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Recent Trends in Risk Factors Associated with Kidney Diseases

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Authors' contributions

This work was carried out in collaboration among all authors. Author OBN designed the study and wrote the first draft of the manuscript. Author ADN managed the analyses of the risk factors in the study. Authors GOMI and NJD managed the literature searches and made sure that all materials cited are properly referenced. All authors read and approved the final manuscript.

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ABSTRACT

The kidneys play a vital role in our overall health and well-being. Their ability to filter waste, reabsorb essential nutrients and maintain a balance of fluids and electrolytes in our body is essential for our health. However, various factors such as age-related changes, exposure to toxins, and lifestyle habits can contribute to a decline in kidney function, leading to potential health issues. Therefore, it is crucial to identify the risk factors that can cause kidney damage and take early interventive measures to slow down the progression of chronic kidney disease. By raising awareness of these risk factors, we can work towards preventing the development of chronic kidney disease and reducing the incidence of end-stage renal disease. It is important to note that several

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of these risk factors are modifiable, and early diagnosis and treatment of kidney disease can prevent severe complications. Through regular check-ups, identifying these risk factors through panels of tests, and taking a proactive approach towards our health, we can ensure that we maintain healthy kidney function and prevent potential health problems. In conclusion, by taking a constructive approach towards our health and being aware of the risk factors that can cause kidney damage, we can work towards maintaining healthy kidney function and preventing chronic kidney disease. Let us prioritize our health and make changes to our lifestyle habits to reduce the risk of kidney disease and ensure our long-term well-being.

Keywords: Kidney; toxins; risk factors; age; diabetes; chronic; end-stage.

1. INTRODUCTION

The kidneys are essential organs located in the retroperitoneal space of vertebrates. They have a reddish-brown, bean-shaped appearance and typically measure around 10-12 centimeters in length, 5-7 centimeters in width, and 2-3 centimeters in thickness, with a weight of around 120-150 grams [1,2]. Positioned above them are the adrenal glands, while the posterior abdominal wall and diaphragm muscles are located behind them [3]. The kidneys perform several critical functions in the body, such as regulating fluid balance, maintaining acid-base balance, eliminating toxins, reabsorbing vital nutrients, regulating blood pressure, and producing hormones. To function correctly, kidneys require adequate blood flow and filtration, with selective reabsorption of nutrients from the filtrate before waste removal through the ureter and urethra. Kidney function tends to decline with age, with almost half of those aged 80 years or older having an estimated glomerular filtration rate (eGFR) of ≤ 60ml/min/1.73m² [4,5]. This decline occurs due to various factors such as glomerulosclerosis, interstitial fibrosis, tubular atrophy, vascular degenerative changes, and senile nephrosclerosis, as well as others [6,7]. Therefore, it is crucial to take care of these organs and implement preventive measures to minimize the risk of developing kidney disease.

1.1 Ageing Effects on Kidneys

According to research conducted by Epstein [8], kidney function declines with age in humans starting at around 40 years old. While ageing kidneys can still maintain homeostasis under normal circumstances, their ability to function diminishes when they encounter stressful situations, as suggested by Chaudhury *et al*. [9]. In 2007, Devaraj's study provided a detailed outline of the important anatomical [10] and, physiological changes that occur in the kidneys as we age [11], which can be found in Tables 1 and 2. The rate of Glomerulosclerosis and tubulo-interstitial sclerosis may vary among individuals due to factors such as angiotensin II, transforming growth factor, nitric oxide, advanced glycosylation end products, oxidative stress, and lipids.

Table 1. Anatomical changes in kidney with ageing

1	Renal Mass	Decreased by 30%, mainly due to cortical loss
2	Glomerular Changes	Glomerulosclerosis
		Ischemia of cortical glomeruli- decrease in the number of glomeruli by 30% to 50% by age 70.
		Relative sparing of medullary glomeruli.
3	Mesangium	Increase in mesangial volume
4	Renal Tubules	Decrease in number, sclerosis and atrophy leading to distal diverticula. (The diverticula may represent the earliest formation of acquired cysts as seen in the aged kidneys or may collect bacteria and debris possibly predisposing to pyelonephritis)
5	Vascular	Intra-renal Vascular changes occur independently of hypertension or other renal disease.
		Increased arteriosclerosis of intra-renal vessels and interlobular and arcuate arteries.
		Cortical efferent arteriole obliteration.
		In juxtamedullary glomeruli, afferent to afferent arteriolar shunting renders redistribution of blood flow to the renal medulla.

Table 2. Functional changes in kidney with ageing

1.	**Renal Plasma Flow (RPF)**	**Reduced rate of approximately 10% per decade from age 30 years [12].**
2.	Glomerular Filtration Rate (GFR)	Creatinine clearance decreases linearly from 140 ml/min/1.73m² during the third or fourth decade to about 97ml/min/1.73m² by 80 years of age. This is a decline at the rate of about 0.8ml/min/1.73m² per year or by about 7% every decade after the age of 40 years [12,13].
3.	Renal Blood Flow	Preferential decrease in cortical blood flow and preservation of medullary flow with age paralleling histologic changes of loss of selective cortical vasculature [12].
4	Ability to concentrate or Dilute Urine	Impaired in ageing kidney.
		Other contributing factors include blunted response to anti-diuretic hormone (ADH) on renin-angiotensin cascade, ald0sterone and ADH in the elderly [14].
5	Acid, Base and Electrolyte	The ability to conserve sodium in the face of hyponatraemia (possibly secondary to decreased distal reabsorption) or excrete it when required is decreased [14].
		Under the stress of acid load, an aged kidney shows impairment in excreting it [9].
		While calcium handling is not affected much by the ageing kidney, potassium excretion is affected. This is due to decreased plasma renin and aldosterone, in turn leading to a relative hypoaldosteronism and also due to blunting of the response to aldosterone [9].

1.2 Toxic Agents Effects on Kidneys

“Humans are exposed to various harmful conditions and agents both in their natural and occupational environments. These factors can cause health issues such as dehydration, exposure to bacteria and viruses, temperature changes, or exposure to chemicals. The kidneys play a crucial role in maintaining body balance and waste management, making them highly vulnerable to toxic effects caused by environmental hazards” [15,16]. “Environmental toxins, which we are unintentionally exposed to through oral, inhalational, or transdermal routes, are a common yet underappreciated cause of kidney injury” [17,18]. “The kidney's susceptibility to damage can be explained by its unique physiological features, such as the highest blood flow per 100 g tissue, the largest endothelial surface by weight, highly active multiple metabolizing enzyme systems, the high concentration of filtered chemicals in tubular fluid adjacent to tubular cells, protein unbinding of chemical compounds in the tubules, and further intrarenal biotransformation of chemicals. Renal toxicity can occur through two main mechanisms. The first mechanism involves toxins being absorbed through transport systems and damaging the cells in the proximal tubules” [17]. The second mechanism involves the kidney's ability to concentrate substances leading to the formation of crystals in the tubules [17].

