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RESEARCH ARTICLE

Biomarkers of Kidney Function and Injury Across Fire Seasons and During a Mid-Season Fire Incident in the Wildland Firefighter Exposure and Health Effect (WFFEHE) Study

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ABSTRACT

Background: Occupational heat stress among wildland firefighters (WFFs) performing arduous work or working in hot work environments may cause kidney dysfunction and injury.

Methods: Kidney function and injury biomarkers (serum and urine) were measured among 39 WFFs pre- and post-fire season in 2018–2019. The same biomarkers were measured in 19 of these 39 WFFs over 3 days during a 2019 mid-season fire incident. Median differences in biomarker concentrations across the fire season and across the mid-season incident were evaluated using the Sign test. The primary outcome of interest was the cystatin C-based estimated glomerular filtration rate ($eGFR_{cys}$).

Results: The $eGFR_{cys}$ decreased (median difference = −5 mL/min/1.73 m^2; interquartile range [IQR] = −8, −2 mL/min/1.73 m^2; $p = 0.008$), and 53% of participants lost ≥ 2% of their body weight across the first day of the mid-season fire incident. Median $eGFR_{cys}$ did not decrease across the fire season (median difference = 0 mL/min/1.73 m^2; IQR = −5, 5 mL/min/1.73 m^2; $p = 0.52$). The albumin-creatinine ratio and the ratios of urine kidney injury molecule-1 and neutrophil gelatinase-associated lipocalin concentrations to urine osmolality increased across ≥ 1 day during the mid-season incident.

Conclusions: A temporary decrease in kidney function and changes in biomarkers of kidney injury were observed during a wildland fire incident. Additional research is warranted to confirm these findings, assess associations with occupational heat stress, and determine whether persistent, clinically relevant kidney injury and dysfunction occur among WFFs over time. The findings also support the need for continued efforts to promote optimal hydration of WFFs.

Institution at which the work was performed: Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health.

1 | Introduction

Wildland firefighters (WFFs) are at risk of exertional and environmental heat stress due to the arduous nature of their work, which is often performed in hot environmental conditions [1, 2]. As a result, WFFs may be at risk of acute kidney injury (AKI) and chronic kidney disease (CKD) from occupational heat stress. Generally, exertional and environmental heat stress lead to hyperthermia and dehydration [3], which may impact the kidneys through various mechanisms [4].

Concern about potential occupational heat-related effects on kidney function arose due to an epidemic of CKD of unknown etiology among sugarcane workers in Central America [5]. These workers perform arduous work in the heat with wet bulb globe temperatures (WBGTs; a measure of environmental heat stress that accounts for air temperature, humidity, radiant heat from the sun, and wind speed) often exceeding 30°C (86°F) [6, 7]. Though the etiology is debated [8, 9], substantial evidence exists linking CKD in this epidemic to occupational heat stress [10, 11]. CKD has also been reported among other agricultural and non-agricultural workers who were exposed to heat at work [5, 11–14]. Some researchers hypothesize that affected workers experience repeated episodes of heat-related AKI, which leads to CKD [6, 15, 16].

Although WFFs are at risk of dehydration [17], and have experienced hyperthermia [18], and heat-related illnesses (HRIs), including heat stroke [19], the risk of AKI and CKD among WFFs is unknown. However, the work of WFFs may sometimes be as physically demanding as, if not more demanding than, that of sugarcane workers. The metabolic heat generated by WFFs during fire suppression has been reported to average 7.5 kcals/min [19–22], whereas Crowe et al. [23] reported a metabolic load of 6.8 kcals/min among Costa Rican sugarcane workers. In addition, WFFs, like some sugarcane workers [11, 24, 25], work long hours. When responding to a wildland fire, WFFs typically work 12–16 h per day for 14 days straight [26–28]. However, WFFs, in contrast to sugarcane workers [29], may spend a lower proportion of their workday engaged in physically demanding work [30, 31]. Although ambient conditions during wildland firefighting vary considerably [18], WFFs may also sometimes work when the WBGT is as high as that commonly experienced by Central American sugarcane workers. While there are few published data on WBGTs during wildland firefighting, the National Institute for Occupational Safety and Health (NIOSH) reported an estimated WBGT of 34°–35°C (93.2°–95°F) at one wildland fire location [19].

Furthermore, WFFs are at risk of rhabdomyolysis [32], which may increase their risk of heat-related kidney effects. Rhabdomyolysis, which has been increasingly recognized among WFFs in the last decade [33], is a condition characterized by muscle tissue breakdown and the release of muscle cell contents into the bloodstream that can cause AKI. Subclinical rhabdomyolysis is also a proposed mechanism for heat-related AKI [12, 34]. Studies of WFFs undergoing critical training preseason have demonstrated that physiologic stressors designed to mimic their occupational demands can result in muscle damage in the absence of clinical rhabdomyolysis [35, 36].

Other proposed mechanisms of pre-renal or intrinsic AKI that may be related to dehydration or arduous work include release of vasopressin (antidiuretic hormone), elevated uric acid concentrations with or without the formation of urate crystals in urine, activation of the aldose reductase-fructokinase pathway, localized hypoxia, and adenosine triphosphate depletion [4, 12, 37–39]. Combinations of these factors may lead to inflammation and oxidative stress-related cell damage [4, 37, 38].

Given the potential occupational risk factors for adverse kidney effects among WFFs, the primary aim of this study was to evaluate changes in the estimated glomerular filtration rate (eGFR), a measure of overall kidney function, among WFFs. Researchers assessed biomarkers of kidney function, kidney injury, hydration, and two possible mechanisms of heat-related AKI (inflammation and elevated uric acid concentrations [4, 37, 40, 41]) across a fire season among a cohort of WFFs who participated in the Wildland Firefighter Exposure and Health Effect (WFFEHE) study [42, 43] in 2018–2019. In addition, researchers assessed the same biomarkers among a subset of this cohort over a 3-day period during a 2019 mid-season deployment to a live wildland fire incident. The study team hypothesized that the eGFR would decrease and that uric acid concentrations and markers of kidney injury, hydration (except for body weight), and inflammation would increase over the course of fighting wildland fires.

