AMERICAN JOURNAL OF PHYSIOLOGY
REGULATORY, INTEGRATIVE AND COMPARATIVE PHYSIOLOGY

Am J Physiol Regul Integr Comp Physiol 321: R141–R151, 2021.
First published June 23, 2021; doi:10.1152/ajpregu.00103.2021

REVIEW

Don't Deny Your Inner Environmental Physiologist: Investigating Physiology with Environmental Stimuli

Occupational heat exposure and the risk of chronic kidney disease of nontraditional origin in the United States

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Abstract

Occupational heat exposure is linked to the development of kidney injury and disease in individuals who frequently perform physically demanding work in the heat. For instance, in Central America, an epidemic of chronic kidney disease of nontraditional origin (CKDnt) is occurring among manual laborers, whereas potentially related epidemics have emerged in India and Sri Lanka. There is growing concern that workers in the United States suffer with CKDnt, but reports are limited. One of the leading hypotheses is that repetitive kidney injury caused by physical work in the heat can progress to CKDnt. Whether heat stress is the primary causal agent or accelerates existing underlying pathology remains contested. However, the current evidence supports that heat stress induces tubular kidney injury, which is worsened by higher core temperatures, dehydration, longer work durations, muscle damaging exercise, and consumption of beverages containing high levels of fructose. The purpose of this narrative review is to identify occupations that may place US workers at greater risk of kidney injury and CKDnt. Specifically, we reviewed the scientific literature to characterize the demographics, environmental conditions, physiological strain (i.e., core temperature increase, dehydration, heart rate), and work durations in sectors typically experiencing occupational heat exposure, including farming, wildland firefighting, landscaping, and utilities. Overall, the surprisingly limited available evidence characterizing occupational heat exposure in US workers supports the need for future investigations to understand this risk of CKDnt.

biomarker; exercise; heat strain; heat stress; Mesoamerican nephropathy

INTRODUCTION

There is growing global concern regarding the development of kidney injury and chronic kidney disease (CKD) in individuals whose occupation requires frequent physically demanding work in the heat (1–3). The pathophysiology of this work-related kidney disease may vary regionally due to differences in predisposing risk factors of the population (e.g., conditions of metabolic disease, nutrition, genetic predisposition), work conditions (including intensity, duration and frequency), and environmental exposures (e.g., toxins). However, a common characteristic shared among these regions is that workers are frequently exposed to occupational heat stress (3), where heat stress is defined as the net heat load to which an individual is exposed, a function of environmental conditions, work intensity/duration, clothing, and acclimatization.

In Central America, an epidemic of CKD of nontraditional origin (CKDnt) is occurring among manual laborers, where severe and sustained reductions in glomerular filtration rate (GFR) typically occur in the absence of traditional risk factors such as older age, hypertension, obesity, and diabetes (3). The prevalence of CKDnt has been reported to be as high as 42% among male Nicaraguan sugarcane workers (4), but CKDnt has also afflicted nonagricultural sectors in Central

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Submitted 13 April 2021 / Revised 11 June 2021 / Accepted 23 June 2021

America, including construction, brick making, mining, and the fishing industry (5). Moreover, hotspots of CKDnt have emerged in India and Sri Lanka (3), and there is growing concern of CKDnt affecting US workers (6).

A consensus does not exist whether these hotspots of kidney disease, especially in agricultural communities, are primarily caused by occupational heat stress (3, 7). However, it is plausible that heat stress serves as a catalyst, whereby frequent increases in core temperature in the setting of physically demanding work in the heat accelerates existing underlying pathology (such as those with traditional kidney disease risk factors) or increases the susceptibility of the kidneys to damage during exposure to nephrotoxins, including environmental or chemical toxins (3, 8–10). As such, this heat stress hypothesis contends that physical work in the heat causes injury to the kidneys. This injury can be low-grade, as assessed with kidney injury markers (8, 10), or overt acute kidney injury (AKI), which is a clinical diagnosis that typically occurs subsequent to exertional heat stroke in the setting of occupational heat exposure (11) and is assessed via specific criteria for increased serum creatinine and/or decreased urine output (12, 13). CKDnt may then develop following repeated exposures to low-grade kidney injury and/or a singular bout of clinically diagnosed AKI brought about by physical work in the heat (3, 8–10). Identifying the impacts of occupational heat exposure on kidney injury is made challenging by the fact that the normal physiological response to physical work (i.e., exercise) in the heat is a transient increase in serum creatinine, which is reflective of exercise/heat strain-induced reductions in GFR and/or in some situations may reflect muscle damage caused by engaging in strenuous manual labor (8, 10). Thus, studies measuring acute changes in serum creatinine may be overestimating kidney injury/AKI incidence in workers due to the inability to distinguish between physiological and pathological rises in serum creatinine. This has seemingly led to a controversy in the literature with regards to the interpretation of acute changes in serum creatinine across a work shift, which has promoted the use of kidney-specific urinary markers to better understand the acute impact of occupational heat exposure on kidney injury/AKI (8, 10).