1.3 Signs and Symptoms of Kidney Diseases

When the kidneys fail to function correctly, harmful toxins and substances can accumulate, leading to symptoms such as fatigue, poor sleep, itchy skin, swollen face and feet, muscle cramps, shortness of breath, cloudy thinking, decreased appetite, bad breath, foamy/brown/bloody urine, and changes in urinary frequency. As kidney function declines, the organ may struggle to regulate the body's mineral and nutrient balance, leading to electrolyte imbalances, oedema, and bone disorders. Sodium retention due to impaired renal function can cause fluid buildup, leading to swelling in the face, hands, feet, and ankles. Additionally, protein loss through urine leakage can cause puffiness around the eyes. It is essential to monitor kidney function regularly to prevent these complications. Poor kidney function can cause cramps, dizziness, concentration difficulties, memory loss, nausea, vomiting, and stomach discomfort. A buildup of urea and toxins in the blood can lead to bad breath or give food an off taste. Severe symptoms that could mean the kidneys are progressing into kidney failure include nausea, decreased sex drive, hyperkalaemia, inflammation of the pericardium, pain or pressure in the chest, seizures, and coma.

1.4 Risk Factors for Developing Kidney Disease

Kidney disease can develop due to various sources such as metabolic, occupational, environmental, lifestyle/habits, genetic factors, age, and gender [19,20]. Recent research has grouped these sources into five major risk factors that can generate kidney disease either alone or in combination [21].

These risk factors are:

A. Diabetes Mellitus, which is the leading cause accounting for 44% of cases [19].
B. High Blood Pressure.
C. Having other family members with kidney disease- genetic or lifestyle.
D. Elderly [19].

Diabetes and High Blood Pressure are the most common causes of kidney disease, especially, chronic kidney disease (CKD) [22]. Too much glucose in the blood can damage the kidneys' filters, which can eventually hinder their ability to filter waste and extra fluid from the blood. When the filters are damaged, a protein called albumin, which is essential for maintaining a healthy body, passes out into the urine. A healthy kidney does not allow albumin to pass from the blood into the urine.

High Blood Pressure can also damage blood vessels in the kidney, making it difficult to remove waste and excess fluid, leading to an increase in blood pressure of the vessels surrounding the kidney cells. This cycle, if not checked, can cause gradual damage to some or most cells of the kidney.

Other causes of kidney disease include genetic disorders that produce multiple cysts in the kidneys (Polycystic Kidney Disease-PKD), infections, drugs toxic to the kidneys, diseases affecting the entire body (Lupus), IgA Glomerulonephritis, disorders wherein the body's immune system attacks its cells and organs (Anti-GBM-Goodpasture's Disease), heavy metal poisoning such as lead poisoning, rare genetic conditions (Alport Syndrome), haemolytic Uraemic Syndrome in children, IgA Vasculitis and renal artery Stenosis.

1.5 Types of Kidney Diseases [23]

Kidney diseases can be broadly classified into two types:

A. **Acute kidney disease**, which occurs suddenly when the kidneys stop functioning properly and,
B. **Chronic kidney disease**, which develops over time.

Five different types of kidney disease fall under these two broads categories:

1. **Acute Pre-renal kidney disease (APrRKD):** This type is caused by insufficient blood flow to the kidneys and can result in acute pre-renal kidney failure. Without enough blood flow, the kidneys cannot filter toxins from the blood. Once the cause of the decreased blood flow is identified, APrRKD can usually be cured.

2. **Acute Intrinsic Kidney Disease (AIKD):** This type results from direct trauma to the kidneys, such as physical impact or an accident. Other causes include toxin overload, ischemia (a lack of oxygen to the kidneys), severe bleeding shock, obstruction of the renal blood vessel, and glomerulonephritis (a condition where the tiny blood vessels in the kidneys become inflamed).

3. **Chronic Pre-renal kidney disease (CPrRKD):** This type occurs when there is not enough blood flowing to the kidneys for an extended time. The kidneys begin to shrink and lose their ability to function.

4. **Chronic Intrinsic Kidney Disease (CIKD):** This type occurs when there is long-term damage to the kidneys due to a disease that develops from direct trauma to the kidneys, such as severe bleeding or a lack of oxygen.

5. **Chronic Post-renal kidney disease (CPoRKD):** This type arises due to the long-term blockage of the urinary tract, which prevents urination and leads to increased backflow pressure and eventual kidney damage.

1.6 Urine Elimination Problems [23]

The inability to expel urine from the body can lead to the accumulation of toxins, resulting in an overload of the kidneys. This condition can be attributed to various types of cancer, including but not limited to prostate, colon, cervical, or bladder cancer. Furthermore, other health

conditions can hinder the process of urination and potentially lead to renal disease and failure, such as kidney stones, an enlarged prostate, blood clots in the urinary tract, and nerve damage that regulates bladder control.

1.7 Complications of Kidney Disease

Inadequate management of kidney disease can lead to a range of complications, such as anaemia, bone weakness, fluid retention, heart disease, hyperkalaemia, metabolic acidosis, and secondary complications.

Anaemia: One of the critical consequences of kidney disease is anaemia, which can result from inadequate production of erythropoietin. This hormone plays a vital role in the production of red blood cells and can affect several body functions, such as glucose metabolism, electrolyte and fluid balance, and brain cell metabolism. [22]

Bone Weakness: Kidney damage can also disrupt the mineral balance in the body, especially phosphorus and calcium, leading to weakened bones. [22]

Fluid Retention: Additionally, the kidneys' ability to filter water from the blood may be impaired, resulting in an increased risk of fluid retention, particularly in the lower parts of the body. [22].

Heart Disease: Heart disease is a common complication of kidney disease, and vice versa. People on dialysis are at a higher risk of dying from heart disease [22].

Hyperkalaemia: Kidney disease frequently results in elevated potassium levels in the blood, which can worsen heart disease (heart failure) in severe cases. [22]

Metabolic Acidosis: Disrupted kidney function can also lead to metabolic acidosis, whereby the body fluids have too many acids. This can result in the deposition of stones in the kidneys or bone disease. [22]

Secondary Complications: People with kidney disease are susceptible to developing secondary complications, such as depression, liver failure, fluid build-up in lumps, gout, nerve damage, and skin infections. Proper management of kidney disease is, therefore, crucial to minimize these complications. [22]

The purpose of this paper is to review the risk factors associated with kidney diseases. Specifically, we will analyse the variables of age, gender, race, ethnicity, family history, drug use, smoking, socio-economic status, hypertension, diabetes and also the recent discoveries of the links between other conditions and toxins to the development of kidney diseases.

Kidney disease is a growing concern, and understanding the risk factors that contribute to its development is critical. By analysing the factors in question, we hope to better understand the causes of kidney disease and to develop more effective prevention and treatment strategies.

It is important to note that both traditional and non-traditional risk factors are associated with kidney disease. Traditional risk factors include age, gender, race, ethnicity, family history, and concurrent diseases such as hypertension and diabetes. Non-traditional risk factors include drug use, smoking, chemical use and socio-economic status. These factors, when examined collectively, can provide a comprehensive understanding of the risks associated with kidney disease.

2. LITERATURE REVIEWS

2.1 Risk Factors Associated with Kidney Diseases

Kidney disease is a global health concern that affects millions of people worldwide. Medical emergency updates indicate that over 1.4 million patients are currently receiving renal replacement therapy due to this condition [23]. Early intervention is essential in reducing the economic burden associated with kidney diseases. According to Rumeyza [24], “early identification of individuals with an increased risk of renal diseases can help prevent the development of chronic kidney disease and reduce the incidence of end-stage renal disease (ESRD), which is a condition where the kidney reaches advanced state of loss of function”. “This causes changes in urination, fatigue, swelling of feet, high blood pressure, and loss of appetite” [24].