2 | Methods

2.1 | Overview

The WFFEHE study was a 2-year prospective study of exposure and health among WFFs. The rationale, design, and methods of the study, which were reviewed and approved by the NIOSH Institutional Review Board (IRB; Protocol #18-WSD-01), are described in detail elsewhere [42]. Participants were recruited from six federal WFF crews, five of which were Type 1 Interagency Hotshot Crews (IHCs) and one Type 2 Initial Attack Crew. A total of 154 WFFs provided written informed consent and participated in the study. All six crews participated in pre-fire season (mid-April to mid-May) and post-fire season (late September/early October) study intervals in 2018 and 2019. Each year, one crew (IHC 4 in 2018, IHC 5 in 2019) was selected to participate in an assessment of biomarkers of kidney function and injury during each study interval. In 2019, one IHC (IHC 5) also participated in a 3-day mid-season study interval while responding to a wildland fire incident.

2.2 | Cohort Description

The cohort for this evaluation comprises participants from IHC 4 in 2018 and IHC 5 in 2019, who provided blood and urine samples for an assessment of kidney function and injury. Both crews were based in Idaho. Although all types of wildland fire crews are responsible for wildland fire suppression and management, their experience, training, and physical fitness requirements vary [28]. Given the higher qualifications their crewmembers are required to hold, IHCs perform the most complex tasks in the most dangerous and intense parts of a wildfire. Additionally, they are a nationally available resource deploying anywhere in the United States, often deployed to

complex large fires, and in high demand during the fire season. As a result, they work longer shifts with limited time for rest and recovery during and between fires. Thus, these WFFs are expected to be at greater risk of heat stress than other WFFs.

2.3 | Description of Mid-Season Incident and Work Tasks

The mid-season study interval occurred while IHC 5 responded to the Cove Creek Fire at the Salmon–Challis National Forest. Briefly, as described elsewhere [44], crewmembers used chain saws and hand tools to remove vegetation (e.g., trees, brush) down to mineral soil (i.e., prepared and dug firelines, tasks requiring high physical activity) on Day 1 and most of Day 2. In the evening on Day 2, some crewmembers ignited unburnt vegetation between the main fire and control line using drip torches (i.e., conducted a firing operation, a task requiring high physical activity) while other crewmembers ensured that the fire did not cross the control line (i.e., performed holding, a task requiring high physical activity). On Day 3, crewmembers extinguished smoldering material (i.e., mop-up, a task requiring moderate physical activity) and systematically inspected and felt with their bare hands to detect areas of heat (i.e., cold-trailing, a task requiring moderate physical activity). Individuals in overhead positions directed crewmembers performing these tasks (which required light physical activity) and performed these tasks themselves. Crewmembers also spent time on other tasks, including sedentary tasks (e.g., operational breaks, driving, and staging). The physical activity indicated for these job tasks is based on West et al. [30].

2.4 | Data Collection

2.4.1 | Questionnaires

Participants from IHC 4 and IHC 5 completed self-administered questionnaires at pre-season (mid-May) and post-season (late September/early October) study intervals. Participants from IHC 5 also completed a questionnaire at the beginning of the mid-season study interval in early August of 2019. The self-completed questionnaires collected demographic information, employment and exposure histories, and data on health conditions and tobacco, alcohol, medication, and dietary supplement use.

2.4.2 | Physical Measurements

Height was measured using a stadiometer (SECA 213) when the participant enrolled in the study. Weight was measured with clothes (crew t-shirt, green Nomex® pants [pockets emptied] with or without cloth belt with metal buckle, and socks) but without shoes using a digital scale (SECA 813) pre-season, post-season, and for participants from IHC 5, pre-shift on Day 1 and post-shift on Days 1, 2, and 3 of the mid-season study interval. Values of $\geq 2\%$ loss of body weight were identified because the American College of Sports Medicine (ACSM) and the National Athletic Trainers' Association recommend fluid replacement to avoid this level of dehydration [45, 46].

2.4.3 | Blood and Urine Samples

Trained phlebotomists collected venous blood samples from IHC 4 and IHC 5 pre-season and post-season, and from IHC 5 pre-shift on Day 1 and post-shift on Days 1, 2, and 3 of the mid-season study interval. Serum was separated from whole blood by centrifugation in the field, aliquoted into various tubes for analysis, stored frozen at −20°C to −80°C, and shipped on dry ice to Quest Diagnostics for the analyses of the serum biomarkers described below.

Single void, spot urine samples were collected pre-season and post-season from IHC 4 (2018) and pre-season, post-season, and pre- and post-shift on Days 1, 2, and 3 of the mid-season study interval from IHC 5 (2019). Pre-shift samples were not necessarily first morning urine void samples. The urine samples were aliquoted into various tubes for analysis, stored at −20°C to −80°C without preservatives, and shipped on dry ice to Quest Diagnostics or the NIOSH laboratory in Cincinnati, Ohio, for the analyses of the urine biomarkers described below. Quest Diagnostics analyzed serum and urine within 1 week of blood and urine collection. The NIOSH laboratory stored urine samples at −20°C to −80°C upon receipt until the day of analysis.

