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REVIEW

OPEN

Climate change and its influence in nephron mass

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Purpose of review
The consequences of climate change, including heat and extreme weather events impact kidney function in adults and children. The impacts of climate change on kidney development during gestation and thereby on kidney function later in life have been poorly described. Clinical evidence is summarized to highlight possible associations between climate change and nephron mass.

Recent findings
Pregnant women are vulnerable to the effects of climate change, being less able to thermoregulate, more sensitive to the effects of dehydration, and more susceptible to infections. Exposure to heat, wildfire smoke, drought, floods and climate-related infections are associated with low birth weight, preterm birth and preeclampsia. These factors are associated with reduced nephron numbers, kidney dysfunction and higher blood pressures in offspring in later life. Exposure to air pollution is associated with higher blood pressures in children and has variable effects on estimated glomerular filtration rate.

Summary
Climate change has important impacts on pregnant women and their unborn children. Being born too small or too soon is associated with life-time risk of kidney disease. Climate change may therefore have a dual effect of impacting fetal kidney development and contributing to cumulative postnatal kidney injury. The impact on population kidney health of future generations may be significant.

Keywords
chronic kidney disease, climate change, developmental programming, low birth weight, preterm birth

INTRODUCTION

Many risk factors, such as hypertension, diabetes and obesity contribute to this disease burden, but they do not explain all the observed risk [1]. Environmental and climate-associated factors are being increasingly associated with the risk of kidney disease [2▪▪]. Hot weather is associated with an increased risk of acute kidney injury (AKI), kidney stones and urinary tract infections (UTIs) [3]. Heat stress and repeated episodes of dehydration likely contribute to the risk of chronic kidney disease (CKD) [4,5]. Droughts threaten food supplies and increase risks of wild fires [6]. Floods are associated with increased risks of infections [7]. Air pollution contributes to climate change, but has also been associated directly with the risk of AKI, CKD, and transplant dysfunction [8–10].

The impact of climate change on adult kidney function is therefore becoming increasingly clear. Climate change disproportionately impacts children and may directly or indirectly impact kidney function [11▪,12▪▪]. Less is known about the impact of climate change on pregnancy. Normal pregnancy is associated with impaired thermoregulation and immune responses [13▪▪,14▪▪]. Pregnant women are more sensitive to temperature, fluid and infection challenges posed by climate change, which may impact fetal development. The potential impact of climate change on development of the fetal kidney, and the long-term risk of kidney disease has seldom been investigated [14▪▪,15].

Low birth weight (LBW, <2.5 kg), small for gestational age (SGA, <10th weight percentile), preterm birth (PTB, <37 weeks), and/or exposure to

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KEY POINTS

- The risk of low birth weight and preterm birth are increased in pregnant women exposed to the diverse impacts of climate change.
- Low birth weight and preterm birth are associated with reduce nephron number at birth and throughout life.
- Low birth weight and preterm birth are associated with increased later life risks of elevated blood pressure and kidney disease.
- The risk of kidney disease is amplified among vulnerable populations exposed to the compound risks of social determinants of health and climate change on kidney health.
- Mitigation of climate change promises to reduce the risk of kidney disease in future generations.

maternal obesity, diabetes and preeclampsia during gestation, are associated with higher blood pressure, risk of proteinuria and kidney dysfunction later in life [reviewed in detail in [16■■,17■]. These risks are independent and cumulative [18,19].

This paradigm, termed developmental programming, was suggested by Barker *et al.* [20], who reported that adults with LBW had a greater risk of premature cardiac death compared with those with normal birth weights. Around the same time, Brenner and colleagues [21], based on the observations that hypertension and CKD tend to be more prevalent in more disadvantaged populations, where LBW rates are also higher, proposed that LBW may be associated with a congenital reduction in nephron number, which may predispose an individual to hypertension and kidney disease later in life. Autopsy studies of individuals with varying birth weights have revealed a 13-fold variation in nephron number, likely reflecting the sensitivity of nephrogenesis to gestational exposures [22■]. Nephron number increases with increasing birth weight and gestational age [22■,23]. Nephron number does not increase after birth, therefore gestational exposures impact an individual's reservoir of nephrons for life [17■]. As nephron numbers cannot be routinely counted in living humans, the best surrogate markers for programmed risk of kidney disease remain LBW, SGA, and PTB.

