%) Former (*n* = 12,545; 10.1%) Never (*n* = 88,410; 71.4%)	Not reported	Smoking	None
Yang (2018) [26]	31,574	15,649	15,925	Not reported	Not reported	CKD (KDIGO guideline)	4882	4504	Current (n = 4402; 13.9%) Former (*n* = 5574: 17.7%) Never (*n* = 21,572; 68.3%)	Not reported	Smoking	Statistically significant protective factors against CKD: Higher education

Table 2 (continued)

Author (Year)	Total Sample Size	Sample Size (female)	Sample Size (male)	Mean (SD) or Range of Age Male in years	Mean (SD) or Range of Age Female in years	Diagnostic Method	CKD in females	CKD in males	Current/ Former/ Never Smoking History (n and %)	Mean (SD) or Range of Pack Year Smoking History	Identified Risk Factors for CKD	Social Determinants of Health
Anupama (2014) [37]	2,091	1,138	953	Not reported	Not reported	eGFR < 60 mL/ min/1.73 m^2	54	77	Smoked (*n* = 150; 7.2%) Never Smoked (*n* = 1941; 92.8%)	Not reported	Smoking; Male sex	None
Chang (2020) [39]	297,603	144,260	153,343	Not reported	Not reported	eGFR < 60 mL/ min/1.73 m^2	35,035	53,184	Smoked (*n* = 20,047; 6.7%) Never Smoked (*n* = 276,610; 93.0%)	Not reported	Smoking	Widowed/ divorced/separated or never married compared to married and poor socioeconomic status
Gjerde (2012) [29]	422	167	255	Not reported	Not reported	eGFR < 60 mL/ min/1.73 m^2	16	13	Current (*n* = 190; 43.9%) Former (*n* = 243; 56.1%) Never (*n* = 0; 0%)	Not reported	Female sex	None
Gummidi (2020) [38]	2,402	1,222	1,180	46.8 ± 13.99	44.57 ± 12.49	CKD (KDIGO criteria)	209	297	Smoked (*n* = 1032; 42.96%) Never Smoked (*n* = 1370; 57.04%)	Not reported	Smoking; Male sex	Statistically significant protective factors against CKD: Higher education Not statistically significant association with CKD: Income, outdoor workers

Table 2 (continued)

Author (Year)	Total Sample Size	Sample Size (female)	Sample Size (male)	Mean (SD) or Range of Age Male in years	Mean (SD) or Range of Age Female in years	Diagnostic Method	CKD in females	CKD in males	Current/ Former/ Never Smoking History (n and %)	Mean (SD) or Range of Pack Year Smoking History	Identified Risk Factors for CKD	Social Determinants of Health
Lew (2017) [27]	88,765	47,331	41,434	Not reported	Not reported	CKD (eGFR < 60 mL/ min/1.73 m^2 or 1 + dipstick proteinuria excretion)	11,768 (95% CI: 24.5–25.3)	11,247 (95% CI: 26.7–27.6)	Smoked (*n* = 8562; 9.7%) Never Smoked (*n* = 80,203; 90.3%)	Not reported	Male sex	Those of Malay ancestry were more likely and those of Indian ancestry were less likely to have CKD than those of Chinese ancestry
Miguez-Burbano (2009) [41]	536	230	306	Not reported	Not reported	GFR < 60 ml/ min/1.73 m2)	23	52	Current (*n* = 296; 55.2% Former (*n* = 50; 9.3%) Never (*n* = 190; 35.5%)	CKD: 12.7 ± 0.9 Non-CKD: 8.8 ± 1.3	Smoking; Male sex	Black Caribbeans and African Americans more likely to have CKD than non-Black individuals
Nakamura (2015) [35]	34,622	19,154	15,468	57.4	58.0	CKD (eGFR < 60 ml/ min per 1.73 m(2)) and/or dipstick proteinuria)	1054	1083	Current (*n* = 9685; 28.0%) Former (*n* = 4281; 12.4%) Never (*n* = 20,656; 59.6%)	Not reported	Smoking	None
Nitsch (2006) [30]	6,317	3,217	3,100	51.8 ± 11.4	52.5 ± 11.4	eGFR < 60 ml/ min/1.73 m^2	538	141	Current (*n* = 841; 27.1%) Not-current (*n* = 2259; 72.9%)	Not reported	Smoking; Female sex	None