2.4.4 | Laboratory Analysis

Serum and urine samples were analyzed for biomarkers during the pre-season, mid-season, and post-season intervals to test for evidence of decreases in kidney function, kidney injury, hypohydration, and mechanisms of kidney damage over the course of fighting wildland fires. Detailed rationales for the biomarkers in this component of the WFFEHE study are indicated in Supporting Information S1: Table S1. Briefly, biomarkers were analyzed to assess eGFR as a measure of overall kidney function (cystatin C and creatinine), kidney tubular function (serum electrolytes), glomerular injury (urine microalbumin), tubular injury (urine neutrophil gelatinase-associated lipocalin [NGAL] and kidney injury molecule-1 [KIM-1]), dehydration (blood urea nitrogen [BUN]; serum electrolytes to estimate serum osmolality; urine osmolality; and urine specific gravity), inflammation (high-sensitivity C-reactive protein [hsCRP]), and mechanisms involving uric acid (serum and urine uric acid, urine pH). Urine creatinine and osmolality were also measured to take urine concentration into account when evaluating urine microalbumin, NGAL, KIM-1, and uric acid.

Serum was analyzed for sodium, potassium, and chloride by ion-selective electrode; creatinine, BUN, glucose, calcium, phosphate (as phosphorus), and uric acid by spectrophotometry; cystatin C by particle-enhanced turbidimetric immunoassay; and hsCRP by turbidimetric/immunoturbidimetric assay. Serum was analyzed for creatinine, BUN, sodium, potassium, and calcium in 2019 only. Urine was analyzed by Quest Diagnostics for microalbumin by immunoturbidimetric assay, creatinine by a kinetic modification of the Jaffe procedure, uric acid by spectrophotometry, and osmolality by freezing point depression. The NIOSH laboratory measured urine specific gravity using a handheld refractometer (ATAGO®, Bellevue, WA), pH using a pH meter (IQ Scientific Instruments Inc., Carlsbad, CA), and NGAL and KIM-1 using commercially available high-sensitivity enzyme-linked immunosorbent assay (ELISA)

PicoKine™ kits (Boster, Pleasanton, CA). Urine specific gravity and pH were measured 3–4 weeks after urine collection. NGAL and KIM-1 were initially analyzed in all urine samples collected in 2018 over the course of 2 days and in all urine samples collected in 2019 over the course of 3 days. Any repeated sample analyses of NGAL and KIM-1 were completed when the urine samples collected in 2019 were initially analyzed and the following week.

Serum osmolality in mOsm/kg was estimated as 2× (sodium in mmol/L) + (glucose in mg/dL)/18 + (BUN in mg/dL)/2.8 [47]. The eGFR was calculated using the 2012 Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) cystatin C equation ($eGFR_{cys}$) [48] because of the potential for serum creatinine to be affected by the work-related physical activity of the study participants [49]. AKI during the mid-season study interval was identified according to the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines as an increase in serum creatinine from the pre-shift Day 1 concentration of ≥ 0.3 mg/dL within 48 h (i.e., by post-shift Day 1 or post-shift Day 2) or ≥ 50% within 7 days (i.e., by post-shift Day 1, post-shift Day 2, or post-shift Day 3) [50]. The ratios of urine albumin, NGAL, KIM-1, and uric acid to urine osmolality were calculated to account for urine concentration because of the potential for urine creatinine concentrations to reflect, in part, muscle breakdown from performing arduous work [51].

2.4.5 | Environmental Conditions

Researchers assessed data on environmental conditions that are routinely collected by WFFs during work periods to eliminate overburdening study participants. During the mid-season study interval, IHC 5 crewmembers collected dry bulb (ambient) temperature, relative humidity, and WBGT approximately every hour (≤ 80 min) with a Kestrel 5400FW Fire Weather Meter (Kestrel Instruments, Boothwyn, PA) while the study participants were working but not during sedentary or light physical activities (e.g., driving, breaks, refurbishing saws). Two exceptions occurred where these measurements were collected 2 h apart.

2.5 | Statistical Analysis

All analyses were restricted to crewmembers who participated in both the pre-season and post-season study intervals. Summary statistics for characteristics of the study participants based on questionnaire data and measured height and weight were obtained using SAS version 9.4 [52]. Exact non-zero numbers of participants are generally not provided when < 5 or when numbers < 5 could be derived to protect confidentiality.

Biomarker results less than the limit of detection (LOD) were assigned values of the LOD/√2 [53]. Values of hsCRP > 10 mg/L ($n < 5$) were arbitrarily assigned a value of 12.5 mg/dL. This arbitrary assignment does not affect the summary statistics reported herein.

For each biomarker, differences were calculated between (a) the post-season and pre-season results, (b) the post-shift results on Days 1, 2, and 3 of the mid-season study interval and the pre-shift result on Day 1 (hereafter called the mid-season baseline), and (c) the mid-season and pre-season results. Because the distributions of these differences were almost always non-normal, these differences were tested using the Sign test. The Sign test is a non-parametric test of the median difference between paired observations. In this study, the null hypothesis was that the median difference is zero.

In supplemental analyses, differences in the eGFR estimated from the 2021 CKD-EPI creatinine equation ($eGFR_{cr}$) [54]; urine NGAL, KIM-1, and uric acid; and ratios of urine albumin, NGAL, KIM-1, and uric acid to urine creatinine were evaluated for comparison purposes. Differences in serum electrolyte concentrations were also evaluated in supplemental analyses. Post-hoc analyses were conducted using the Wilcoxon rank sum test to assess whether the change in $eGFR_{cys}$ across Day 1 of the mid-season study interval varied among select subgroups. In these analyses, urine osmolality was dichotomized using a cut-point of 700 mOsm/kg because the ACSM [45] considers a first-morning urine osmolality ≥ 700 mOsm/kg indicative of hypohydration. In post-hoc analyses, the correlation of the change in $eGFR_{cys}$ across Day 1 of the mid-season study interval with the change across Day 1 and the pre- and post-shift concentrations on Day 1 of selected biomarkers of kidney injury, dehydration, inflammation, uric acid, and urine pH was also evaluated using Kendall's tau (τ), a non-parametric rank correlation test. Analyses of serum and urine biomarkers were conducted in R version 4.1.3 [55].