Multiple molecular mediators are involved in kidney programming, such as gene expression alterations, apoptosis modulation, accelerated senescence, and gender effects, all of which may be susceptible to gestational exposures [24]. Furthermore, diabetes, cardiovascular, and preeclampsia risks are also associated with developmental programming, adding multiple factors that may contribute to the individual variability in long-term risk of CKD throughout life [16■■].

Considering that almost 20 million babies worldwide were born with LBW in 2020, one in ten live births was preterm, and one in five was SGA [25■■], developmental programming of kidney disease risk is important to consider at the population level [18,19]. CKD has been described in individuals with extremely low birth weights or gestational ages, but not all individuals born too small or too early develop hypertension and kidney disease [16■■]. It is therefore likely that overt hypertension or kidney disease may mostly manifest only after exposure to second 'hits' occurring later in life [26,27]. Such second hits may include diabetes, age, primary kidney disease, genetic susceptibility, overweight/obesity, social determinants of health or climate, and environmental stresses [26,28■,29].

Here, we examine the potential impact of various environmental and climate-associated factors on birth outcomes, as markers of fetal kidney development, and thus their impact the risk of CKD in future generations (Fig. 1). These risks are considered individually, using the Lancet Countdown indicators: heat, extreme weather events; climate-sensitive diseases; climate-sensitive infections and food security, but may risk overlap (Fig. 2) [12■■]. Additional programming effects of air pollution and environmental toxins are also considered.

HEAT

Exposure to extremes of heat is increasing everywhere. Those generally considered most vulnerable are the elderly, however pregnant women are also highly vulnerable to heat [12■■]. Recent analysis of 126 273 women in India and Pakistan identified an increased risk of PTB and LBW with heat exposure during the second trimester, and an increased risk of preeclampsia with heat exposure in the third trimester [30]. Similarly, a recent meta-analysis of 70 studies revealed a 9% higher risk of LBW and a 16% higher risk of PTB during hotter temperatures [31].

Potential pathophysiological mechanisms contributing to adverse birth outcomes in pregnant women exposed to heat include alternations of the microbiome, reduced physical activity, psychological stress, sleep deprivation, altered nutrition hormonal disbalance and immunological changes which lead to LBW and PTB [32].

WILDFIRES

The consequences of wildfire smoke exposure extend beyond the respiratory system [6]. Particulate matter (PM) reflects the organic and inorganic particles in solid and liquid form suspended in the air [33]. PM is