A recent review has suggested that CKD and/or AKI are present in 15% of individuals who frequently work in hot environments (1), yet there are limited reports of CKDnt related to occupational heat exposure in the United States. (14–16). It is unclear if this lack of evidence stems from differences in the working conditions that may protect US workers against CKDnt or whether it reflects a lack of appropriate study of CKDnt, which is further complicated by the wide ranging climate in the United States (3). Hotspots of end-stage renal disease of unknown causes have been identified in rural agricultural areas in the United States, including in the Mississippi river valley, southeast, California, and Texas (17). There are also a few preliminary reports of AKI in agricultural workers in California and Florida based on increased serum creatinine (18–22), and a recent retrospective analysis revealed that 40% of US military service members hospitalized with exertional heat stroke were diagnosed with AKI, but none required dialysis (11). To our knowledge, no study has investigated whether in situ occupational heat exposure increases markers of kidney injury among US workers. This is a significant gap in the literature, particularly considering the CKDnt epidemic in Central America and increased global temperatures and frequency of extreme heat events with climate change (15). In addition, the US Occupational Safety and Health Administration (OSHA) recognizes that millions of additional workers in the United States are exposed to heat stress in outdoor (e.g., construction, landscaping, mail/package delivery, oil/gas well operators) and indoor (e.g., electrical utilities, fire service, manufacturing) environments (23). Therefore, it is plausible that there are occupations in the United States that place workers at risk for kidney injury and therefore, CKDnt.

With this background, the aim of this narrative review is to preliminarily identify populations of workers in the United States at risk of CKDnt due to occupational heat exposure. First, we briefly describe the hypothesized pathophysiology of CKDnt. Then, we summarize available scientific literature pertaining to occupational heat exposure in US workers. Finally, we will qualitatively examine the risk of kidney injury and CKDnt in these workers and identify current knowledge gaps.

PATHOPHYSIOLOGY OF HEAT STRESS-RELATED CKDnt

As briefly alluded to in the INTRODUCTION and has been recently described in detail (3, 8–10), one of the leading hypothesized pathophysiological mechanisms leading to the development of CKDnt involves kidney injury occurring in the setting of physical work carried out in hot environments. The current literature suggests that this kidney injury is tubular in nature, with several laboratory-controlled studies reporting increased markers of kidney injury following physical work in the heat, including urinary neutrophil gelatinase-associated lipocalin (NGAL, marker of general renal tubular injury) (24–26) and urinary insulin-like growth factor binding protein 7 (IGFBP7, renal cell cycle arrest marker preferentially secreted in the proximal tubule) (25). These findings are consistent with renal biopsies from at-risk workers in Nicaragua demonstrating acute tubular cell injury and chronic tubulointerstitial nephritis (27). The mechanisms underlying this kidney injury have not been fully elucidated, but data support that increases in markers of kidney injury following physical work in the heat are exacerbated by longer work durations (28) and the magnitude of hyperthermia and/or dehydration (25) (Fig. 1). In addition, nephrotoxic insults such as those evoked by muscle-damaging exercise (26) and/or the intake of sugar-sweetened beverages high in fructose (24), which is a common in the workplace (29), have been observed to elicit greater increases in urinary NGAL. The current belief is that reductions in renal blood flow caused by physical work in the heat create localized hypoxic environments that reduce renal tubular oxygen delivery. Renal adenosine triphosphate (ATP) can be depleted by this reduced renal perfusion, particularly in the presence of increased tubular sodium reabsorption, an ATP-dependent process that is upregulated during physical work in the heat to mitigate the extent of dehydration (8, 10). This tubular ATP depletion can promote inflammation and oxidative stress, and ultimately cause renal tubular injury (8–10). This