“Several factors can increase an individual's risk of developing kidney disease. These include genetic and phenotypic make-up, age, gender, race, and family history. For example, research has shown that individuals of African-American

descent, older age, low birth weight, and those with a family history of kidney disease are at higher risk of developing chronic kidney disease" [24].

"In addition, several lifestyle factors can contribute to the development of kidney disease. These include smoking, obesity, hypertension, and diabetes mellitus. Exposure to heavy metals, excessive alcohol consumption, smoking, and the use of analgesic medications also increase the risk of kidney disease. Furthermore, other health conditions such as acute kidney injury, a history of cardiovascular disease, hyperlipidaemia, metabolic syndrome, hepatitis C virus, HIV infection, and malignancy can also increase the risk of chronic kidney disease" [24].

"It is important to note that chronic kidney disease can lead to end-stage renal disease and increase cardiovascular morbidity and mortality. Some of these risk factors can be modified, and early intervention can prevent or slow down the progression of chronic kidney disease to end-stage renal disease. Therefore, it is crucial to raise awareness of these risk factors to help prevent the development of chronic kidney disease and reduce the incidence of end-stage renal disease" [25].

Genetic Component: Kidney disease (CKD) has been found to have a hereditary component. A study by Kottgen et al. [26] conducted "genome-wide association studies to identify susceptibility loci for glomerular filtration rate (GFR) in four population-based cohorts of European ancestry participants. The study discovered that uromodulin mutations, which encode the Tamm-Horsfall protein in urine, were associated with differences in renal function". Moreover, the study identified mutations related to APOL1, which has an autosomal recessive pattern of inheritance and is associated with a substantially higher risk of ESRD. These APOL1 mutations are found exclusively among individuals of African descent [27], making them more prone to CKD. Renin-angiotensin system genes have also been found to play a significant role in CKD development. According to a study conducted by Su et al. [28] with a sample size of 135 CKD patients and 270 healthy controls among Han Chinese in Taiwan, significant associations in ACE-A2350G and AGTR1-C573T polymorphism in CKD patients were observed. The participants were genotyped for angiotensinogen and angiotensin II type 1 receptor (AGTR1-A1166C, C573T, C-52IT) polymorphism by polymerase chain reaction-restriction fragment length polymorphism analysis.

Family History: Research has shown that family members of chronic kidney disease (CKD) patients are more likely to have CKD and its related risk factors. A study conducted by Song et al. screened incident dialysis patients in the US between 1995 and 2003 and found that 23% of them had close relatives with End-Stage Renal Disease (ESRD), after excluding patients with ESRD caused by hereditary disorders or urologic issues. Therefore, it's crucial to screen the relatives of CKD patients, as they are at a higher risk of developing kidney disease [29].

Gender: Studies conducted by Iseki [30] and Takamatsu et al. [31] have demonstrated that men are more likely to develop ESRD. In one of the studies, conducted in Okinawa, Japan, over 10 years, 107,192 participants over 18 years of age (51,122 men and 56,070 women) were screened, and the odds ratio for ESRD was 1.41 among the male participants [30].

Ethnicity: "Research carried out in the United States has confirmed that African Americans have a higher risk of developing ESRD than Caucasians. The risk of hypertensive ESRD is approximately five times higher in African Americans than in Caucasians" [32]. "In another study, the lifetime risk of ESRD was found to be 7.8% for 20-year-old black women, 7.3% for black men, 1.8% for white women, and 2.5% for white men" [25].

Age: "Renal function decreases with age in both men and women (Iseki, 2005). In the elderly population, more than half of the subjects screened had CKD stages 3-5 (GFR<60ml/min per 1.73m^2) according to the National Kidney Foundation, Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines. Therefore, the elderly population is more prone to develop CKD after various renal insults" [33]. "In Turkey, a study found that the odds ratios of CKD ranged from 1.45 to 2.18 for every 10-year increase in age among subjects older than 30 years" [34].

Low Birth Weight: In the 1980s, Brenner and colleagues hypothesized that intrauterine growth restriction might cause a low nephron number, which could predispose to hypertension and renal disease (Barker Hypothesis) [35]. "Supporting this hypothesis, research has shown that there is an increase in nephron numbers by 257,426 glomeruli per kg increase in birth weight"

[36]. “Low nephron number leads to intraglomerular hypertension and hyperfiltration in the available nephrons, resulting in lower overall GFR and higher urine albumin-to-creatinine ratio. In a recent cohort study with a maximum follow-up of 38 years, low birth weight and intrauterine growth restriction were significantly associated with an increased risk of ESRD among Norwegians” [37].

Obesity: “Numerous studies have demonstrated that obesity is a significant, yet modifiable, risk factor for End-Stage Renal Disease (ESRD) in the twenty-first century. It has been observed that obese individuals are linked to glomerular hypotrophy and hyperfiltration, which may accelerate kidney injury by increasing capillary wall tension of the glomeruli and decreasing podocyte density” [38]. “A large-scale epidemiological study from Sweden has also identified the role of obesity in chronic kidney disease (CKD). According to the study, overweight patients (BMI=25kg/m²) at age 20 were associated with a significant threefold excess risk for CKD compared to those with a BMI<25kg/m². Furthermore, obesity (BMI=30kg/m²) among men and morbid obesity (BMI=35kd/m²) among women at any time during their lifetime were linked to three-to-four-fold increases in CKD risks” [39]. “Obesity is known to contribute to kidney damage through inflammation, oxidative stress, endothelial dysfunction, prothrombotic state, hypervolaemia, and adipokine derangements” [40]. Bedside high BMI, along with carrying excess weight around the abdomen, is associated with an increased risk of CKD. Kwakernaak et al. [41] found that “a higher waist-to-hip ratio was linked to lower GFR, lower effective renal plasma flow, and higher filtration fraction, even after adjusting for sex, age, mean arterial pressure, and BMI, in multivariate analyses”.

Socio-economic Status: Various factors, including income, occupation, education level, wealth, and housing situation, tend to determine an individual's health. Based on a study conducted by Krop et al. [42], people with an income less than $16,000 had a 2.4 times higher chance of developing chronic kidney disease (CKD) than those earning over $35,000. “Another case-control study found that individuals with CKD were more likely to belong to families with unskilled workers. NHANES results showed that unemployed non-Hispanic black and Mexican American individuals in the US had twice the prevalence of CKD compared to their employed counterparts. Lastly, the ARIC study indicated that individuals with less than a high school education had a 1.7 times higher risk of CKD compared to those with a college education” [42].

Smoking: Smoking is a well-documented cause of CKD, as it increases inflammation, oxidative stress, endothelial dysfunction, and other factors that contribute to kidney damage [43]. A study found that each additional five cigarettes smoked per day increased serum creatinine levels by 31%, which is a marker for kidney function decline [44].

Nephrotoxins: “Nephrotoxins, including alcohol, recreational drugs, analgesics, and exposure to heavy metals, have also been linked to CKD progression” [33]. For instance, taking more than 1000 pills containing acetaminophen has been associated with a 2.4 odds ratio for ESRD [45].