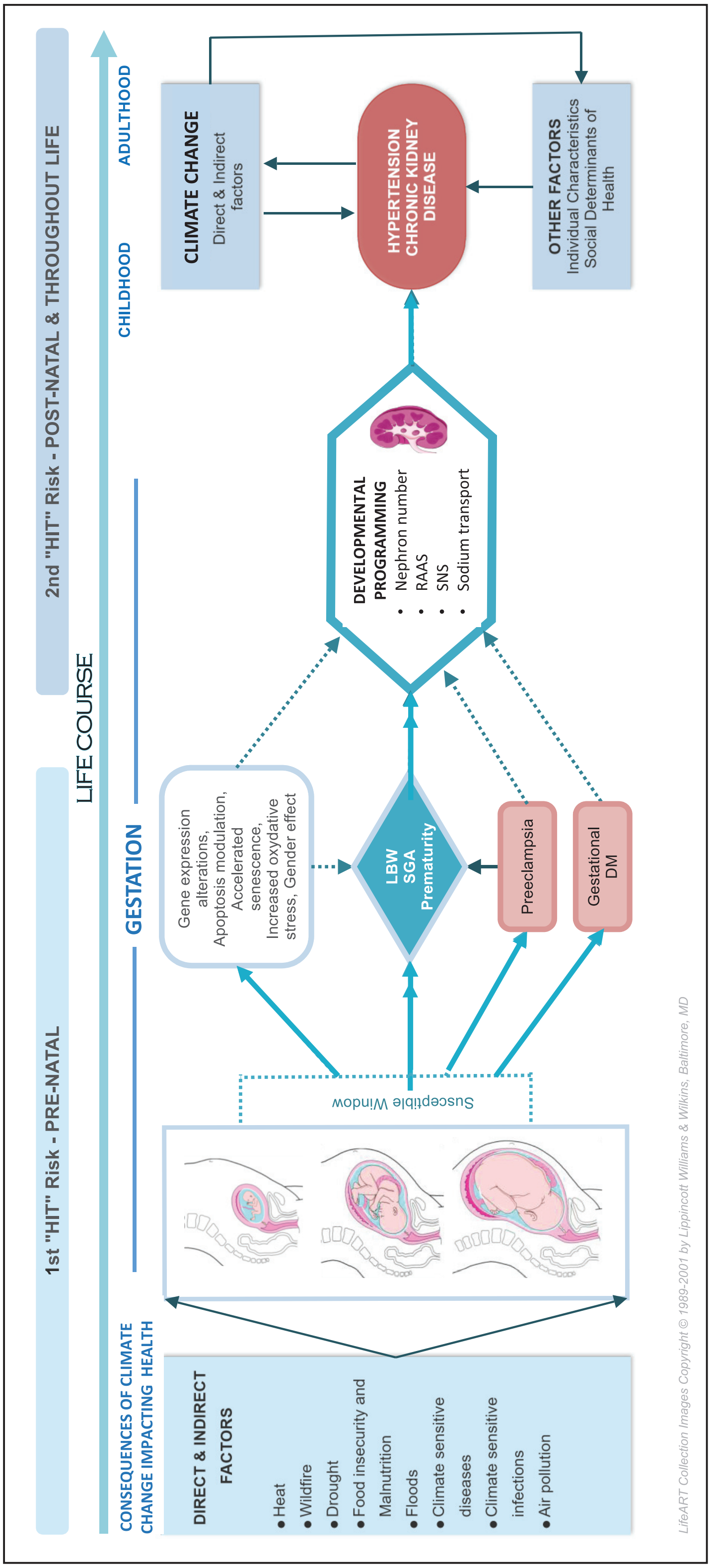

FIGURE 1. Potential impact of climate change on kidney development and developmental programming of blood pressure and kidney function in later life. The dashed arrows symbolize the hypothetical pathways based on available evidence from animal data and limited clinical data. The solid arrows symbolize the pathways with the strongest evidence available. Importantly other noncommunicable diseases are also associated with developmental programming – especially cardiovascular disease and diabetes – which may additionally impact kidney disease risk in later life. DM, diabetes mellitus; LBW, low birth weight; RAAS, renin–angiotensin–aldosterone system; SGA, small for gestational age; SNS, sympathetic nervous system.