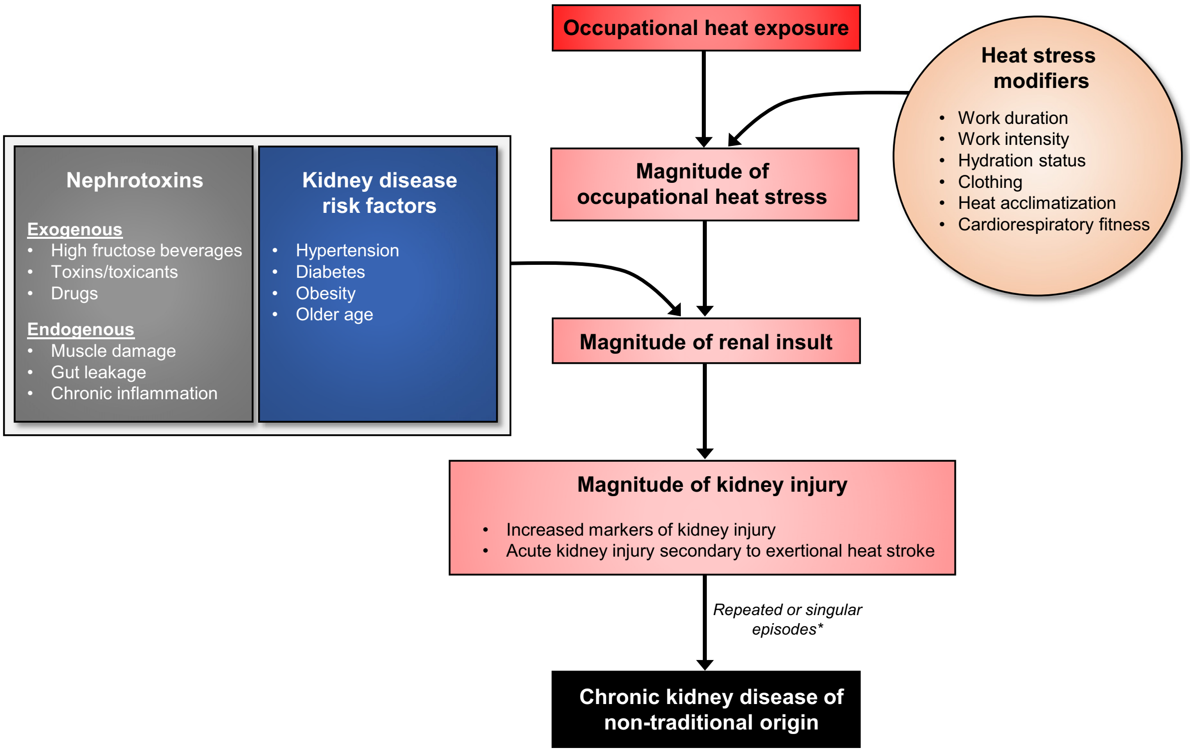

Figure 1. Proposed framework by which the magnitude of kidney injury experienced by US workers subjected to occupational heat exposure is modified by heat stress, nephrotoxins, and underlying risk factors for kidney disease. It is believed that frequent occupational heat exposures that elicit kidney injury progresses to chronic kidney disease of nontraditional origin. There is also potential that clinically diagnosed episode of acute kidney injury, which is typically subsequent to exertional heat stroke, may develop into kidney disease. *Magnitude/combination of heat stress modifiers, nephrotoxins, underlying kidney disease risk factors, and magnitude of kidney injury required to elicit chronic kidney disease of nontraditional origin in workers frequently exposed to occupational heat stress is not known.

hypothesis is supported by rodent model data demonstrating that greater magnitudes of hyperthermia (i.e., increase in core temperature) during repetitive exposures to heat cause greater kidney damage and the onset of tubulointerstitial and functional maladaptation consistent with kidney disease (30). In addition, similar recurrent heat exposure models have reported that kidney disease develops when rodents are not allowed access to water during heat stress, whereas drinking water during heat exposure is protective (31).

In Central America, there is growing support from field studies linking heat stress-induced kidney injury to CKDnt. The intense heat stress observed in low-altitude areas is associated with higher prevalence of CKDnt in sugarcane workers in several Central American countries, despite otherwise similar occupational exposures between low- and high-altitude settings (3). Over the duration of a harvest season, field studies have revealed that sugarcane cutters in these hotter low-altitude regions had elevated urinary NGAL that was four-times greater than the reference group (32). Moreover, estimated GFR (eGFR) was reduced in the workers experiencing elevations in urinary NGAL at the end of the harvest season (32). In a Nicaraguan community, ~82% of heavy laborers that were classified with AKI were diagnosed with CKDnt within 3 mo (33). Strikingly, a recent field intervention in Nicaragua, designed to reduce the magnitude of heat stress and dehydration experienced by workers by mandating increased rest and providing easier access to shade, potable water, and electrolyte solutions decreased the incidence of reductions in eGFR at the end of a harvest season (34). Overall, although the evidence for heat stress-induced CKDnt in Central America is becoming more convincing, whether occupational heat stress is the primary causal agent or serves to accelerate injury/disease progression secondary to other nephrotoxins and/or risk factors remains contested (7) and may vary depending on the population (e.g., presence of risk factors), nature of the work, and circumstances related to a particular region (e.g., exposure to toxins/toxicants) (Fig. 1). However, given the current state of the evidence and high prevalence of kidney disease and risk factors (i.e., hypertension, diabetes, obesity) in the US population, it is worth examining the available scientific literature to assess if workers in the United States are exposed to conditions of occupational heat stress that may evoke kidney injury and increase the risk for the progression of kidney disease.

LITERATURE SEARCH

The primary research questions guiding our literature search were: are there US working populations with heat stress exposure levels commensurate with those reported in populations with a documented high risk of work-related kidney injury/AKI and CKDnt? If so, in which US occupational sectors and geographical regions are these heat stress exposures observed? The literature search was meant to be comprehensive and transparent, but not a systematic review per se (e.g., we did not register in a database). Thus, the literature search was executed using the following parameters, which was modeled after the approach of Jay and Brotherhood (35). The published literature indexed in PubMed from inception to January 2021 was evaluated using search terms to identify settings of occupational heat exposure in the United States (see Supplemental Fig. S1; all Supplemental Material is available at https://doi.org/10.5281/zenodo.4670996). Titles and abstracts were then screened for eligibility. Studies were deemed eligible if they: *1*) were performed in an in situ US workplace; *2*) reported occupational activities only (sport-related studies were excluded); *3*) were an original research article, peer-reviewed conference paper, or commissioned report (review papers and case reports were excluded); and *4*) reported environmental conditions [i.e., ambient temperature, relative humidity, or wet bulb globe temperature (WBGT)] and at least one element of relevant physiological strain (i.e., heart rate, core temperature, dehydration) or work duration. Studies were excluded a priori if only heat stress and/or heat strain data were reported following extreme heat events or acute adverse health events (e.g., exertional heat stroke) to avoid biasing our findings toward isolated exposures, which would limit the generalizability of our literature search results. The reference list of included studies and articles that cited the included studies were also screened for eligibility to identify publications missed by the initial database search.