Acute Kidney Injury: Acute kidney injury (AKI) episodes are also significant risk factors for the development of CKD [46]. According to a United States Renal Data Systems report in 2009 [47], adults with a history of AKI during hospitalization are ten times more likely to develop ESRD in the next 12 months than those without AKI episodes [46]. Even a single episode of experimental AKI can lead to focal tubulointerstitial fibrosis, which impairs histologic repair and can lead to CKD [46].

Diabetes Mellitus: “Diabetes mellitus is the primary risk factor for CKD and ESRD in both developed and developing countries. According to the Turkish Society of Nephrology registry, 37.3% of the hemodialysis population in Turkey is comprised of diabetic patients” [34]. “Similarly, USRDS data indicates that half of the new ESRD patients in the United States have diabetic nephropathy” [48]. “In diabetes, the mechanisms that lead to kidney disease include hyperfiltration injury, advanced glycosylation end products, and reactive oxygen species” [48]. “At the molecular level, numerous cytokines, growth factors, and hormones such as transforming growth factor-beta and angiotensin II cause pathologic changes associated with diabetic nephropathy” [48].

“It is now documented that 8% of new patients with type 2 DM already have proteinuria at diagnosis” [48]. “Among those initially free of proteinuria, the 20-year risk of diabetic nephropathy is 41%” [25]. “After the onset of proteinuria, the subsequent 10-year risk of

progressive CKD is 11%" [25]. "This means that about half of those with type 2 DM will eventually develop nephropathy, and 10% of these individuals will experience progressive loss of renal function" [48].

Hyperglycaemia: "Hyperglycaemia, including previously diagnosed diabetes and impaired fasting glucose, is another component of metabolic syndrome that is significantly associated with CKD" [49]. "Increased glomerular filtration rate, also called hyperfiltration, is a proposed mechanism for renal injury in diabetes, which has been hypothesized to cause intraglomerular hypertension leading to albuminuria and reduced glomerular filtration rate. Hyperfiltration also occurs in patients with impaired fasting glucose and can be used as a predictor of nephropathy" [50,51,52,53]. "Some studies have shown that hypertriglyceridemia or low HDL-C levels are only significantly associated with the development of CKD in patients with metabolic syndrome" [54,55].

Hypertension: "Hypertension has long been a known risk factor for both CKD and ESRD. It accounts for 27% of all ESRD patients in the United States and 28% of haemodialysis patients in Turkey" [34,48]. "Systematic hypertension transmits to intraglomerular capillary pressure leading to glomerulosclerosis and loss of kidney function. Thus, a variable risk of impaired renal function has been reported among hypertensive subjects" [48]. "In a similar study, among the 8683 participants, 2.3% of those with serial serum creatinine measurements above 1.5mg/dl experienced a clinically significant loss of renal function over 5 years" [56].

Essential hypertension is generally diagnosed between 25 and 45 years of age, but overt kidney dysfunction does not develop unless the patient sustains at least 10 years of uncontrolled hypertension [48]. A history of cardiovascular disease, hyperlipidaemia, metabolic syndrome, hepatitis C virus, human immune-deficiency virus infection, and malignancy are further risk factors for CKD.

Kidney diseases, especially chronic kidney disease is a global public health concern and its associated risk factors vary between climes. The rising prevalence of this non-communicable disease calls for serious attention to the risk factors of this disease. The study of Omeire et al. [57] "to ascertain the pattern of distribution of the risk factors of chronic kidney disease was carried out on 750 participants with males being 244 and females 506 in Owerri, Nigeria. About 484 (64.5%) of the participants had hypertension (males 152 (62.2%), females 332 (65.6%). Concerning diabetes, 76 (10.1%) of the participants had diabetes (males 36 (14.8%) and females 40 (7.9%). Obesity was recorded in 145 (19.3%) of the study participants, out of which 17 (7.0%) and 128 (25.3%) of the males and females had obesity respectively. More so, 33 (13.5%) of the males and 7 (1.4%) of the females currently smoke and an overall percentage prevalence of 40 (5.3%) was recorded for cigarette smoking. Alcohol use was found in 258 (34.4%) of the participants, with males and females recording 144 (59.0%) and 114 (22.5%) respectively. Co-morbidity of hypertension and diabetes was found to be 56 (7.5%), while 207 (27.6%) and 14 (1.9%) of the participants were not aware they had hypertension and diabetes respectively. Hypertension was found to be more prevalent among the study participants. Screening people from time to time will help to detect these risk factors on time, thereby aiding the prevention and control of chronic kidney disease (CKD). It is also imperative that prevention and control be focused on lifestyle changes which form the bedrock of the primary level of prevention". Recently, some newly identified risk factors have been defined as:

Obstructive Sleep Apnoea: Obstructive Sleep Apnoea (OSA) is a serious medical condition that causes complete or partial breathing disruptions during sleep, occurring at least five times per hour [40]. Studies have found that 30.1% of OSA patients also suffer from chronic kidney disease (CKD) [40]. Not only do OSA and CKD share common risk factors, but OSA also has an independent effect on the risk and progression of CKD [40].

Heart Rate: Another risk factor for CKD is heart rate. A study conducted on 6,759 Japanese subjects (20-84 years of age) found that subjects with higher heart rates had a greater magnitude of decreasing estimated glomerular filtration rate (eGFR) and a higher odd ratio of developing proteinuria [58]. Each increment in the heart rate category led to a 1.1 times increased risk of developing proteinuria in middle-aged or older subjects [58].

Periodontal Diseases: Periodontal diseases, initiated by gram-negative tooth-associated microbial biofilms, have also been identified as a risk factor for CKD [59].

Uric Acid: Furthermore, studies have shown that uric acid levels are positively associated with CKD risk. In a study conducted on 21,475 healthy volunteers from the Vienna Health Screening Project, individuals with a slightly elevated uric acid level (7.0 - 8.9mg/dl) had a double risk for CKD, while those with an elevated uric acid level (≥ 9.0mg/dl) had a tripled risk [60].

A recent study by Lu et al. [49] on 400 participants found that the overall proportion of participants with CKD was 20.5%, with the highest proportion found in those aged 75 years and over. Multiple logistic regression analysis revealed that elevated blood pressure, hyperglycaemia, hyperuricaemia, and metabolic syndrome were significantly associated with CKD in middle-aged and elderly populations in Taiwan [49]. These findings are consistent with several other studies conducted in different countries and among different races, which have all identified metabolic syndrome as a significant risk factor for developing CKD [61–65].

Tozawa et al. [66] followed up on 6,371 people without CKD or diabetes mellitus for 5 years, finding that those with metabolic syndromes had a relative risk of developing CKD of 1.86 after adjusting for age, sex, current cigarette smoking, and alcohol drinking habits. Kurella et al. [67] enrolled 10,096 non-diabetic participants with 9 years of follow-up and also found that metabolic syndrome was independently associated with an increased risk for incident CKD in non-diabetic adults, with an odds ratio of 1.24 after adjusting for the development of diabetes and hypertension. Lu et al. [49] also found metabolic syndrome to be an independent risk factor for the development of CKD in middle-aged and elderly populations in Taiwan after adjusting for age, sex, BMI categories, and uric acid.