Table 2 (continued)

Author (Year)	Total Sample Size	Sample Size (female)	Sample Size (male)	Mean (SD) or Range of Age Male in years	Mean (SD) or Range of Age Female in years	Diagnostic Method	CKD in females	CKD in males	Current/ Former/ Never Smoking History (n and %)	Mean (SD) or Range of Pack Year Smoking History	Identified Risk Factors for CKD	Social Determinants of Health
Noborisaka (2013) [36]	6,998	2,877	4,121	41.2 ± 9.7	42.3 ± 9.3	Proteinuria (dipstick method)	369	492	Current (*n* = 2085; 29.8%) Former (*n* = 537; 7.7%) Never (*n* = 4376; 62.5%)	Not reported	Smoking	Occupation not associated with CKD
Roseman (2017) [94]	1,852	981	871	64.3 ± 9.2	63.9 ± 9.2	eGFR < 45 mL/min/1.73 m^2	58	62	Current (*n* = 343; 18.5%) Former (*n* = 573; 31.0%) Never (*n* = 936; 50.5%)	Not reported	Smoking; Male sex	None
Stengel (2000) [42]	537	197	340	Not reported	Not reported	serum creatinine > 150 micromole/L	17	57	Smoked (*n* = 272; 50.6%) Never smoked (*n* = 265; 49.4%)	Not reported	Smoking; Male sex	None
Hallan (2006) [31]	65,193	34,708	30,485	Not reported	Not reported	eGFR < 45 mL/min/1.73 m^2	375	246	Smoked (*n* = 36,358; 55.8%) Never smoked (*n* = 28,835; 44.2%)	GFR ≥ 45: 6.9 ± 10.8 GFR < 45: 8.5 ± 16.1	Smoking	None
Kalyesubula (2017) [43]	955	640	315	30 (24–40)	32 (25–43)	creatinine clearance < 60 mls/min/1.73 m^2	104	41	Current (*n* = 54; 5.6%) Former (*n* = 39; 4.1%) Never (*n* = 862; 90.3%)	Not reported	None	Statistically significant risk factors for kidney disease: High socioeconomic status

Table 2 (continued)

Author (Year)	Total Sample Size	Sample Size (female)	Sample Size (male)	Mean (SD) or Range of Age Male in years	Mean (SD) or Range of Age Female in years	Diagnostic Method	CKD in females	CKD in males	Current/ Former/ Never Smoking History (n and %)	Mean (SD) or Range of Pack Year Smoking History	Identified Risk Factors for CKD	Social Determinants of Health
Korbut (2019)[81]	360	260	100	Not reported	Not reported	eGFR < 45 mL/ min/1.73 m^2	149	35	Smoked (*n* = 34; 9.4%) Never Smoked (*n* = 326; 90.6%)	Not reported	Smoking; Female sex; Male sex	Not reported
Su (2015) [40]	10,463	5,245	5,218	Not reported	Not reported	eGFR < 60 mL/min	2302	3026	Smoked (*n* = 2090; 20.6%) Never Smoked (*n* = 8035; 79.4%)	Not reported	Male sex	Low income
Tohidi (2012) [44]	3,313	1,859	1,454	Non-CKD: 39.28 ± 12.56 CKD: 53.87 ± 11.64	Non-CKD: 35.52 ± 10.67 CKD: 45.63 ± 12.17	eGFR < 45 mL/ min/1.73m^2	517 (95% CI: 25.77–29.85)	206 (95% CI: 12.38–15.96)	Current (*n* = 322; 18.2%) Former (*n* = 135; 7.6%) Never (*n* = 1312; 74.2%)	Not reported	Smoking; Female sex	None