A total of 21 published journal articles were included in the final assessment. These studies were stratified according to the occupation industry (agriculture, emergency services, energy, government, military, mining, utility, and other) and job type. Climate regions in the 48 contiguous states were stratified according to the National Oceanic and Atmospheric Administration (Fig. 2; 36).

OCCUPATION AND WORKER CHARACTERISTICS

In total, 15 occupations were identified with some studies performed in multiple climate regions throughout the United States (Table 1). Overall, studies were identified in the following climate regions: Central (57), Northeast (6), Northwest (57), South (57), Southeast (58), Southwest (57), West (45), and West North Central (57). There were no studies identified in the East North Central climate region, nor in Alaska and Hawaii. The largest sample size of participants studied was in agriculture (total n = 1,232) and emergency services (total n = 309). Not all studies reported complete demographic data. Of the 1,829 total workers studied, 553 (30.2%) were reported as female, 1,060 (57.9%) Hispanic/Latino, and 46 (2.5%) Black/African American. The mean age ranged between 27 and 46 yr (range: 18–82 yr). Body mass index was reported in nine studies with mean values between 26 and 36 kg/m^2.

ENVIRONMENTAL CONDITIONS

The hottest conditions were reported in the summer months (June–September) (Table 2). Agricultural workers in the Southeast and West regions experienced mean WBGT ranging between 26°C and 28°C. In the Northwest, tree fruit harvesters experienced greater heat exposure in August (WBGT: 22.3°C) compared with September (WBGT: 15.9°C). Wildland firefighters experienced mean ambient dry bulb temperatures ranging between 22°C and 29°C and relative humidity 33%–50%, but localized radiant heat due to close proximity to fires were difficult to quantify in this population. In the Southeast region, workers in the landscaping industry experienced mean WGBT during the summer of ~28°C and maximum reported WBGT reached ~35°C–36°C. Other outdoor workers, including the US Marine Corps, park employees, and electrical utility workers, experienced mean dry bulb temperatures ranging between 31°C and 47°C and

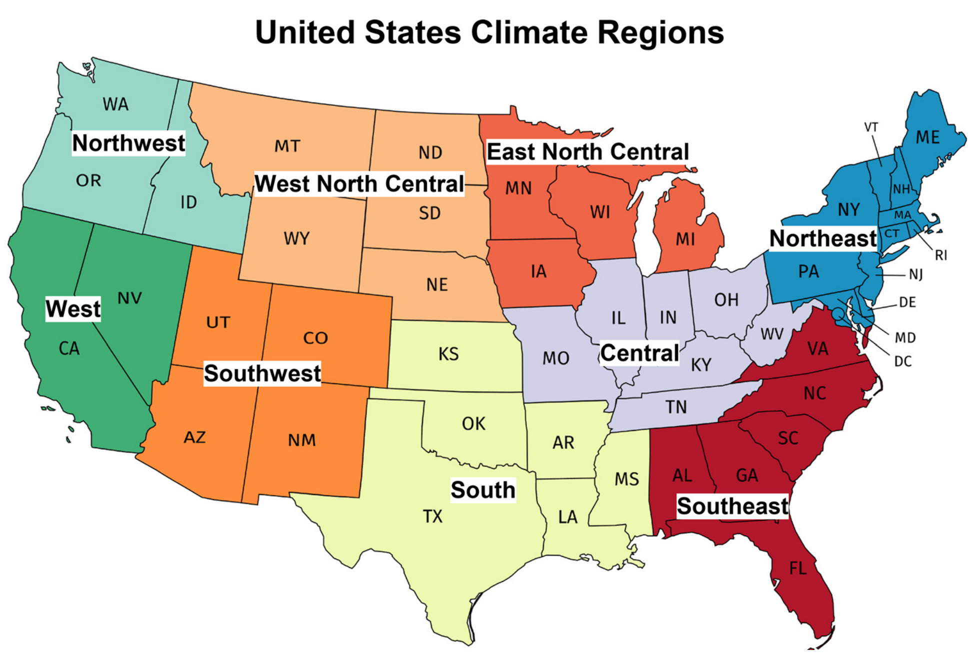

Figure 2. Climatically consistent regions within the contiguous United States identified by the National Centers for Environmental Information division of the National Oceanic and Atmospheric Administration (36). Figure created with MapChart (https://mapchart.net).