3 | Results

Forty WFFs participated in the pre-season study interval, 39 of whom also participated in the post-season study interval. These 39 participants (19 from IHC 4 in 2018 and 20 from IHC 5 in 2019) were included in the analysis of cross-season changes in biomarker results. Nineteen WFFs from IHC 5 participated in the 2019 mid-season study interval, all of whom also participated in the pre- and post-season study intervals. None of the participants from IHC 4 in 2018 were also participants from IHC 5 in 2019. To protect worker confidentiality, the number of non-participants was blinded to NIOSH researchers. However, the standard number of IHC crewmembers is 20–22 with a maximum of 25 [28]. This suggests that ≥ 78% and likely between 88% and 98% of the pre-season crewmembers of IHC 4 and IHC 5 participated in both the pre-season and post-season study intervals, and that ≥ 76% and likely between 86% and 95% of the pre-season crewmembers of IHC 5 participated in the mid-season study interval.

Characteristics of the participants at the pre-season study interval are shown in Table 1. Most (> 87%) participants were non-Hispanic white men. The median age was 28 years. Few (< 5) participants reported ever having an HRI due to fighting fires diagnosed by a health professional. Fourteen (36%) of the 39 participants self-reported ever experiencing heat stress while fighting fires before participating in this component of the study. Characteristics of the participants at each study interval are shown in Supporting Information S3: Table S2. In the post-season questionnaire, 7 (18%) of 38 participants reported experiencing heat stress while fighting fires since the beginning of the fire season.

Data on participants' work as a WFF are shown in Supporting Information S3: Table S3. For the fire season in which they

participated, participants from IHC 4 in 2018 were more likely than participants from IHC 5 in 2019 to have started working as a WFF more than a week before the pre-season study interval (> 74% vs. 35%). At the post-season study interval, participants from IHC 5 tended to have been engaged in fire suppression activities more recently than participants from IHC 4 (IHC 5: 15 [75%] of 20 participants last engaged 7 days prior; IHC 4: 6 [33%] of 18 participants with non-missing data last engaged 10–14 days prior with none reporting more recent fire suppression activities). The median number of wildland fire incidents and prescribed fire

TABLE 1 | Characteristics of study participants at the pre-season study interval, Wildland Firefighter Exposure and Health Effect Study, 2018–2019.[a]

Characteristic	*n* (%)	Median (IQR)
Age in years		28 (25–33)
Body mass index		25.8 (23.7–26.3)
Year of participation[b]		
2018	19 (49%)	
2019	20 (51%)	
Sex[c]		
Female	< 5 (< 13%)[d]	
Male	> 34 (> 87%)[d]	
Race[c]		
White	> 34 (> 87%)[d]	
Other	< 5 (< 13%)[d]	
Spanish, Hispanic, or Latino origin[c]	< 5 (< 13%)[d]	
Current[e] cigarette smoker	< 5 (< 13%)[d]	
Current[f] cigar smoker	< 5 (< 13%)[d]	
Current[f] e-cigarette smoker	< 5 (< 13%)[d]	
Current[f] smokeless tobacco	20 (51%)	
Current[f] alcohol use	> 34 (> 87%)[d]	
Current[f] binge drinking[g]	24 (63%)[h]	
Family history of chronic kidney disease or kidney failure[i]	0 (0%)	
Medical conditions diagnosed by a health professional[i]		
Diabetes	0 (0%)	
Hypertension	< 5 (< 13%)[d]	
Kidney stones	0 (0%)	
Decreased kidney function	0 (0%)	
Gout	0 (0%)	
Heat-related illness due to fighting fires	< 5 (< 13%)[d]	
Heat stroke due to fighting fires	0 (0%)	
Rhabdomyolysis	< 5 (< 13%)[d]	
Ever experienced heat stress while fighting fires[c]	14 (36%)	
Medication and supplement use in the past 2 weeks		
Creatine supplements	7 (18%)	
Aspirin[j]	6 (15%)	
Non-steroidal anti-inflammatory agents[j]	19 (49%)	
Acetaminophen[j]	12 (31%)	
Diuretics	0 (0%)	
Medication use on a regular[k] basis[i]		
Aspirin[j]	5 (13%)[h]	
Non-steroidal anti-inflammatory agents[j]	10 (26%)	

(Continues)

TABLE 1 | (Continued)

Characteristic	*n* (%)	Median (IQR)
Acetaminophen[j]	10 (26%)	
Diuretics	< 5 (< 13%)[d,h]	

Abbreviations: IQR, interquartile range; *n*, observed number.
[a]These characteristics are generally based on pre-season data in 2018 for participants from IHC 4 and in 2019 for participants from IHC 5; exceptions to this are noted in Footnotes (c) and (i).
[b]Year crewmembers participated in the more detailed assessment of biomarkers related to kidney function.
[c]For IHC 5 crewmembers who participated in the WFFEHE study in both 2018 and 2019, these data are based on data collected in 2018.
[d]Exact non-zero numbers are not provided when < 5 or when numbers < 5 could be derived to protect confidentiality.
[e]Reported smoking at least 100 cigarettes in their life and smoking some days or every day for new participants from IHC 4 in 2018 and from IHC 5 in 2019; reported smoking in the past 30 days at the 2019 pre-season study interval for participants from IHC 5 who participated in both 2018 and 2019.
[f]In the past 30 days.
[g]Drank five or more drinks, for men, or four or more drinks, for women, on one occasion.
[h]Data missing for one participant.
[i]For IHC 5 crewmembers who participated in the WFFEHE study in both 2018 and 2019, these data are based on data collected in 2018 and 2019.
[j]Includes medications containing these substances.
[k]At least two times each week for 2 months or more.

TABLE 2 | Environmental conditions during the mid-season study interval, Wildland Firefighter Exposure and Health Study, 2019.