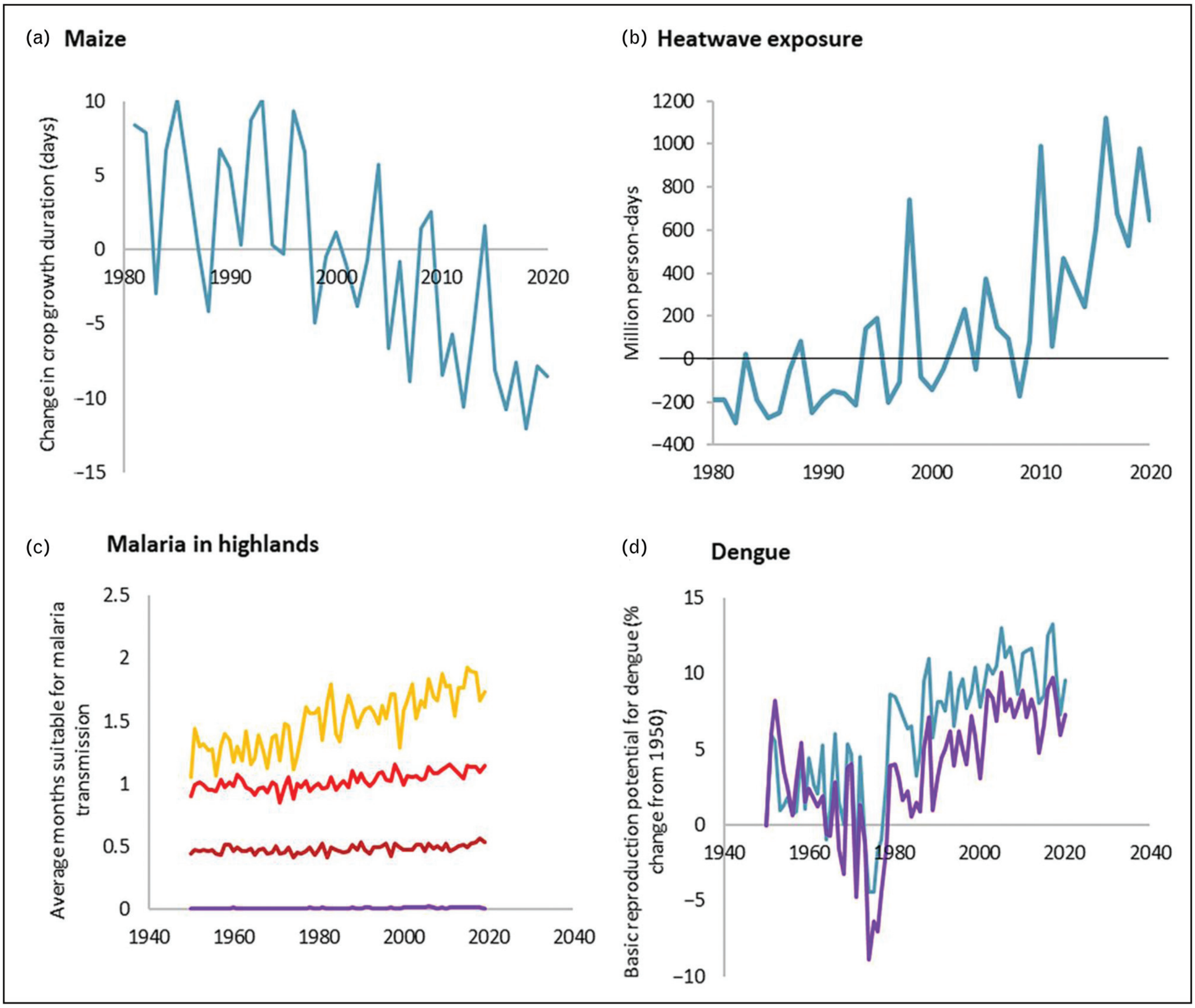

FIGURE 2. Simultaneous impact of climate change. Diverse impact of increasing heat on factors which may impact fetal kidney development: reduce crop yields and reduce protein and micronutrient content of crops; direct impact of heat on pregnant women who are less able to thermoregulate; increasing risk of vector borne diseases which impact pregnancy outcomes. Reproduced with permission under Attribution 4.0 International (CC BY 4.0) from Romanello *et al.*, J Paediatr Child Health, Vol. *57*, Issue: 11, pp. 1736–1740 [11▪].

classified by particle size. $PM_{2.5}$ refers to the smaller than 2.5 microns particles, considered most hazardous for health [34▪]. $PM_{2.5}$ concentrations vary by region and season. Wildfire smoke comprises multiple pollutants in addition to $PM_{2.5}$, and is more hazardous than air pollution resulting from other sources [6,14▪▪]. Wildfire pollutants induce systemic inflammation and immune system dysregulation, infections, psychological stress and cardiac events [6]. On the cellular level these toxic pollutants induce oxidative stress, cell death, fibrosis and epigenetic changes [6]. Pregnant women and fetuses may therefore experience negative consequences of wildfire smoke exposure. Indeed, among 330 884 birth records from New South Wales, Australia, maternal wildfire-specific PM_{25} exposure accounted for 14% of preterm and 8% of LBW births [35]. Similar findings have been reported by others [14▪▪].