Table 1. *Occupation and worker characteristics*

Classification	Ref.	State/Region	n	Sex	Age, yr	Body Mass, kg	Body Mass Index, kg/m²
Agriculture							
Farming	37	California/West	587	389 males; 198 females	38.7 [18–82]	–	–
Farming	38	California/West	259	168 males; 91 females	38.4 (11.7)	–	–
Farming	39	Florida/Southeast	105	44 males; 61 females	Median: 38 [19–54]	–	–
Fernery	40	Florida/Southeast	43	13 males; 30 females	36 (8)		28.3 (4.8)
Fernery	18	Florida/Southeast	192	76 males; 116 females	38 (8.2)	–	Male: 27.9 (4.2); female: 29.2 (4.5)
Tree fruit harvesting	41	Washington/ Northwest	46	39 males; 7 females	39 (14)	–	27.9 (4.2)
Tree fruit harvesting[a]	42	Washington/ Northwest	46	39 males; 7 females	39 (14)	–	27.9 (4.2)
Emergency Services							
Wildland firefighting	43	Northwest, Southwest, West, West North Central	289	272 males; 27 females	18–53[b]	–	26.8 (3.9)
Wildland firefighting	44	Montana/West	5	3 males; 2 females	–	84 (9)	–
Wildland firefighting	44	Montana/West	6	6 males	–	89 (8)	–
Energy							
Coal-fueled plants	45	–	20	–	–	–	–
Government							
Hazardous response team	46	New Hampshire/ Northeast	5	5 males	31 [25–33]	79 [68–92]	–
Municipal outdoor worker	47	Florida	49	45 males; 4 females	–	–	86% overweight or obese[c]
Park employee	48	California/West	9	8 males; 1 female	46 [28–59]	–	–
Park ranger	49	Arizona/Southwest	21	11 males; 10 females	[27–44]	–	–
Military							
US Marine Corps	44	Virginia/Southeast	5	5 males	26 (1)	79.8 (9.0)	–
Mining							
Metal	50	West	31	–	40 (12)	97 (24)	30 (6.9)
Metal	51	–	6	6 males	[25–60]	–	–
Utility							
Electrical	52	Texas, West Virginia/ Central, South	32	–	36 (10)	97.1 (17.3)	29.9 (3.8)
Other							
Groundskeeping	53	North Carolina/ Southeast	453[d]	–	–	–	–
Landscaping	54	Alabama/Southeast	19	16 males;3 females	Median: 44 [24–57]	–	Male: 29.2 [18.3–38.4]; Female: 36.1 [25.7–36.6]
Smelting (aluminum)	55	Indiana/Central	31	–	–	–	–
Smelting (aluminum)	56	Texas/South	60	57 males;3 females	32 [19–50]		30.5 [19.4–47.3]

Values within parentheses represent SD (excluding reference numbers); values within brackets represent min and max, respectively. [a]Subset of data from Quiller et al. (41); [b]92% of participants 18–35 yr; [c]3 underweight; 6 normal weight; 18 overweight; 21 obese; [d]Wet bulb globe temperature indices.

relative humidity of ~57%. Environmental conditions for mineworkers were reported as mean dry bulb temperature of ~33°C and ~70% relative humidity, with mean WBGT's of up to ~29°C. Coal-fueled plants and smelting reported mean WBGT of ~27.7°C with maximum WBGT >44°C.

WORK DURATION, INTENSITY, AND PHYSIOLOGICAL STRAIN

Work Duration and Intensity

Daily work duration ranged from 2 to 3 h (US Marine Corps and electrical utility workers) to 16 h (aluminum smelting workers working double shifts; Table 3). Mean daily work duration ranged between 5 and 10 h, with most reporting work durations of 6–8 h. Work intensity estimated from heart rate ranged between 91 and 128 beats/min, reflecting ~43%–70% of estimated heart rate maximum.

Heat Strain

Core temperature was measured in 13 studies (Table 3). Seven studies reported maximum core temperature which ranged between 37.8°C and 38.5°C for agricultural workers, wildland firefighters, US Marine Corps, metal mineworkers, and electrical utility workers, and up to 39.3°C in aluminum workers. One study reported that 57% of agricultural workers experienced maximum core temperatures >38.0°C. Mean core temperature was between 37.6°C and 37.9°C for park rangers and electrical utility workers.

Table 2. *Environmental conditions*

Classification	Ref.	T_{dry}, °C	T_{wet}, °C	T_{globe}, °C	Relative Humidity, %	Mean WBGT, °C	Minimum WBGT, °C	Maximum WBGT, °C
Agriculture								
Farming	37	–	–	–	–		–	31.2 [24.5–36.5]
Farming	38	–	–	–	–	25.6 (3.8)	–	–
Farming	39	29.0 (2.6)	–	–	74.5 (14.3)	–	–	–
Fernery	40	–	–	–	–	27.2 (0.8)	25.6	28.6
Fernery	18	28.3 [17.7–37.7]	–	–	77 [40–100]	–	–	–
Tree fruit harvesting	41	–	–	–	–	27.9 [22.0–33.1]	–	–
Tree fruit harvesting[a]	42	–	–	–	–	27.9 [22.0–33.1]	–	–
Emergency Services								
Wildland firefighting	43	25.9 (4.9)	–	–	33 (14.4)	–	–	–
Wildland firefighting	44	29.0 (3.0)	–	–	25	–	–	–
Wildland firefighting	44	22.0 (3.5)	–	–	50	–	–	–
Energy								
Coal-fueled plants	45	–	–	–	–	∼30.0	26.2	44.3
Government								
Hazardous response team	46	∼30.0	–	∼40.6	∼40.5	∼25.3	–	–
Municipal outdoor worker	47	∼26.6	–	–	∼74.9	–	–	–
Park employee	48	[31–47]	–	–	–	[20–34.4][b]	–	–
Park ranger	49	–	–	–	–	[25.5–33.3]	–	36.6
Military								
US Marine Corps	44	30.0 (0.5)	–	–	60 (2)	–	–	–
Mining								
Metal	50	32.8 (1.2)	–	–	69.9 (10.1)	–	–	–
Metal	51	–	–	–	–	[13.5–28.9]	–	–
Utility								
Electrical	52	33.0 [27–47]	–	–	54 [44–100]	–	–	–
Other								
Groundskeeping	53	20.7 (5.1)	24.8 (5.9)	34.5 (8.6)	53.0 (19.3)	23.9 (4.6)	–	36.5
Landscaping	54	–	–	–	–	28.1 (3.5)	–	35.0
Smelting (aluminum)	55	∼27.7[c]	–	–	–	–	–	>39.0[d]
Smelting (aluminum)	56	–	–	–	–	–	28.3	48.9