	Ambient temperature range		Relative humidity range	WBGT range	
Day	°C	°F	%	°C	°F
Day 1	24–33	75–91	17–52	17.7–24.5	63.8–76.1
Day 2	14–31	57–88	20–65	11.6–22.6	52.8–72.6
Day 3	23–32	73–90	29–56	19.0–23.6	66.2–74.5

Abbreviation: WBGT, wet bulb globe temperature.

incidents that WFFs who participated in the mid-season study interval reported working at during the 2019 fire season was 16 (interquartile range [IQR] = 16, 16) and 1 (IQR = 1, 2), respectively. During the mid-season study interval, the maximum WBGT was 24.5°C (76.1°F) on Day 1, 22.6°C (72.6°F) on Day 2, and 23.6°C (74.5°F) on Day 3 (Table 2).

3.1 | Cross-Season Changes

Summary data for the pre- and post-season biomarker results, including the cross-season differences, are shown in Table 3. The pre- and post-season $eGFR_{cys}$ were similar (median difference = 0 mL/min/1.73 m^2; IQR = −5, 5 mL/min/1.73 m^2; $p = 0.52$). The results for biomarkers evaluated in supplemental analyses are shown in Supporting Information S3: Table S4. Statistically significant differences were seen in at least one biomarker in each category (Table 3, Supporting Information S3: Table S4). Pre- and post-season biomarker results by crew are shown in Supporting Information S3: Table S5. The $eGFR_{cys}$, on average, was lower post-season than pre-season among IHC 4 in 2018 (median difference = −2 mL/min/1.73 m^2; IQR = −8, 0 mL/min/1.73 m^2; $p = 0.02$), but not among IHC 5 in 2019 (median difference = 2 mL/min/1.73 m^2; IQR = −4, 8 mL/min/1.73 m^2; $p = 0.26$).

3.2 | Changes During the Mid-Season Study Interval-Biomarkers of Kidney Function and Injury

Summary results for $eGFR_{cys}$ and biomarkers of kidney injury during the mid-season study interval are shown in Figure 1 and Supporting Information S3: Table S6. Figure 1 also shows the pre- and post-season summary results for mid-season participants. During the mid-season study interval, the $eGFR_{cys}$ was lower, on average, at the end of Days 1 and 2 than at the mid-season baseline (end of Day 1: median difference = −5 mL/min/1.73 m^2; IQR = −8, −2 mL/min/1.73 m^2; $p = 0.008$; end of Day 2: median difference = −5 mL/min/1.73 m^2; IQR = −7, 3 mL/min/1.73 m^2; $p = 0.06$). The median $eGFR_{cys}$ was lowest at the end of Day 1. At the end of Day 3, the $eGFR_{cys}$, on average, was similar to the mid-season baseline (median difference = −1 mL/min/1.73 m^2; IQR = −5, 6 mL/min/1.73 m^2; $p = 1.00$). However, the $eGFR_{cys}$ was lower, on average, at the mid-season baseline than at the pre-season study interval (median difference = −4 mL/min/1.73 m^2; IQR = −11, 0 mL/min/1.73 m^2; $p = 0.02$; Supporting Information S3: Table S7). At the end of Day 1, the $eGFR_{cys}$ was 14 mL/min/1.73 m^2 less, on average, than at the pre-season study interval (IQR = −18, −8 mL/min/1.73 m^2; $p < 0.001$; Supporting Information S3: Table S7). The $eGFR_{cys}$ remained lower, on average, at the end of Day 3 than at the pre-season study interval (median difference = −5 mL/min/1.73 m^2; IQR = −13, 2 mL/min/1.73 m^2; $p = 0.17$; Supporting Information S3: Table S7). None of the participants had an $eGFR_{cys}$ less than 60 mL/min/1.73 m^2 (the threshold for a mild to moderate decrease in kidney function [56]) during the mid-season study interval.

The urine albumin creatinine ratio (uACR) increased across Day 1 of the mid-season study interval (median difference = 2 mcg/mg creatinine; IQR = 0, 3 mcg/mg creatinine; $p = 0.004$). One participant had a uACR (a marker of glomerular injury) of 30 mcg/mg or greater (the threshold for moderately increased albuminuria [56]) at the beginning, and another participant had a uACR of 30 mcg/mg or greater at the end of Day 1 of the mid-season study interval. None of the participants had a uACR of 30 mcg/mg or greater at the end of Day 2

TABLE 3 | Cross-season changes in biomarkers, Wildland Firefighter Exposure and Health Effect Study, 2018–2019.

Biomarker	Pre-season median (IQR)[a]	Post-season median (IQR)[a]	Difference[b] median (IQR)[a]	*p* value[c]
Overall kidney function				
$eGFR_{cys}$ (mL/min/1.73 m^2)	118 (104, 124)	115 (106, 123)	0 (−5, 5)	0.52
Glomerular injury				
uACR (mcg/mg Cr)	3 (2, 5)	3 (2, 6)	0 (−2, 1)	0.75
Urine albumin osmolality ratio (mg/dL)/(Osm/kg)	0.75 (0.41, 1.18)	0.43 (0.24, 0.78)	−0.25 (−0.77, −0.05)	**< 0.001**
Tubular injury				
Urine NGAL osmolality ratio (pg/dL)/(mOsm/kg)	127 (73, 209)	148 (88, 283)	12 (−62, 126)	0.52
Urine KIM-1 osmolality ratio (pg/dL)/(mOsm/kg)	49 (20, 96)	35 (16, 71)	−7 (−35, 7)	0.05
Dehydration				
Weight (kg)	78.7 (73.6, 87.0)	78.4 (72.7, 85.0)	0.2 (−1.6, 2.3)	0.75
BUN creatinine ratio	17 (14, 19)	18 (16, 21)	1 (−1, 5)	0.65
Serum osmolality (mOsm/kg)	290 (288, 293)	291 (290, 293)	1 (−1, 3)	0.12
Urine osmolality (mOsm/kg)	226 (127, 580)	724 (464, 839)	311 (90, 556)	**< 0.001**
Urine specific gravity	1.009 (1.007, 1.018)	1.018 (1.012, 1.021)	0.003 (−0.002, 0.012)	**0.02**
Inflammation				
hsCRP (mg/L)	0.7 (0.5, 1.7)	0.3 (0.2, 0.7)	−0.4 (−1.4, 0.0)	**< 0.001**
Mechanisms involving uric acid				
Serum uric acid (mg/dL)	5.4 (4.8, 6.2)	5.6 (5.0, 6.3)	0.2 (−0.4, 0.5)	0.50
Urine uric acid osmolality ratio (mg/dL)/(Osm/kg)	105 (80, 159)	66 (52, 87)	−29 (−90, −6)	**< 0.001**
Urine pH	6.3 (6.0, 6.8)	6.2 (5.4, 6.8)	−0.1 (−1.0, 0.5)	0.52