Annual daily population exposure to wildfires has increased in 152 of 196 countries between the periods of 2001–2004 to 2015–2018 [12▪▪]. In India, this increase means an additional 21 million annual daily exposures. India is now the most populace country in the world, and already has a high rate of LBW and a high burden of CKD [25▪▪,36]. If the exposure to wildfire smoke continues to increase, this may well increase the risks of LBW and of kidney disease in future generations. The broader potential impact of air pollution *per se* is on developmental programming in the kidney is further discussed below.

DROUGHT

Prolonged drought threatens health by affecting hygiene and sanitation and increasing food insecurity [12••]. In 2022, 37.5 million people were exposed to droughts [37]. Water loss though sweating increases during pregnancy therefore pregnant women exposed to drought, frequently accompanied by heat, are at increased risk of dehydration and poor fetal growth [38•]. In drought endemic regions such as sub-Saharan Africa, food scarcity increases during droughts through crop failures, loss of livestock and increases in food prices [14••]. Maternal malnutrition is therefore common, and is associated with increased risks of PTB, SGA, and LBW [6,39•].

FOOD INSECURITY AND MALNUTRITION

The association between maternal dietary composition (especially low protein intake) and LBW and low nephron number has been reproducibly shown in animal studies [17•,40]. Nephron number and an reduced kidney function have also been observed in offspring of animals with zinc and iron restriction during gestation (reviewed in [41]) In humans, individuals exposed to the Dutch, Biafran, and Chinese Famines during various stages of gestation had increased blood pressures, plasma glucose and microalbuminuria in later life (reviewed in [41,42]).

Food insecurity in pregnant women is associated with increased risks of gestational hypertension and diabetes, LBW and PTB [12••,14••]. In addition to droughts, increasing ambient temperatures also lead to a reduction in crop yields (Fig. 2) and a reduction in protein and micronutrient content (zinc, iron) of plants, and therefore reduced food quality [11•,43]. Warming and acidification of the oceans resulting from climate change threatens fisheries and aquaculture, and impacts protein intake especially of people living in small island states [12••].

FLOODS

Floods can affect pregnant women in many ways, impacting access to safe food and water, increasing the risk of water-borne diseases, through potential exposure to hazardous chemicals, and the consequences of forced displacement [14••]. In 2022, 55 million people were affected by floods [37]. Floods often coincide with extreme weather events such as hurricanes. The risk of PTB and LBW are both increased after hurricanes and floods [14••]. The risk of gestational hypertension and preeclampsia also increase with hurricane exposure [14••]. Increased blood pressure during gestation is associated with fetal growth restriction.

Rising sea levels as a consequence of global warming also increases the risks of coastal flooding, which may lead to displacement and infection risks [14••]. Increased salinity of inland drinking water sources, as a consequence of rising sea levels has also been associated with increased risk of gestational hypertension and preeclampsia [13••].

CLIMATE-SENSITIVE DISEASES

Climate change has a direct impact on the risk of multiple kidney disease in adults, including AKI, kidney stones, UTIs and CKD. All of these conditions may impact a mother's health during pregnancy, impact fetal growth and may increase the risk of PTB. Crucially important also is maternal mental health [13••,14••]. Anxiety and distress with exposure to heat, pollution and extreme weather events, can impact the health of a pregnancy, maternal safety and nutrition, and fetal wellbeing.

CLIMATE SENSITIVE INFECTIONS

Much of the discussion about climate change and health has centered around acute infections and antimicrobial resistance [44]. Although these are important consequences, the long term impact of maternal infection on fetal development and future risk of chronic diseases has not garnered as much attention. Droughts, flooding and increasing ambient temperatures all contribute to changes in pathogen and disease vectors such as ticks and mosquitoes [11•]. Pregnant women are at increased risk of infections, which may compromise fetal health. Diarrheal diseases increase after floods [12••]. The risk of mosquito-borne infections is increasing with rising global temperatures and with flooding. In 2010 it was estimated that malaria contributed to around 900 000 LBW births in Africa [45]. The risk of dengue virus infection is increasing globally. Maternal dengue infection has also been associated with preeclampsia, PTB and LBW [14••].

AIR POLLUTION

Greenhouse gas emissions coming from large urban areas are major contributors to climate change. In turn, climate change affects air quality and worsens pollution due to the impact on ground level ozone, perpetuating a cycle of environmental and human health interactions [46]. Air pollution contributes to over 4 million deaths annually [34•].