Table 3 CKD prevalence in males and females per region and country

Region (*n* = number of studies)	Prevalence of CKD – Female (%)	Prevalence of CKD – Male (%)
East Asia (11)		
China (4) [23–26]	7.4–31.2	5.2–28.3
Japan (5) [32–36]	5.5–21.0	7.0–15.4
Taiwan (2) [39, 40]	24.3–43.9	34.7–58.0
South Asia (2)		
India (2) [37, 38]	4.7–17.1	8.1–25.2
South-East Asia (1)		
Singapore (1) [27]	24.9	27.1
West Asia (4)		
Jordan (1) [90]	68.1	48.9
Iran (3) [44, 87, 92]	26.5–30.8	14.2–24.1
Western Europe (2)		
United Kingdom (1) [30]	16.7	4.5
France (1) [42]	8.6	16.7
Northern Europe (3)		
Norway (3) [28, 29, 31]	0.1–9.6	0.3–5.1
Central and Western Europe (1)		
Russia (1) [81]	57.4	35.0
Australia (1) [91]	51.5	48.5
North America (2)		
United States (2) [41, 94]	5.9–10.0	7.1–17.0
Africa (1)		
Uganda (1) [43]	16.2	13.0

94], eight were prospective cohort studies [23, 28, 33–35, 38, 44, 92], two were retrospective cohort studies [32, 36], and three were case–control studies [40–42] (Tables 1 and 2).

None of the included studies provided suitable data for meta-analysis on CKD prevalence stratified by both sex and tobacco exposure.

Discussion

This systematic review reveals significant variability in study results and quality across the literature, including differences in exposure and outcome definitions, study designs, methodologies, sourced populations, and follow-up durations. While aiming to explore the association between sex, tobacco exposure, and CKD development through a meta-analysis of CKD prevalence, none of the included studies provided data on all three components. Two studies reporting CKD prevalence stratified by sex showed high heterogeneity, precluding meta-analysis [27, 44]. Among the 28 included studies, 22 identified smoking as a CKD risk factor, while 12 and eight studies recognized male and female sex as risk factors, respectively (Table 2).

Table 4 Quality of the 28 included articles as per the Newcastle–Ottawa Scale

Author (Year)	Selection	Comparability	Outcome	Quality
Dehghani (2022) [87]	2	0	1	Poor
Alramly (2013) [90]	2	0	1	Poor
Briganti (2002) [91]	2	1	1	Poor
Dong (2021) [23]	3	0	2	Poor
Hallan (2011) [28]	3	1	3	Good
Huang (2016) [24]	3	1	1	Poor
Noborisaka (2013) [32]	3	1	2	Good
Sepanlou (2017) [92]	2	1	1	Poor
Umesawa (2018) [33]	4	1	2	Good
Xue (2014) [25]	3	0	1	Poor
Yamagata (2007) [34]	4	1	2	Good
Yang (2018) [26]	2	1	1	Poor
Anupama (2014) [37]	3	1	1	Poor
Chang (2020) [39]	2	1	1	Poor
Gjerde (2012) [29]	2	1	1	Poor
Gummidi (2020) [38]	3	1	2	Good
Lew (2017) [27]	3	1	1	Poor
Miguez-Burbano (2009) [41]	3	1	2	Good
Nakamura (2015) [35]	3	2	2	Good
Nitsch (2006) [30]	4	2	2	Good
Noborisaka (2013) [36]	4	2	2	Good
Roseman (2017) [94]	3	2	1	Poor
Stengel (2000) [42]	3	1	1	Poor
Hallan (2006) [31]	3	2	1	Poor
Kalyesubula (2017) [43]	3	2	1	Poor
Korbut (2019) [81]	3	1	1	Poor
Su (2015) [40]	3	2	1	Poor
Tohidi (2012) [44]	4	2	2	Good

Despite these limitations, this analysis hints at a potential sexually dimorphic relationship between smoking and CKD development, emphasizing the need for further research on CKD prevalence and sex-specific risk factors.

Tobacco exposure has been identified as a primary contributor to CKD development, with evidence suggesting a dose-dependent relationship [45, 46]. Risk factors for tobacco exposure and dependence include age, sex, genetics, substance use, education, income, race, and geographic location [47]. It is crucial to explore the association between sex and CKD, while accounting for tobacco exposure and other influential variables such as older age, diabetes mellitus, and hypertension [48]. Sex-related disparities in CKD progression

reveal that factors like smoking may contribute to sex differences, with females more likely to abstain from smoking and experience lower rates of end-stage renal disease and death compared to males [49]. Similarly, there are lower total smoking doses and rare occurrences of kidney failure progression in females, despite equal current smoking prevalence in males [28]. Additionally, there is higher CKD prevalence in females but faster disease progression in males [2]. The reasons for these sex differences remain unclear and could involve a combination of intersectional factors such as biological differences, socioeconomic, political, and structural inequities, and cultural differences. While tobacco use is declining among males according to the World Health Organization, there is a notable increase among females in low- and low-middle countries [50]. Gender norms further influence smoking behaviors, with women often associating smoking with femininity, attractiveness, and rebellion, while men see it as a symbol of strength, virility, independence, and mystery [51–53]. Women typically start smoking later out of curiosity, while men tend to imitate [54]. This gender disparity in smoking initiation may contribute to the higher prevalence of CKD in men, given their longer and heavier smoking habits compared to women.