Each component of metabolic syndrome can cause renal damage, but not all components contribute equally to the risk of developing CKD [62]. Studies have found gradient associations between CKD risk and the number of metabolic syndrome components [66,67]. Elevated blood pressure and hyperglycaemia have been identified as independent risk factors for CKD, while other components did not reach statistical significance after adjusting for confounding factors [49]. High-normal blood pressure has also been found to be significantly associated with microalbuminuria when compared with optimal blood pressure, leading to injury to tubular cells, interstitial inflammation, and fibrosis [68,69].

2.2 Toxins and Chemical Association with Kidney Diseases

Kidney disease can cause a great deal of stress on your kidneys, making it difficult for them to filter water and toxins from your blood. Unfortunately, it can be challenging to avoid the harmful chemicals found in everyday products and food, which can add to the load on your kidneys [70,71]. Some of the most common harmful substances that you should be aware of include:

1. **Polychlorinated Biphenyls (PCBs):** These toxins are often found in farm-raised salmon, which are fed PCB-contaminated fish feed. Overexposure to PCBs can cause reproductive and immunological problems, especially if you have chronic kidney disease. If you cook fish, it's best to remove the skin, fat, and internal organs where toxins accumulate [72,73].

2. **Phosphorus:** This mineral is essential for filtering waste and repairing tissue in the body. However, high doses of phosphorus, usually consumed through carbonated drinks, can be toxic and harmful to people with chronic kidney disease. Instead of carbonated drinks, experts recommend drinking antioxidant-packed cranberry juice and flat water. It's important to keep in mind that even cranberry juice can be harmful if ingested regularly in large amounts as it can cause kidney stones [72].

3. **Pesticides:** These chemicals are commonly used to control or kill insects in farmlands, orchards, and playgrounds. They find their way into fruits, vegetables, fish, and tubers, such as potatoes and yams. According to the Environmental Working Group (EWG), some of the produce with the highest levels of pesticide residue includes strawberries, spinach, apples, tubers and grapes. If you buy conventional produce, always wash and dry it before eating to remove any potential pesticides. If you have chronic kidney disease, consider using a produce wash for extra assurance. Natural bug sprays are recommended to avoid those that contain DEET [70].

4. **Phthalates:** Phthalates are chemicals used to make plastic pliable. They are

commonly found in product packaging such as plastic wrap, plastic bottles and plastic food storage containers. Phthalates can leach into food or drinks from plastic, especially when heated. To reduce exposure to toxins, switch to a thermos or glass water bottle and use paper or reusable non-plastic containers and covers, such as those made from beeswax. This will not only reduce waste but also decrease exposure to harmful chemicals [70].

5. **Copper:** "Copper is a heavy metal that is essential for building tissues in the human body but needs to be consumed in moderation. Drinking water can contain a large amount of copper, which can build up and cause health problems. If the faucet has not been used for more than six hours, it is advisable to run it for a minute before using it to remove any accumulated copper. Cold water is preferable for cooking and drinking as it contains less copper than hot water. An easy solution is to invest in an attachable faucet filter that specifically filters out copper. Additional copper can be problematic for people whose kidneys already find it challenging to regulate heavy metals in their bodies, leading to symptoms of copper poisoning such as chills, diarrhoea, and jaundice" [74].

Certain occupational products can contribute to kidney damage and failure, including benzene, organic solvents like fuels, paints, and degreasing agents, as well as agrochemicals such as fertilizers and pesticides. Workplace exposure to heavy metals like cadmium and lead can also cause toxic injury to the kidneys.

Drinking water is crucial for kidney health, especially when working outside on hot days. Water removes waste from the body in the form of urine and helps to open blood vessels so that nutrients can reach the kidneys. Dehydration forces the kidneys to work harder to remove waste and deliver nutrients, causing fatigue and impairing some normal body functions. Severe dehydration can lead to kidney damage, so it is crucial to drink enough when working outside or exercising hard, especially in warm and humid weather. Frequent dehydration may lead to permanent kidney damage.

"Due to its high rate of perfusion, active transport capabilities, and concentrating functions, the mammalian kidney is often exposed to much higher concentrations of chemicals than other organs. These high concentrations of chemicals may not affect the kidney, produce a beneficial therapeutic response, or produce harmful (toxic) effects on the organ" [75].

"Some chemicals may produce direct renal cytotoxicity, such as heavy metals (mercury, chromium), therapeutic agents (aminoglycoside antibiotics, analgesics), or a variety of widely used chemicals (chloroform, carbon tetrachloride)" [76]. "Certain other chemicals in the environment may produce biochemical changes in the kidney that alone appear to have no functional correlation (that is, no functional nephropathy can be measured) yet may alter the kidney's response to other agents. The former chemicals produce identifiable functional lesions that may be life-threatening. Their effects are predictable and dose-related. The judicious use of therapeutic agents, careful monitoring of the workplace, and so forth can minimize the dangers of these compounds to humans. The latter chemicals, on the other hand, produce no functional lesion and are, therefore, more insidious in their effects and may pose a greater hazard to humans" [75].

"The kidney can metabolically alter a wide variety of endogenous and exogenous chemicals. Although many of these reactions produce compounds with reduced biological activity, in some specific instances, the metabolic transformation of a chemical may result in a compound with greater (or different) biological activity. Metabolism of chemicals within the kidney may, therefore, be an important factor in determining the kidney's response to chemical exposure. This article discusses the relationship between exposure to environmental pollutants and changes in renal biochemistry that may adversely affect kidney function" [76].

"Over the past 40 years, more than 84,000 new synthetic chemicals have been registered with the U.S. Environmental Protection Agency (EPA), with almost 3000 of them classified as high production volume (HPV) chemicals, producing over one million pounds annually. These chemicals are widely dispersed in the environment, and children may be exposed to them through air, drinking water, and food" [77]. "Measurable quantities of 200 HPV chemicals are routinely detected in the blood and urine of virtually all Americans, as well as in breast milk and cord blood" [78]. However, a large proportion

of these chemicals remain untested for their potential toxic effects in children.

6. **Arsenic:** a heavy metal, is especially dangerous when exposed to high doses. Exposure to contaminated drinking water and food is the primary cause of chronic environmental exposure. Previous use of copper chromated arsenate in pressure-treated lumber, occupational exposure in mining and smelting, industrial applications, and agricultural use of pesticides, fertilizers, and antimicrobial additives for animal and poultry feed have also contributed to the contamination [79,80]. The Environmental Protection Agency (EPA) has set the standard arsenic limit in water at 10 µg/L. However, millions of people still live in areas where the standard is exceeded.

Recent studies suggest that chronic low-level exposure to arsenic may be associated with CKD. A cross-sectional analysis of 3851 adults participating in the Strong Heart Study in the USA reported an adjusted odds ratio of prevalent CKD comparing the 75th to 25th percentile of arsenic exposure (defined as the sum of inorganic and methylated arsenic) to be 0.7 [95% confidence interval (CI) 0.6–0.8]. A prospective analysis of 3119 participants showed a positive relationship between urinary arsenic and incident CKD, with an adjusted hazard ratio of 1.2 (95% CI 1.03–1.41) [81]. These findings indicate that chronic exposure to arsenic can negatively impact kidney health and increase the risk of developing CKD.