Abbreviations: BUN, blood urea nitrogen; Cr, creatinine; $eGFR_{cys}$, estimated glomerular filtration rate obtained using the 2012 CKD-EPI cystatin C equation; hsCRP, high-sensitivity C-reactive protein; IQR, interquartile range; KIM-1, kidney injury molecule 1; NGAL, neutrophil gelatinase-associated lipocalin; uACR, urine albumin creatinine ratio.

[a] $n = 20$ for BUN creatinine ratio and serum osmolality, $n = 38$ for serum uric acid, and $n = 39$ for all other biomarkers.

[b] Post-season minus pre-season.

[c] Bold text indicates $p < 0.05$.

or Day 3. The urine albumin osmolality ratio was increased at the end of Day 1 (median difference = 0.27 (mg/dL)/(Osm/kg); IQR = 0.07, 0.73 (mg/dL)/(Osm/kg); $p = 0.004$) and Day 2 (median difference = 0.99 (mg/dL)/(Osm/kg); IQR = 0.20, 2.02 (mg/dL/Osm/kg); $p < 0.001$) compared to the mid-season baseline.

The urine NGAL osmolality ratio increased across the 3 days of the mid-season study interval (median difference = 157 (pg/dL)/(mOsm/kg); IQR = 8, 418 (pg/dL)/(mOsm/kg); $p = 0.004$). The urine KIM-1 osmolality ratio increased across the first 2 days of the mid-season study interval (median difference = 38 (pg/dL)/(mOsm/kg); IQR = 16, 98 (pg/dL)/(mOsm/kg); $p = 0.004$).

Summary mid-season results for $eGFR_{cr}$ and other biomarkers evaluated in supplemental analyses are shown in Supporting Information S3: Table S8 and Supporting Information S1: Figure S1 and Supporting Information S2: Figure S2. At the end of Day 1, one participant met the creatinine-based KDIGO criterion for AKI. This participant had a 68% increase in serum creatinine and a 54% increase in serum cystatin C across Day 1.

3.3 | Changes During the Mid-Season Study Interval-Biomarkers of Dehydration and Hydration Status

Summary mid-season results for biomarkers of dehydration and hydration status are shown in Figure 2 and Supporting Information S3: Table S6. Ten (53%) of 19 participants lost 2% or more of their body weight on Day 1 (median difference = −1.6 kg; IQR = −2.1, −0.9 kg; $p < 0.001$). The median BUN creatinine ratio was 20 or higher and similar throughout the mid-season study interval. Pre-shift on Day 1 and post-shift on each day, a majority of participants (≥ 13 of 19) had a urine specific gravity greater than 1.020.

3.4 | Changes During the Mid-Season Study Interval-Biomarkers Related to Inflammation and Uric Acid

Summary mid-season results for biomarkers related to inflammation and uric acid are shown in Figure 3 and Supporting