Estrogen has been extensively documented to exert multiple beneficial effects on kidney structure and function, mediated through both genomic and non-genomic pathways involving estrogen receptors (ERs). A 15-year prospective population-based study revealed a 2.66 hazard ratio of CKD incidence in females with lower endogenous estrogen exposure (EEE) during later stages of life when compared to females with higher EEE [55]. Estrogen significantly mitigates glomerulosclerosis, a key pathological feature of CKD characterized by the sclerosis of glomeruli and subsequent impairment of renal function. The anti-sclerotic effects of estrogen are likely mediated through the attenuation of mesangial cell proliferation and the suppression of extracellular matrix protein deposition [56]. Similarly, estrogen plays a crucial role in reducing tubulointerstitial fibrosis. These anti-fibrotic effects are thought to be mediated through the modulation of inflammatory responses and the regulation of key fibrotic mediators such as transforming growth factor-beta (TGF-β) [56]. A critical aspect of estrogen's role in renal physiology is its regulation of phosphorus-calcium balance, a process predominantly occurring in the proximal renal tubules. Estrogen promotes the reabsorption of calcium and phosphate, which helps maintain serum levels within physiological norms and prevents complications such as renal osteodystrophy. The regulation of these minerals is particularly crucial in CKD, where dysregulation can lead to significant morbidity [56]. Estrogens are also pivotal in maintaining mitochondrial integrity and function within renal cells, potentially influencing cellular energy dynamics and apoptosis pathways [57]. Moreover, estrogen modulates the endothelin-1 system, which is integral to maintaining vascular tone and ensuring adequate renal blood flow and glomerular filtration rate (GFR), thus supporting overall kidney function [57]. Emerging research highlights the significance of ERα polymorphisms in influencing the susceptibility and progression of renal diseases. These genetic variations may alter the normal signaling pathways of estrogen and its receptors, potentially affecting the individual's response to endogenous or exogenous estrogens [57]. Men, lacking the protective effects of estrogen, might experience more pronounced renal tissue damage under similar conditions of stress or disease, leading to a higher prevalence and faster progression of CKD. Understanding these sex-based differences in CKD, mediated through estrogenic effects, is crucial for developing targeted therapies that could leverage the protective effects of estrogen or its analogs.

The literature on the impact of testosterone on kidney function presents conflicting findings. Animal studies have indicated detrimental effects of testosterone on the kidney, including glomerular and tubular damage, kidney fibrosis, proteinuria, and hypertensive effects [58–65]. Conversely, testosterone has also been associated with positive effects on the kidney, such as renal vasodilation, reduced inflammation, and decreased kidney injury, as observed in both animal and human studies [58–65]. Additionally, the testosterone precursor hormone dehydroepiandrosterone sulfate is believed to influence kidney function through various mechanisms, although its overall impact on kidney function remains uncertain [66]. A meta-analysis revealed that lower testosterone levels may increase the risk of CKD in the general population and elevate the risk of all-cause mortality and cardiovascular events in males with CKD [66]. These findings are consistent with a prospective population-based study that identified a higher hazard ratio of CKD progression in male adults with hypogonadism compared to those with normal testosterone levels in later life [67, 68].