The association of air pollution, especially $PM_{2.5}$, is with kidney dysfunction as reviewed elsewhere [33,47]. Literature on the impact of $PM_{2.5}$ on kidney development is scarce, however $PM_{2.5}$ and ozone exposure are associated with an up to 20% increased risk of LBW, therefore a programming impact on fetal kidney development must be considered [34▪]. Several studies have evaluated the longer term impact of $PM_{2.5}$ exposure during gestation on blood pressure in childhood (summarized in Table 1) [48▪,49▪,50]. Child blood pressures (at 3–9 years) increased with increasing gestational $PM_{2.5}$ exposure, more significantly in the 2nd and 3rd trimesters, and in one study was modulated by low maternal folate levels [50]. Estimated glomerular filtration rate (eGFR) was assessed in children aged 8–10 years, born at term and followed longitudinally with daily $PM_{2.5}$ estimates in Mexico [51]. A bidirectional effect was observed with prenatal exposure being associated with higher eGFR and postnatal exposure with a reduced eGFR [51]. Urine albumin excretion and kidney size were not assessed, birth weights were not reported. More research is needed to assess kidney function in these children over time and determine whether the higher eGFRs may reflect early hyperfiltration.

Air pollution is comprised of ambient air pollution, and indoor air pollution. A major cause of indoor pollution is cooking with biomass fuel. Of the 2.8 billion people exposed to indoor pollution in lower resource settings, most are women [52]. Exposure to such indoor pollution in pregnant women was associated 74% increased risk of LBW in Ethiopia [52]. The impact of such 'hidden' exposure must be recognized as this is preventable with provision of clean fuel and reduction in poverty [53]. The impacts of other environmental pollutants that may impact kidney development are highlighted in Table 1.

SOCIAL DETERMINANTS OF HEALTH AND CLIMATE CHANGE

Climate change has a disproportionate impact on disadvantaged populations around the world. High-

Table 1. Summary of the clinical evidence on the association of air pollution $PM_{2.5}$ with impaired kidney development evaluated with estimated glomerular filtration rate and blood pressure assessment in postnatal offspring

Author/year	Study design	Country	*n*/population	Exposure assessment	Outcome assessment	Main results
Rosa, *et al.*/ 2022 [51]	PROGRESS birth cohort/ Prospective	Mexico	427/mother & child	Two exposure periods of daily $PM_{2.5}$ exposure were estimated at each participant's residence using a validated satellite-based spatial-temporal model: 1) early life exposure (periconceptional through age 8 years) and 2) preadolescent exposure	Kidney function assessed in the preadolescent period using estimated glomerular filtration rate (eGFR), serum cystatin C, and blood urea nitrogen (BUN) in children aged 8–10 years	5 μg/m3 ↑ prenatal $PM_{2.5}$ exposure was associated with an ↑ eGFR of 4.44 ml/min/1.73 m^2 (95% CI: 1.37, 7.52); 5 μg/m^3 ↑ $PM_{2.5}$ exposure in the first 14 months after birth was associated with a ↓ eGFR of 10.36 ml/min/ 1.73 m^2 (95% CI: −3.04, −17.68)
Ni, *et al.*/2021 [50]	CANDLE study cohort	USA	822/mother & child	Pre- and postnatal estimation of nitrogen dioxide and $PM_{2.5}$, obtained from annual national spatial-temporal models	Hypertension using SBP and DBP ≥90th percentile in children at 4 and 6 years of age	SBP percentile ↑ 14.6 (95% CI 4.6,24.6), and DBP percentile ↑ 8.7 (95%CI 1.4,15.9) with each with each 2-mg/m^3 ↑ $PM_{2.5}$ exposure in the second trimester. Stronger associations with low maternal folate levels
Rosa, *et al.*/ 2020 [48▪]	PROGRESS birth cohort/ Prospective	Mexico	537/mother & child	Prenatal daily $PM_{2.5}$ exposure using a validated satellite-based spatial-temporal model. Seasonality of $PM_{2.5}$ exposure.	SBP and DBP percentiles, calculated based on the clinical guidelines published in 2017 in children 4–6 years	SBP ↑ by 2.6 mmHg (CI: 0.5, 4.6) and DBP ↑ 0.88 mmHg (CI: 0.1, 1.6) at ages 4–6 years for each 10 μg/m^3 ↑ in $PM_{2.5}$ during gestation
Zhang, *et al.*/ 2018 [49▪]	Boston Birth Cohort/ Prospective	USA	1,293/mother & child	Evaluation of ambient particulate matter ≤2.5 μm concentration during pregnancy matching mother's residential address to the US Environmental Protection Agency's air quality monitors.	Pediatric systolic BP (SBP) percentile according to the US fourth Report and classified elevated BP as SBP ≥90th percentile in children 3–9 years	↑ SBP percentile with $PM_{2.5}$ exposure ≥13 μg/m^3 in the third trimester. The 5-μg/m^3 ↑ $PM_{2.5}$ during the third trimester associated with a 3.49 (95% confidence interval: 0.71–6.26) percentile ↑ in SBP