A survey conducted on 1043 Taiwanese adults revealed that the odds of elevated β2-microglobulin and an estimated GFR (eGFR) value of ≤ 90 mL/min/1.73 m2 increased as urinary total arsenic levels increased above the reference group (≤35 µg/g creatinine) [82]. In another study, 125 patients with CKD and 229 age-matched controls were examined. It showed that total urinary arsenic level was significantly associated with CKD in a dose–response relationship, with those in the highest percentile of total arsenic having 4.3 (95 % CI 1.9–9.7) higher odds of CKD versus controls [83]. Another case–control study of 132 patients with renal cell carcinoma revealed that estimated GFR was also significantly negatively associated with total urinary arsenic concentrations, in comparison to age- and sex-matched controls [84].

7. **Cadmium:** This toxic metal is commonly used to make batteries and is present in the environment due to industrial dumping. Cadmium is often found in cigarette smoke, and leafy and root vegetables. According to Anis Rehman, cadmium may also be found in soil from industrial areas, fuel, and fertilizers, which can find its way into the leaves of veggies. Again, washing your produce goes a long way towards lowering cadmium intake [85].

“Cadmium is another nephrotoxin that targets the proximal tubule in the kidney. Exposure occurs through various sources like fossil fuel combustion, tobacco smoking, agricultural use of phosphate fertilizers, battery manufacture, copper and zinc smelting, and welding” [86]. “The largest source of cadmium exposure for nonsmoking adults and children in the USA is through dietary intake of contaminated food and water. Unlike lead, exposure to second-hand smoke has not been linked to elevated urinary cadmium levels in children” [87]. “Cadmium bioaccumulates in the liver and kidney. Therefore, urine cadmium levels are considered a good biomarker of the cumulative internal dose and kidney and body burden of cadmium, whereas blood levels are considered more indicative of recent exposure. Several studies have reported that people with high environmental exposures to cadmium have an increased risk of chronic kidney disease” [88,89]. “Cross-sectional studies have also reported nephrotoxicity at lower levels of exposure to cadmium” [90,91]. Moreover, co-exposure to lead and cadmium increases the risk of albuminuria and CKD [91].

8. **Lead:** Lead is a heavy metal that is toxic when it accumulates in the body. It is mostly found in old and rusty pipes, paint, gasoline, and soil. Lead enters the body through breathing or unintentional swallowing. The Mayo Clinic recommends washing hands and toys regularly, removing shoes before entering your house to avoid tracking in soil with lead, running cold water from your pipes for a minute or so before use and regularly cleaning dust-attracting surfaces. Houses built before 1978 may have Lead-based paint, so watch for peeling and cracking, which can release lead dust, according to the Environmental Protection Agency [92].

Lead is a well-known environmental nephrotoxin that has been extensively studied. Human activities such as the Industrial Revolution, leaded gasoline, lead-based paint, mining, plumbing, and other industrial applications have led to over 1,000-fold increase in environmental levels of lead over the past three centuries [79]. Acute lead poisoning, characterized by blood lead levels greater than 80-100 µg/dL, affects both the structure and function of the proximal tubules. Histologically, acute lead poisoning results in the formation of intranuclear inclusion bodies that contain lead-protein complexes and mitochondrial swelling in proximal tubular cells [79]. The molecular mechanism of toxicity is believed to be due to the effects of lead on mitochondrial respiration and phosphorylation [93]. Clinically, acute lead poisoning is characterized by the development of glucosuria, aminoaciduria, phosphaturia, or Fanconi's syndrome. Lead is bio-accumulative, and detectable lead levels in the bones of chronically exposed individuals can be mobilized by the body and contribute to ongoing endogenous exposure [94]. Lead poisoning is also known to reduce 1,25-dihydroxyvitamin D synthesis [95] and has been associated with bone demineralization and rickets in children [96]. "The kidney manifestations of acute lead poisoning are usually reversible after cessation of lead exposure and, if necessary, chelation therapy" [93,97].

Chronic lead poisoning, characterized by blood lead levels greater than 60 µg/dL, has been reported in both children and adults and may result in lead nephropathy [98]. Lead nephropathy is characterized by tubulointerstitial fibrosis, tubular atrophy, glomerular sclerosis, and ultimately diminished GFR [99,100]. Inflammatory cells are typically absent, and intranuclear inclusion bodies are also often absent [100]. Chronic lead exposure has also been shown to cause hypertension in animal models [101] and humans [102].

"Fortunately, mitigation efforts in the USA and worldwide have significantly reduced childhood exposure to lead over the past 50 years" [96]. However, lead persists in the soil and to a lesser extent in the air and water (and consequently in the food chain), which may cause chronic, low-level environmental exposure. Therefore, research efforts have recently focused on populations with lower levels of environmental lead exposure. Multiple cross-sectional studies in adults have shown a significant positive association between blood lead levels and serum creatinine [103-105], as well as increased all-cause and cardiovascular mortality [106].

"The hypothesis of reverse causality attributes higher lead levels to reduced lead excretion as a consequence—rather than cause—of decreased kidney function and is raised as an explanatory factor for negative associations between higher blood lead and kidney function in cross-sectional studies. Longitudinal studies are useful to address the potential impact of this mechanism on associations between lead and kidney function. A prospective study of 121 patients with CKD showed that a 1 µg/dL increase in blood lead level was associated with a 4.0 mL/min/1.73 m2 decline in GFR over 48 months of observation" [107].

"In a series of randomized experimental trials, a research group in Taiwan observed that chelation with EDTA slows CKD progression in adults, even at lead levels considered to be normal" [108]. "The same group reported an increase in GFR of 6 mL/min/1.73 m^2 in a group of diabetic CKD patients treated over 2 years with chelation therapy (average of 7.0 g $CaNa^2EDTA$) compared to a GFR decline of 1.4 mL/min/1.73 m2 in the untreated group" [109]. "However, this research is preliminary and requires replication in other populations, including children, before chelation at lower lead levels can be recommended" [110].

9. **Mercury:** Mercury is a toxic metal that occurs naturally in the environment and is increased through industrialization. It is mostly bioaccumulated in fish and water animals and plants grown near riverbanks. All fish contain some mercury, but big-eye tuna, marlin, and king mackerel contain high levels. Mercury exposure has been linked to kidney disease deaths, according to one study published in the American Journal of Epidemiology. To reduce risks, avoid consuming large amounts of high-mercury fish. Instead, consume small amounts of low-mercury fish such as grouper, snapper and catfish, no more than twice a week [72].

"Mercury exposure can occur through ingestion, inhalation, or skin contact. There are three forms of mercury: elemental, inorganic, and organic, each with its distinct clinical toxidromes. Inhaling mercury vapour from coal-fired power plants, cinnabar ore smelting, gold extraction/processing

plants, dental amalgams, thermometers, and caustic soda production can cause exposure to elemental mercury. Acute exposure to mercury vapour can result in chemical pneumonitis, while chronic exposure can lead to excessive salivation, intention tremor, and various psychiatric symptoms. Inorganic mercury exposure can occur through mercury mining and various medicinal uses, such as skin-lightening creams and calomel powder used for teething in small children. Children exposed to inorganic mercury can develop acrodynia (Pink disease), characterized by red discolouration of the skin of the hands and feet, fever, profuse sweating, photophobia, and psychiatric manifestations" [111]. Organic mercury compounds are found in seafood and can cause methylmercury poisoning, which poses a significant health risk to infants and the developing fetus.