DM is considered the most common cause of CKD and ESRD with type 2 DM (T2DM) accounting for 30–50% of cases and type 1 DM (T1DM) accounting for 3.9% of cases [69–72]. The most common medication for diabetes management is metformin. A previous long-term study, the DPP Outcomes Study, showed that metformin induces a greater effect in reducing coronary artery calcium in men that can suggest a protective cardiovascular effect. This can suggest that despite the use of metformin, women are at a greater risk of renal infarct or progressive CKD compared to men [73]. Another study evaluated

creatinine levels in patients with acute myocardial infarction with diabetes. Females were found to have higher creatinine levels, which was an independent predictor for a longer stay in the hospital [74]. Furthermore, a longitudinal study, the REGARDS trial, showed that being male was associated with a relative risk (RR) of 0.95 (95% CI: 0.84–1.09) risk of developing CKD. This is compared to diabetes and smoking which had a RR of 1.91 (95% CI: 1.65–2.20) and 1.30 (95% CI: 1.08–1.57) respectively [75]. On the contrary, a study examining 8413 individuals with T2DM and CKD in the UK showed a hazard ratio of 0.84 (95% confidence interval: 0.77 to 0.92) for all-cause mortality for female compared to male. The hazard ratio for smoking, regardless of sex, was 1.62 (95% CI: 1.39 to 1.88) [76]. These studies show that females may be at risk for worse renal function in the context of diabetes, but other systemic factors are still protective against mortality. One thing is for certain, risk factor modification, especially tobacco cessation, is an important component of managing CKD in the context of diabetes.

One included study looked at IgAN and found a dose–effect relationship in chronic renal failure. It reported odds ratios (OR) of 1.9 vs 1.3 for ≤ 20 cigarettes/day and an OR of 5.2 vs 3.0 for > 20 cigarettes/day, and an OR of 1.9 vs 1.4 for ≤ 15 pack years and 3.9 vs 2.0 for > 15 pack years [42]. IgAN was focused in this study due to its higher prevalence relative to other glomerular diseases such as IgG4-related disease, lupus nephritis, ANCA-associated vasculitis, and amyloidosis. IgAN is the most common primary glomerulonephritis worldwide, with significant implications for patient outcomes. Additionally, potential sex-specific differences in the incidence and progression of IgAN further justify its inclusion in this discussion [77]. IgAN has an estimated incidence of 2.5/100,000 people, with a greater burden observed in Asian populations [6, 78, 79]. A higher risk of major susceptible loci in mucosal immunity, IgA production, and complement activation pathways were found in Chinese patients [80]. White patients with minimally symptomatic IgAN showed slower disease progression, with only 4% experiencing significant proteinuria (> 1 g/day) over a span of 108 months, compared to 33% in Chinese and Japanese cohorts [81]. Considering IgAN's heavier burden in Asian nations, particularly in populous countries like India, where it has a prevalence of 16.5%, its impact on global CKD rates must be recognized [17].

In India, the bidi industry constitutes a significant segment of the tobacco market. Bidis are manually crafted cigarettes formed using dried tendu leaves encasing tobacco. This sector not only sustains millions financially but also presents substantial health risks to its workforce, which predominantly consists of females and children [82–85]. These workers, originating from socioeconomically vulnerable demographics, are exposed to occupational hazards that are often under-recognized and poorly addressed, thereby emphasizing profound disparities in workplace health and safety standards. During bidi production, workers are subjected to both direct and passive inhalation of nicotine and tobacco dust [83, 86]. This exposure leads to the transdermal and respiratory absorption of nicotine [83, 86]. Prolonged exposure to these substances has been documented to precipitate a multitude of health issues. Specifically, the ingestion and dermal absorption of nephrotoxic substances, such as heavy metals found in tobacco, are implicated in various forms of kidney damage [83, 85–89]. This exposure could heighten the risk of chronic kidney disease (CKD) and is exacerbated by the socioeconomic status of these workers, who frequently lack adequate access to healthcare, thereby delaying the diagnosis and management of CKD and other health issues. The majority of bidi rollers are women and children, drawn to this home-based, labor-intensive employment as it allows for the concurrent management of household responsibilities [82–85]. There is a critical need for targeted research to elucidate the long-term health effects of tobacco exposure among bidi rollers, particularly regarding renal and overall health. Policy initiatives to enhance health equity among bidi rollers must incorporate preventive and remedial strategies. Preventive measures should include the enforcement of stringent regulations on occupational exposure to tobacco, enhancement of workplace safety, and provision of protective equipment. Remedial strategies should concentrate on providing accessible and affordable healthcare to these workers. Health interventions might include regular health screenings, subsidized healthcare services tailored to the specific needs of bidi rollers (especially concerning renal health), and educational programs to raise awareness about occupational risks. Addressing the intricate health, social, and economic challenges faced by bidi rollers, and others in similar circumstances, requires a comprehensive approach that involves governmental action, community support, and international attention to reform labor conditions, enhance healthcare access, and ensure equitable economic opportunities for this vulnerable population.