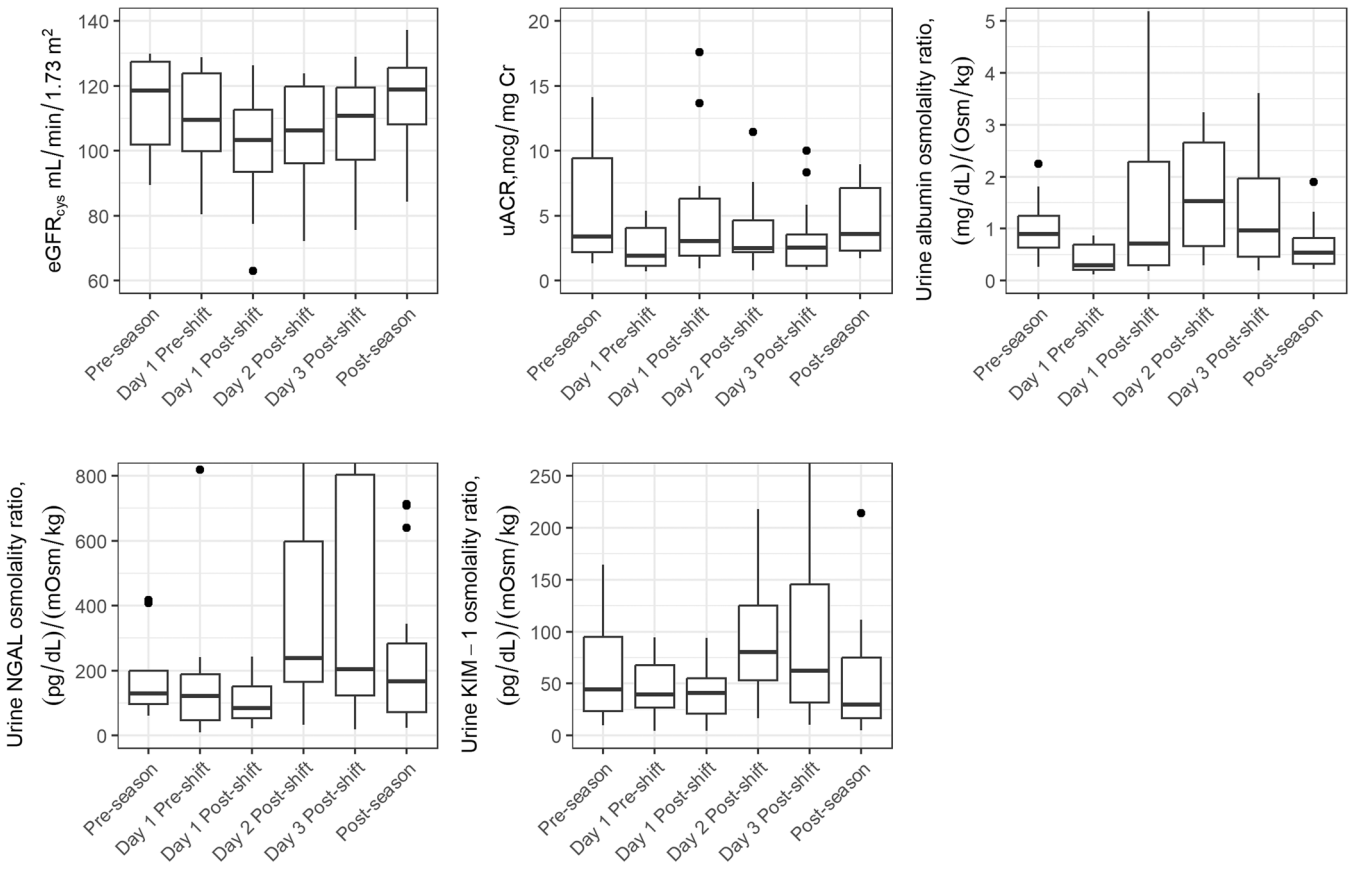

FIGURE 1 | Changes in biomarkers of kidney function and injury across the 2019 fire season among 19 wildland firefighters. Days 1–3 occurred during a mid-season fire incident. Some outliers are not shown (for the uACR and the albumin osmolality ratio during the mid-season study interval and for the NGAL osmolality ratio and the KIM-1 osmolality ratio during the pre- and mid-season study intervals) to better display the change in the median and interquartile range. Cr, creatinine; eGFR$_{cys}$, estimated glomerular filtration rate obtained using the 2012 CKD-EPI cystatin C equation; KIM-1, kidney injury molecule 1; NGAL, neutrophil gelatinase-associated lipocalin; uACR, urine albumin creatinine ratio.

Information S3: Table S6. The hsCRP concentration increased across the 3 days of the mid-season study interval (median difference = 0.2 mg/L; IQR = 0.0, 0.4 mg/L; $p = 0.001$). The urine uric acid osmolality ratio also increased across the mid-season study interval (median difference = 76 (mg/dL)/(Osm/kg); IQR = 34, 137 (mg/dL)/(Osm/kg); $p = 0.02$).

3.5 | Change in eGFR$_{cys}$ by Subgroup

The change in eGFR$_{cys}$ across Day 1 by subgroup is shown in Supporting Information S3: Table S9. The median change in eGFR$_{cys}$ across Day 1 was similar among participants with a pre-shift urine osmolality ≥ 700 mOsm/kg ($n = 14$; median = −5 mL/min/1.73 m^2; IQR = −8, 0 mL/min/1.73 m^2; $p = 0.09$) and participants with a pre-shift urine osmolality < 700 mOsm/kg ($n = 5$; median = −4 mL/min/1.73 m^2; IQR = −8, −3 mL/min/1.73 m^2; $p = 0.06$). The median change in eGFR$_{cys}$ across Day 1 was greater among participants who reported taking non-steroidal anti-inflammatory agents during the past 2 weeks on the mid-season questionnaire ($n = 6$; median = −7 mL/min/1.73 m^2; IQR = −11, −4 mL/min/1.73 m^2; $p = 0.03$) than among participants who did not report taking non-steroidal anti-inflammatory agents ($n = 13$; median = −3 mL/min/1.73 m^2; IQR = −8, 0 mL/min/1.73 m^2; $p = 0.15$), although the difference between the two groups was not statistically significant ($p = 0.15$).

3.6 | Changes During the Mid-Season Study Interval-Correlations Between eGFR$_{cys}$ and Other Biomarkers

The correlations between the change in eGFR$_{cys}$ across Day 1 of the mid-season study interval and other biomarkers are shown in Table 4. The change in eGFR$_{cys}$ on Day 1 of the mid-season study interval was moderately correlated with the change in hsCRP ($\tau = -0.43$, $p = 0.02$) on Day 1 and the concentration of hsCRP ($\tau = -0.57$, $p = 0.001$) at the end of Day 1. The change in eGFR$_{cys}$ on Day 1 was also moderately correlated with the changes in serum uric acid ($\tau = -0.32$, $p = 0.06$), urine pH ($\tau = 0.30$, $p = 0.07$), and weight ($\tau = 0.29$, $p = 0.09$) on Day 1, although these correlations were not statistically significant. The change in eGFR$_{cys}$ on Day 1 was not correlated with markers of kidney injury (uACR and the ratios of urine albumin, NGAL, and KIM-1 to urine osmolality).