CANDLE, Conditions Affecting Neurocognitive Development and Learning in Early Childhood; CI, confidence interval; DBP, diastolic blood pressure; PROGRESS, Programming Research in Obesity, Growth, Environment and Social Stressors; SBP, systolic blood pressure.

income countries (HICs) are responsible for the greatest emission of greenhouse gases and other pollutants that lead to climate change, but the effects of climate change are being felt most acutely in low- and medium-income countries (LMICs) [54]. Even in HICs, however, those living in more crowded settings, with fewer green spaces (often urban minoritized populations) live in 'heat islands' within cities, are more exposed to heat stress, are more exposed to ambient pollution, and are less resilient to extreme weather events [13■■]. Pregnant women in these communities may have fewer resources to protect themselves. Higher temperatures also lead to loss of income. In 2018 45 billion work hours were lost because of the heat [12■■]. People working in jobs at risk are generally from lower socio-economic sectors, therefore the risk of increased poverty, poor maternal nutrition and less access to healthcare also contribute to worse birth outcomes with heat exposure.

Gender inequities are exacerbated by climate change. Increasing exposure to droughts, floods, heat and water pollution are associated with greater risks of child marriage, adolescent births, less access to clean water and to clean fuels [55]. Adolescent pregnancies are associated with higher risks of preeclampsia, LBW and PTB [56,57]. Women and girls are more exposed to indoor pollution which negatively impacts birth weight [52]. When water is scarce, girls, who are most often tasked to fetch water, must travel further and often miss school. Maternal illiteracy is associated with earlier and more frequent pregnancies, less antenatal clinic attendance, increased poverty etc., all of which increase the risk LBW [58].

Protracted food scarcity as occurs with prolonged droughts leads to conflict, political instability and mass displacements of peoples [59]. In 2020, almost 31 million people were displaced because of climate disasters. Women and girls are extremely vulnerable when forced to migrate. The physical, psychological and existential threats experienced by pregnant women lead to adverse pregnancy outcomes, including PTB and preeclampsia [60,61].

CONCLUSION

The risks of LBW and PTB are already highest in lower resource regions of the world [25■■]. These regions are bearing the brunt of climate change, and are highly vulnerable to destabilization as a consequence of climate change [62]. Climate change, on top of the background risks for LBW and PTB in these regions, is likely to further impact life-long risk of kidney disease [63]. LBW and PTB are associated with reduced nephron numbers at birth and throughout life. This 'first hit' may not always lead to overt disease in the absence of additional kidney stressors. The increasingly ubiquitous challenges of climate change, however, clearly impact the risk of kidney diseases in adults. If left unchecked, these consequences of climate change may become inescapable second 'hits' in the kidneys of individuals born LBW or preterm leading to overt kidney disease (Fig. 1).

It is imperative that the risks to pregnant women and their unborn children are more prominently raised in the climate debate, to emphasize that the long-term risks of climate change not only impact the planet, but also directly impact individual (kidney) health of future generations. The time is now to protect future kidney health.

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Conflicts of interest

There are no conflicts of interest.

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■ of special interest
■■ of outstanding interest

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