Study limitations include inconsistent control of second-hand smoke exposure quantity, variability in reporting smoking status, bias towards urban populations in included studies impacting generalizability, differences in CKD diagnostic criteria, study design, follow-up period, and tobacco exposure definition across included studies. Additionally, CKD rates varied due to cultural, genetic, and environmental factors, and 18 of the included studies were rated as 'poor' quality according to the Newcastle–Ottawa Scale. Moreover, the included studies did

not stratify results by caste, which is significant given the higher disease burden and mortality rates observed in lower caste groups due to factors such as poverty, poor sanitation, and limited access to healthcare, potentially introducing bias into the results. However, this systematic review offers a holistic analysis of the complex interplay between tobacco exposure, sex differences, and CKD development, providing an in-depth understanding of how these factors collectively influence disease risk and aiding in the development of tailored prevention and intervention strategies. By including studies from diverse geographic regions and accounting for social determinants of health, it provides a well-rounded perspective on the global and socio-economic factors influencing CKD prevalence.

Conclusion

This comprehensive analysis of CKD encompasses diverse contributors to its development and progression. The roles of sex hormones, cultural influences, and socioeconomic factors add layers of complexity, necessitating continued research to unravel the intricacies of CKD etiology and pathogenesis. From the geographical variations in IgA nephropathy prevalence to the intricate relationship between hypertension, tobacco exposure, and CKD, the multifaceted nature of these factors underscores the need for nuanced, context-specific interventions. This knowledge is vital for developing targeted strategies, especially in vulnerable populations. This review provides evidence supporting male sex and tobacco exposure as risk factors for CKD development, and further research is needed to assess the strength of the association between tobacco exposure, sex, and CKD.

N.W. contributed to the study investigation, data curation, original draft writing, review & editing writing, project administration, and visualization. R.C. contributed to the study conceptualization, methodology, data curation, original draft writing, review & editing writing, and project administration. N.V. contributed to the study investigation and review & editing writing. A.V. contributed to the study investigation and review & editing writing. A.X. contributed to the study investigation. E.F. contributed to the study investigation. O.H. contributed to the study investigation. R.S. contributed to the study methodology. S.J. contributed to the study methodology, review & editing writing,. A.C. contributed to the study methodology, review & editing writing. S.P. contributed to the study conceptualization, methodology, review & editing writing, supervision, and project administration. N.V and A.V contributed equally.

Abbreviations

CI	Confidence Interval
CKD	Chronic Kidney Disease
CRD	Centre for Reviews and Dissemination
CS	Cigarette Smoke
DM	Diabetes Mellitus
DPP	Diabetes Prevention Program
EEE	Endogenous Estrogen Exposure
EMBASE	Excerpta Medica Database
ER	Estrogen Receptor
ESRD	End-Stage Renal Disease
GFR	Glomerular Filtration Rate
GOLD	Global Initiative for Chronic Obstructive Lung Disease
IgA	Immunoglobulin A
IgAN	Immunoglobulin A Nephropathy
NOS	Newcastle-Ottawa Scale
OR	Odds Ratio
RR	Relative Risk
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
TGF-β	Transforming Growth Factor-beta

Supplementary Information

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Supplementary Material 1.

Authors' contributions

N.W. contributed to the study investigation, data curation, original draft writing, review & editing writing, project administration, and visualization. R.C. contributed to the study conceptualization, methodology, data curation, original draft writing, review & editing writing, and project administration. N.V. contributed to the study investigation and review & editing writing. A.V. contributed to the study investigation and review & editing writing. A.X. contributed to the study investigation. E.F. contributed to the study investigation. O.H. contributed to the study investigation. R.S. contributed to the study methodology. S.J. contributed to the study methodology, review & editing writing,. A.C. contributed to the study methodology, review & editing writing. S.P. contributed to the study conceptualization, methodology, review & editing writing, supervision, and project administration. N.V and A.V contributed equally.

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Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study does not require ethics approval as this is a synthesis of existing data, there are no human or animal participants.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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