Values within parentheses represent SD (excluding reference numbers); values within brackets represent min and max, respectively. [a]Subset of data from Quiller et al. (41); [b]Minimum exposure due to driving in an air-conditioned vehicle; [c]National weather service data; indoor/direct exposure not reported; [d]Maximum t_{dry}. T_{dry}, dry bulb temperature; t_{globe}, globe temperature; t_{wet}, wet bulb temperature; WBGT, wet bulb globe temperature.

Dehydration

Nine studies reported dehydration (Table 3). In agricultural workers, serum osmolality increased by ∼1 mosmol/kgH_2O and the mean percent change in body weight was ∼−0.4%, with ∼14% of workers experiencing losses greater than −1.5%. In other studies, postshift urine specific gravity was reported as an increase of 0.004 in fernery workers, or as absolute values with 25%–44% of mineworkers experiencing urine specific gravity >1.030.

DISCUSSION

We identified several occupations in the United States reporting significant heat stress. Although not reported in all studies, the WBGT for some US occupations (i.e., agricultural workers, coal-fuel plants, park ranger, smelting, landscaping) was similar to, or in a few cases exceeded, conditions experienced by workers in Central America at risk for CKDnt, where mean WBGT is ∼31°C but often exceeds 34°C (59, 60). Where reported, the mean heart rate data in US workers ranged between ∼43% and 70% of estimated heart rate maximum (44–46, 49, 50, 52, 55, 56), indicating that work was generally performed at light and moderate intensities over a 5–10-h duration, with some workers experiencing high-intensity work rates during part of their shift (37). By comparison, it has been previously reported that sugarcane workers at risk of CKDnt in El Salvador experience mean work rates of 54% of estimated heart rate maximum, with ∼4.75 h spent at ≥50% of estimated heart rate maximum (61). Although only 62% of studies measured core temperature and 43% measured dehydration, the available data suggest that workers experienced mild-to-moderate hyperthermia and dehydration. Together, these factors suggest that worker populations identified in this review can be exposed to similar environmental and physical conditions that have been previously shown to increase markers of kidney injury (25, 62). Therefore, these workers may be at higher risk for developing CKDnt. It is important to recognize that a knowledge gap exists where the magnitude of occupational heat exposure and magnitude/combination of modifying heat stress factors (including those in Fig. 1) that are required to elicit kidney injury has not been established. Thus, it is possible that the conditions described herein are subthreshold to that required to evoke kidney injury. That said, the current scientific literature suggests that the frequency of occupational heat exposure may be related to the prevalence of kidney injury and kidney disease (1).

There are only three reports of the specific outcome of CKDnt in the United States (14–16). A few studies, although limited by the serum creatinine-defined criteria, have taken the important initial steps in quantifying postshift AKI incidence in US agricultural workers (18–22). In one study, agricultural workers in California experienced increased serum

Table 3. *Work duration, intensity, and physiological strain*

		Work Duration	Work Intensity	Heat Strain		Dehydration		
Classification	**Ref.**	**Time, min**	**Heart rate, beats/min**	**T_{core}, °C**	**Maximum T_{core}, °C**	**Δ Body weight loss, %**	**Serum osmolality, mosmol/kgH_2O**	**Urine specific gravity**
Agriculture								
Farming[a]	37	–	+63 [29, 121]	–	~38.1 [~37.2–40.0]	−0.4 [−3.2– +2.1]	+1	–
Farming[b]	38	360.9 (243.7)	–	–	–	–	–	–
Farming	39	~720	–	–	–	–	–	–
Fernery	40	360 (114)	–	–	>38.0°C in 57% of population	–	–	–
Fernery	18	450 (90)	–	–	–	–	–	+0.004
Tree fruit harvesting	41	408 (90)	–	–	–	–	–	–
Tree fruit harvesting[c,d]	42	–	–	–	–	–	–	NC
Emergency Services								
Wildland firefighting[e]	43	–	–	37.4 (0.3)	–	–	–	–
Wildland firefighting[f]	44	~420	91 (8)	–	~37.8 (0.3)	–	–	–
Wildland firefighting[g]	44	~540	107 (6)	–	~38.0 (0.5)	–	–	–
Energy								
Coal-fueled plants	45	~480–600	[80–121]	–	–	–	–	–
Government								
Hazardous response team	46	~150	~122	–	–	–	–	–
Municipal outdoor worker	47	~600	–	–	–	–	–	–
Park employee	48	–	–	–	–	–	–	–
Park ranger	49	314 (121)	128 (24)	37.6 (0.3)*	–	−1.0 (0.7)	–	–
Military								
US Marine Corps[h]	44	~120	106 (16)	–	~38.5 (0.5)	–	–	–
Mining								
Metal	50	–	102 (12.4)	37.2 (0.6)	38.2 (0.7)	–	–	Postshift: 1.023 (0.008); 44.3% >1.030
Metal[i]	51	–	–	–	–	–	–	50% postshift >1.020; 25% postshift >1.030
Utility								
Electrical[j]	52	187 (104)	124 (18)	37.9 (0.3)	38.3 (0.5)	–	–	62% >1.020
Other								
Groundskeeping	53	540	–	–	–	–	–	–
Landscaping	54	420	–	–	–	–	–	–
Smelting (aluminum)	55	–	~125	~37.1**	–	–	–	–
Smelting (aluminum)	56	~480–960	109 [84–134]	38.2 [37.2–39.3]**	39.3	–	NC	+0.005