Mercury exposure can have two nephrotoxic effects: acute kidney injury and proximal tubule damage. In rare cases, it can also cause an immune-complex-mediated nephrotic syndrome as described in animal models [112] and humans [113]. "Animal data suggest that immature kidneys may have decreased tubular transport, which may lead to less mercury excretion and increased toxicity. Age-related differences in kidney function may influence the severity of mercury toxicity" [4].

10. **Uranium**: Uranium poisoning is known to cause renal toxicity and has been established in multiple animal studies by Arzuaga et al. [114] and Homma-Takeda et al. [115]. Exposure usually happens through groundwater contamination from natural uranium deposits, as well as from uranium mining, milling, and processing. Uranium accumulates in bones but to a lesser extent than lead. The S3 segment of the renal proximal tubule is the primary target of uranium toxicity, which results in tubular dysfunction. Epidemiological data on uranium poisoning are limited, and findings on glomerular filtration rate (GFR) vary. However, some evidence shows that urinary biomarkers indicate proximal tubular damage, as noted by Shelly et al. [116]. A follow-up study of 35 Gulf War veterans who were exposed to depleted uranium found that there was a trend towards increased levels of β2-microglobulin and retinal binding protein in the highest uranium exposure group, but it did not show any association with GFR [117]. A case study of a family exposed to naturally uranium-contaminated well water showed that the youngest child had elevated β2-microglobulin levels, indicating that young children may be particularly vulnerable to uranium poisoning [118]. The child's β2-microglobulin levels decreased after the cessation of exposure. Age-related differences in kidney toxicity have been observed in animal studies [4].

11. **Aristolochic acid Nephropathy:** "Aristolochic acid is a toxic compound that occurs naturally in plants of the Aristolochiaceae family, including the Asarum (wild ginger) genus and the Aristolochia genus. Herbal drugs derived from plants belonging to the genus Aristolochia have been used since ancient times to treat snake bites, obstetrics, arthritis, gout, and rheumatism. In some parts of the world, Aristolochia plants and their extracts are used in traditional Chinese herbal medications" [119].

Aristolochic acid is a family of plant acids that have been associated with kidney problems. It is mainly found in Asarum (wild ginger) and other herbal supplements. While herbal remedies are often considered natural and healthy, you need to be cautious when using them. Make sure to confirm that they do not contain aristolochic acid, which has been linked to kidney cancer and is banned in Europe and Singapore. Aristolochic acid can cause kidney failure as it damages kidney cells and leads to non-functional scar tissue. If you use herbal remedies or homoeopathic medicine, ensure that they have clear ingredient lists and look for the USP seal, which verifies the remedy's ingredients [70].

Aristolochic acid has been linked to end-stage renal disease (ESRD) in a 10-year-old child [120], as well as Balkan endemic nephropathy and Chinese herb nephropathy [121]. Balkan endemic nephropathy is a chronic renal disease characterized by tubulointerstitial damage and an increased risk of urothelial carcinoma. Although heavy metals, viruses, trace-metal deficiencies, and mycotoxins (especially ochratoxin A) were initially considered as possible causes, it is now widely accepted that chronic exposure to dietary aristolochic acid was the most likely culprit [121].

In 2001, the U.S. Food and Drug Administration warned consumers about the dangers of botanical products containing aristolochic acid

due to the risk of permanent kidney damage (including ESRD) and certain types of urinary tract cancers [122]. “The exact mechanism of nephropathy remains unknown, but it has been suggested that the formation of unique aristolochic acid-DNA adducts in human kidney cells and mutation of the tumour suppressor gene TP53 may be implicated in carcinogenesis” [123].

12. **Mycotoxins:** Mycotoxins are toxic secondary metabolites produced by certain species of fungi. They can cause diseases in both humans and animals. Two examples of such mycotoxins are ochratoxin A and citrinin. These toxins are found in Penicillium, Aspergillus, and Monascus species. They are known to have nephrotoxic effects in multiple animal models, although their significance for human health is not yet fully understood [124].

Citrinin and ochratoxin A have been detected in various human food sources, including wheat, oats, rye, barley, and rice. They have also been linked to Balkan nephropathy and yellow rice fever [124]. Animal studies have shown that citrinin is transported in the proximal tubule cell via the organic anion transporter [125]. Additionally, citrinin and ochratoxin A have been found to have a synergistic effect in disrupting RNA synthesis in murine kidneys [124].

13. **Melamine nephropathy:** “Melamine is a synthetic chemical with various commercial applications. It is used to make colourants, glues, laminates, adhesives, dinnerware, dry-erase boards, cleaning products (such as Magic Eraser), and flame retardants” [126]. “However, melamine is not intended for human consumption and is banned by the World Health Organization. It has a high nitrogen content and is known to falsely increase the protein content in food. Unfortunately, it has been used to deliberately contaminate animal and human foods to reduce production costs, leading to several well-known outbreaks of kidney failure and kidney stones in animals and humans in the last decade. One such outbreak occurred in 2007, resulting in a widespread pet food recall, and another in 2008 in China, which involved the consumption of melamine-tainted infant formula, affecting over 294,000 infants and children, 51,900 of whom required hospitalization, and at least six of whom died” [127].

The mechanism of melamine nephrotoxicity in pet and livestock outbreaks is related to its ability to react with cyanuric acid in the bloodstream and form large round melamine-cyanuric acid crystals. These crystals obstruct the urinary tract and cause acute kidney injury [126], which has been associated with extremely high mortality in animal outbreaks. In the tainted Chinese infant formula outbreak, the kidney stones were mainly composed of melamine and uric acid and were radiolucent, making them not visible on plain X-ray films. Symptoms of melamine poisoning include irritability, dysuria, renal colic, haematuria, stone passage, and, in rare cases, acute kidney injury related to urinary obstruction, including elevated creatinine, hypertension, oedema, and/or oliguria. Acute kidney injury occurred in 2.5% of cases [128].

Several environmental agents have been shown to demonstrate acute and/or chronic nephrotoxicity (Table 3). Although limited data exist for children, much of the research has been conducted in adults or animal studies [129].

Heavy metal exposure can harm kidneys, even at low levels. Low-level exposure is widespread in modern society, posing a significant threat to public health. The proximal tubular cell is the main target of heavy metal toxicity, but the underlying mechanisms are not fully understood. Common mechanisms include oxidative stress, apoptosis, and cellular necrosis [130].

14. **CKD of unknown aetiology:** In recent years, an epidemic of CKD of unknown origin has been discovered in Central America, which has been labelled “Mesoamerican nephropathy.” This disease mainly affects young to middle-aged agricultural workers, particularly in Nicaragua, El Salvador, and Guatemala. These workers do not present with traditional risk factors for kidney disease, such as hypertension or diabetes, but instead present with small echogenic kidneys, suggestive of non-glomerular diseases [131]. Patients also present without significant proteinuria or hypertension [132]. A common symptom among patients is dysuria, which is known as “chistata” in Central America. Biopsy findings suggest the presence of chronic tubulointerstitial disease.