Values within parentheses represent SD (excluding reference numbers); values within brackets represent min and max, respectively. NC, no change; T_{core}, core temperature. *Intestinal temperature; **sublingual temperature. [a]Heart rate data were reported as the mean [range] of difference between minimum and maximum heart rate because mean heart rate data were not reported; [b]37/259 lost >1.5% of body weight; 118/259 had t_{core} >38.0°C; 20/259 met both criteria; [c]54% either exceeded heart rate (180 beats/min − minus age for worker) and/or t_{core} (>38.5°C, intestinal pill) recommendations for several minutes; [d]Subset of data from Quiller et al. (41); [e]Equipment weight: 18.5 (3.8) kg; percentage of time at work intensities: sedentary (28%), light (37%), moderate (19%), high (16%); [f]Load carriage of ~16 kg; [g]7/9 employees met one or more criteria for excessive heat strain (i.e., t_{core} >38.5°C; heart rate >180 − age for >3 min; symptoms of heat-related illness; body mass loss >1.5%); [h]Load carriage of ~26 kg; [i]All participants spent an average of ~1 h/shift t_{core} ≥38.0°C; [j]75% of workers achieved a t_{core} >38°C and 22% >38.5°C; unacclimated workers spent ~32% of work period at t_{core} above threshold limit value (38.0°C), whereas acclimated workers spent ~8% of work period above threshold limit value (38.5°C).

creatinine (interpreted as increased AKI incidence) that was associated with greater increases in core temperature and heart rate and was particularly marked when employees were paid by piece rate (i.e., amount of produce harvested) (21). This payment structure, which incentivizes greater work intensities, infrequent breaks and is likely exacerbated by socioeconomic factors, is common in countries that are experiencing high rates of CKDnt (63). This raises the point as to why there are no well-known CKDnt hotspots in the United States despite the presence of occupational heat stress that is consistent with an increased risk of CKDnt, such as is observed in Central America (64). The reason for this is largely unknown. On one hand, it may be that the infrastructure for reporting kidney injury/AKI and/or CKDnt in the occupational setting is not well developed in the United States. This would suggest that CKDnt is prevalent in the US workforce, but it is going unreported. On the other hand, however, it may be that the US workforce is better protected from CKDnt. For instance, it is possible that heat strain is minimized in the US workforce due to workplace adherence to OSHA heat stress and hydration recommendations, work mechanization, and the ability to adequately recovery from occupational heat stress following work shifts because of the availability of air conditioning, potable fluids, etc. To our knowledge, the potential protective effects of these factors on kidney injury/AKI and/or CKDnt have not been explored to date. Notably, access to healthcare and differences in the climate throughout the year (e.g., tropical in Central America versus temperate or subtropical in the US) may also contribute to any apparent differences in CKDnt prevalence between the US and other hotspots throughout the globe. Moreover, little is known regarding the mechanisms underlying how physical work intensity or duration increases markers of kidney injury and may modulate the progression to CKDnt. There is some evidence supporting that longer work durations result in greater increases in kidney injury markers in heat stress (28) and temperate conditions (65), but the independent effect of work intensity during occupational heat stress has never been investigated in a laboratory-controlled study. This is an important knowledge gap given that heat stress independently reduces renal perfusion (58) and a linear relation exists between relative work intensity and reductions in renal blood flow (66).