Table 3. Environmental exposure to nephrotoxin and associated kidney disease manifestations

Agent	Source of exposure	Short-term (acute toxicity)	Long-term (chronic exposure)
Lead	Lead-based paint; soil and dust (paint, gasoline, industrial sources); drinking water (lead pipes), cigarette smoke	Fanconi's syndrome	Lead nephropathy, CKD
Arsenic	Groundwater contamination; food contamination (apple juice, rice, wine)	Acute tubular necrosis	CKD; kidney cancer
Cadmium	Fossil fuel combustion; phosphate fertilizers; iron and steel production; batteries; municipal solid waste incineration; food contamination (rice, root crops)	Acute tubular necrosis	CKD
Mercury	Coal-fired power plants; smelters, gold production; municipal waste incineration; natural sources (volcanoes)	Acute tubular necrosis; immune-complex mediated nephritic syndrome	Limited evidence; possibly microalbuminuria
Uranium	Groundwater contamination of natural uranium deposits; uranium mining, milling, and processing	Acute tubular necrosis	Limited evidence; proximal tubular injury (^{2}-2 microglobulin)
Aristolochic acid	*Aristolochiaceae* family of plants (used in Chinese herbs)	Interstitial nephritis	Interstitial nephritis; urothelial carcinoma
Melamine	Food adulterant; manufacture of colourants, glues, laminates, adhesives, dinnerware, dry-erase boards, cleaning products, and flame retardants	Urinary stones, acute kidney injury	No long-term known outcomes described

(Chronic kidney disease (CKD): Weidemann, D. K., Weaver, V. M., & Fadrowski, J. J. (2016).

A similar pattern of kidney disease has been reported in other parts of the world, such as Sri Lanka, the state of Andhra Prakesh in India, and the El-Minia Governorate in Egypt. This has been labelled CKD of unknown aetiology (CKDu), as the cause(s) are unknown. Unfortunately, dialysis and transplantation are not routinely available in the communities affected by the disease, and CKDu is often considered a terminal diagnosis.

Multiple hypotheses have been proposed regarding the cause(s) of CKDu, including chronic dehydration from hard labour, agrochemicals (such as pesticides), heavy metals, aristolochic acid, medications (nonsteroidal anti-inflammatory drugs), and/or infections, such as leptospirosis [133]. However, the cause(s) remain(s) uncharacterized due to the complexity of the disease and the multiple factors that may contribute to its development. Although this disease typically affects adults in their third to fifth decade of life, pediatric cases have been reported [134].

Although the cause(s) of CKDu remains unknown, it is clinically and histologically similar to previous outbreaks of environmental toxin-mediated nephropathy, such as Balkan endemic nephropathy and Chinese herb nephropathy. Many recent epidemiological studies have observed unexpected positive associations with eGFR when examining low-level chronic nephrotoxicants [135,116,136,137]. This is contrary to the expected outcome with exposure to a nephrotoxin. This association is more often observed with serum creatinine-based eGFR and when urinary levels of a nephrotoxin (exposure) are adjusted for urine concentration using creatinine [138].

The reason for the unexpected association is unclear. It could be due to reverse causality, metal exposure, or the impact of GFR on biomarker concentrations. Research using urinary biomarkers may need to adjust for GFR even in healthy populations. Kidney function is complicated to study due to multiple exposures and host characteristics. Large population studies are necessary to achieve statistical power and address imprecisions. Statistically significant findings do not invalidate the importance of the positive associations observed. Preventative strategies are necessary for risk mitigation and public health [139].

3. DIAGNOSTIC TESTS FOR DETECTING KIDNEY DISEASES [23]

A panel of tests are usually very useful in diagnosing kidney disease. Some of the most common tests include the following:

Urinalysis: A urine sample (usually early morning) is required to test for anything unusual, including detecting the presence of a typical protein or sugar that spills into your urine. It may be necessary to perform a sediment examination to look for red and white blood cells, high levels of bacteria, and high numbers of tube-shaped particles called cellular casts, as well as crystals.

Urine Volume Measurements: Measuring urine output is one of the simplest tests to help diagnose kidney disease. For example, low urinary output may suggest that kidney disease is due to a urinary blockage, which can be caused by multiple illnesses and injuries.

Blood Samples: Blood Samples may be ordered to measure for substances that are usually, under normal circumstances, filtered by the kidneys, such as Blood Urea Nitrogen (BUN), Creatinine, Electrolytes, Albumin and others. A rapid rise in blood urea nitrogen and creatinine is indicative of Acute Kidney Disease.

Imaging: Tests like ultrasounds, MRIS, and CT scans usually provide images of the kidneys and urinary tracts identifying blockage or other problems.

Kidney Tissue Sample: Tissue samples are examined for unusual deposits, scarring, or infectious organisms. Samples are collected using biopsy designs.

In detail, to determine whether an individual is at a higher risk of developing kidney disease, These tests are usually run:

Glomerular Filtration Rate (GFR): These measures how well your kidneys are working and determines the stage of kidney disease. This has been made easy by using the estimated-GFR (eGFR) calculation methods in determining the outcome.

Ultrasound or Computed Tomography (CT) Scan: They produce clear images of your kidneys and urinary tract. The picture allows the clinician to determine if the kidneys are too small or large, and they can also show any tumour or structural problems that may be present.

Kidney Biopsy: The clinician removes a small piece of tissue from the individual's kidney while under sedation. This tissue when processed can help identify the type of kidney disease and how much damage has occurred.

Urine Test: A urine test may be done for Albumin, if present is an indication that the kidneys are damaged.

Blood Creatinine Tests: Creatinine is a waste product released into the body when creative present in muscle cells is broken down. The level of creatinine in your blood will increase if your kidneys are not working properly.

Heart Function Panel of Tests: Blood Pressure, ECG, Echo-Cardiogram, Exercise or Stress tests, Heart (Cardiac) CT scan and Heart (Cardiac) Magnetic Resonance Imaging (MRT) SCAN [92].

Other Blood Tests: FBC, FBS, Total Cholesterol, Low-density lipoprotein Cholesterol (LDL-C), High-density lipoprotein Cholesterol (HDL-C), Triglycerides (TG), Non-HDL Cholesterol, High-sensitivity C-reactive protein(hs-CRP), Lipoprotein-a, Plasma Ceramides, Natriuretic peptides, Troponin T [92].

The reason for including the Heart function panel of tests [92] as part of the Laboratory tests in the treatment of kidney diseases is because of the close relationship the heart has with the Kidneys. In most case scenarios, kidney disease co-exists with a heart disease or vice versa. So, for proper treatment or management, both organs should be evaluated, especially during early diagnosis.

4. CONCLUSION

Increased awareness is developing regarding the detrimental effects of various potential nephrotoxicants on kidney health in both children

and adults. These harmful substances include heavy metals and other chemicals or substances found in the environment. Despite this, there remain several significant challenges in this area of research. High-quality epidemiological studies that examine environmental exposures in both children and adults, with multiple health outcomes, including kidney health, are currently lacking. This is due to various obstacles, such as small sample sizes, inadequate exposure assessment, insufficient control of potential confounders, and the presence of bias. There is also a need to further investigate the unexpected positive associations between urinary biomarkers and kidney outcomes. As environmental exposures can potentially be modified, unlike most causes of acute and CKD, well-designed epidemiological studies should be prioritized to enhance our understanding of and characterize the relationships between potential nephrotoxic exposures and health outcomes in children and adults. Furthermore, clinicians should be aware that environmental exposures are relatively common and should remain vigilant in screening. For each patient, a targeted history based on exposure sources for potential toxicants should be performed, and if exposure is suspected, a more detailed exposure assessment can be considered.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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