It is also important to consider that many of the identified occupations are not exposed to a singular exposure of occupational heat stress. Rather, these workers experience occupational heat stress that can range from several (e.g., hazardous response team) to most (e.g., mining, aluminum workers) days per year. Therefore, protecting the health of the US workforce is dependent on properly understanding how the risk of kidney injury differs during acute versus chronic occupational heat exposure. For instance, heat strain is exacerbated by consecutive days of physical work in the heat (67, 68), yet some beneficial physiological adaptations to heat (e.g., heat acclimatization) can be observed following as few as three consecutive days of physical work in the heat (69). Such adaptations include plasma volume expansion, reductions in core temperature, and improved sweating that become fully developed with 10–14 consecutive exposures (70). Whether heat acclimatization attenuates increases in kidney injury markers or if the potential physiological health benefits are maintained under chronic dehydration is not well studied (8, 57). To our knowledge, the recent publication by Haroutounian et al. (71) is the only study to examine the effect of heat acclimation on the urinary kidney injury marker response. The investigators demonstrated that the rise in urine kidney injury molecule-1 (KIM-1, a marker of proximal tubular injury) during physical work in the heat before a 7-day heat acclimation protocol remained evident following heat acclimation (71). Despite this important initial work, interpreting these data is difficult because the authors did not make direct statistical comparisons between pre to postheat acclimation on the kidney injury marker response to physical work in the heat and the urine samples were collected immediately following physical work in the heat, which likely underestimated the magnitude of rise in urinary kidney injury markers (8, 25, 72). Notably, it is not expected that all US workers will attain maximal adaptations to heat owing to varying regional climatic conditions of the United States and the nature of an individual's occupation. For example, some jobs (e.g., structural firefighters) are not exposed to daily heat stress. Therefore, these workers are not fully able to acclimatize and are at greater risk during occupational heat stress. Furthermore, some workers (e.g., agricultural workers) are not acclimatized early in the season but acclimatize over a harvest due to the daily nature of their work. Last, workers are at greater risks during extreme heat events (e.g., heat waves), which are expected to increase frequency, duration, and intensity (73). Whether these occupational factors contribute to the development of kidney injury and CKDnt remains unknown.

This review identified at-risk workers in climate regions that have been previously identified as hotspots for end-stage renal disease of unknown causes, including the South, Southeast, and West (17). As previously mentioned, the WBGT for some US occupations was similar to, or in a few cases exceeded, conditions experienced by workers in Central America at risk for CKDnt. However, unlike workers in Central America, the US workers in at-risk occupations are generally overweight or obese according to body mass index data reported in the studies in this review and reported elsewhere (74). These individuals likely experience higher heart rates and maintain lower work rates during heat stress due to lower cardiorespiratory fitness compared with individuals who are nonoverweight/obese, but may be at greater risk for kidney injury due to a systemic inflammatory response and associated comorbidities including hypertension and diabetes (75).

Our literature search did not find any publications for several occupations that are associated with occupational heat stress. First, we were surprised by the lack of studies on construction workers given the physical demands and the long exposures to thermal radiation. This population warrants further investigation given that construction workers account for 36% of all heat-related deaths in the United States (76) and that albuminuria associated with construction work has been reported in other countries (77). Second, despite the US OSHA recognizing that mail/package delivery workers are exposed to occupational heat stress, our literature search did not reveal any studies in this population. Heat-related hospitalizations and AKI have been reported in these workers (78), with anecdotal reports of dry bulb temperatures in the cargo area of the delivery vehicles up to ~65°C (79). Third, our literature search identified only a few indoor occupations. It is likely that occupations in other manufacturing sections (e.g., foundry work) and in warehousing are exposed to high temperatures and/or the use of protective impermeable clothing that increases the severity of the heat stress.

In conclusion, we sought to identify and characterize occupations in the United States at risk for heat stress-mediated sKI/AKI, and ultimately increase CKDnt. Overall, epidemiological and experimental mechanistic data in US workers are limited, and several important gaps in the literature have been identified that highlight the need for future investigations to understand and prevent CKDnt in the United States.

SUPPLEMENTAL DATA

All Supplemental material is available at https://doi.org/10.5281/zenodo.4670996.

ACKNOWLEDGMENTS

We acknowledge the intellectual and administrative contributions made by the La Isla Network team during the various phases of developing this manuscript.

GRANTS

This manuscript was supported by awards from the National Institute of Occupational Safety and Health Grant R01OH011528 (to Z.J.S.) and National Heart, Lung, and Blood Institute Grant R01HL144128 (to C.T.M.). R.S. is PI and J.B.-G. is Co-I on the US Centers for Disease Control and Prevention's CKD Surveillance System for the United States (Supporting, Maintaining and Improving the Surveillance System for Chronic Kidney Disease in the US, Cooperative Agreement No., U58 DP006254, funded by the Centers for Disease Control and Prevention).

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

C.L.C., H.W.H., R.A.I.L., J.G., R.S., J.B.-G., D.H.W., E.H., C.T.M., and Z.J.S. conceived and designed research; C.L.C., H.W.H., and Z.J.S. performed experiments; C.L.C. and H.W.H. analyzed data; C.L.C., H.W.H., R.A.I.L., J.G., R.S., J.B.-G., D.H.W., E.H., C.T.M., and Z.J.S. interpreted results of experiments; C.L.C. and H.W.H. prepared figures; C.L.C., Z.J.S., and H.W.H. drafted manuscript; C.L.C., H.W.H., R.A.I.L., J.G., R.S., J.B.-G., D.H.W., E.H., C.T.M., and Z.J.S. edited and revised manuscript; C.L.C., H.W.H., R.A.I.L., J.G., R.S., J.B.-G., D.H.W., E.H., C.T.M., and Z.J.S. approved final version of manuscript.

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