4 | Discussion

4.1 | Kidney Function

The eGFR (the estimated rate at which fluid is filtered from the blood by the glomeruli in the kidneys) is considered a marker of overall kidney function and, more specifically, of glomerular

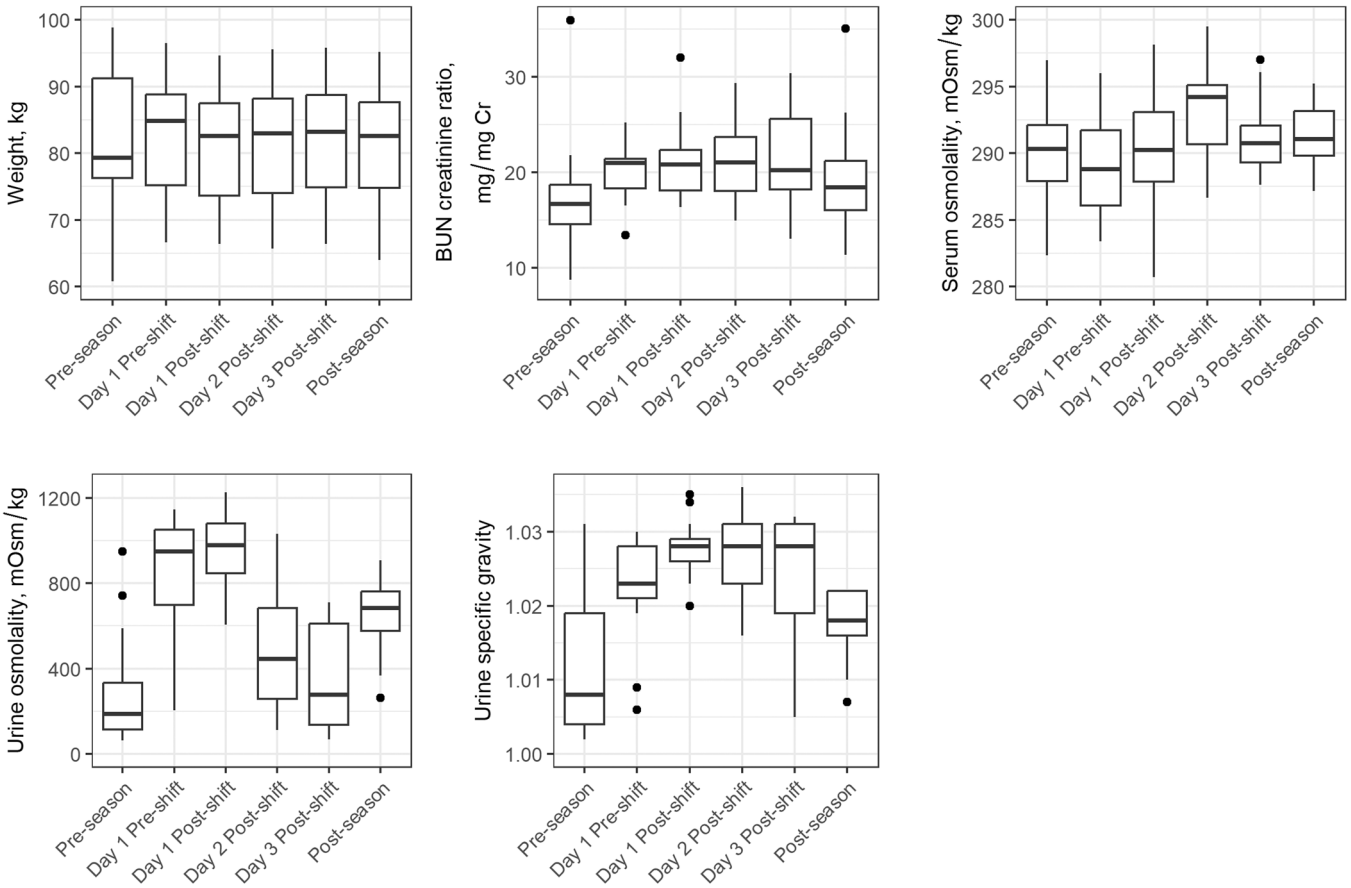

FIGURE 2 | Changes in biomarkers of hydration status across the 2019 fire season among 19 wildland firefighters. Days 1–3 occurred during a mid-season fire incident. BUN, blood urea nitrogen; Cr, creatinine.

function. Thus, our results indicate WFFs can experience reversible decrements in kidney function during the fire season. We observed a statistically significant median decrease of 5 mL/min/1.73 m^2 in the $eGFR_{cys}$ across the first day of the mid-season study interval. The median decrease in $eGFR_{cys}$ was greater among participants who reported taking non-steroidal anti-inflammatory agents in the past 2 weeks on the mid-season questionnaire. The median difference in $eGFR_{cys}$ from the pre-season study interval to the end of Day 1 among participants from IHC 5 was −14 mL/min/1.73 m^2. This decrease in $eGFR_{cys}$ among IHC 5 crewmembers was resolved by the time of the post-season study interval.

In addition, a statistically significant 2 mL/min/1.73 m^2 decrease, on average, in the $eGFR_{cys}$ was observed among IHC 4 across the season, which raises the possibility of a persistent decrease in kidney function among some WFFs. This 2 mL/min/1.73 m^2 decrease in eGFR, if persistent, is at least twice the annual expected decrease in eGFR for healthy adults without CKD [57]. However, this may reflect a reversible decrement. This small decrease in eGFR could also be due to analytical and biological variability in cystatin C levels [58]. The intraindividual biological variation in $eGFR_{cys}$ is approximately 5% [56].

The pattern of results for $eGFR_{cr}$ was somewhat different from that for $eGFR_{cys}$. Elevated creatine kinase levels consistent with muscle breakdown have been observed among WFFs [32, 36]. Serum creatinine levels can also be influenced by muscle mass [59], meat consumption [60], and creatine supplements [61]. In this study, 7 (18%) of participants reported using creatine supplements in the 2 weeks before the pre-season study interval.

Despite the limitations of serum creatinine in our study, the diagnostic criteria for AKI are based on serum creatinine and urine output. However, the development of AKI in one WFF during the first day of the mid-season study interval (based on the change in serum creatinine) was supported by a similar change in cystatin C. The long-term implications, if any, of the mild, reversible work-related AKI observed in this study are unclear [38]. Data from clinical settings indicate the risk of subsequent CKD increases with the duration [62] and severity [63] of AKI and with recurrent episodes of AKI [64].

4.2 | Kidney Injury

We observed a transient increase in biomarkers of glomerular injury (uACR and the urine albumin osmolality ratio) during the mid-season study interval. Elevated levels of uACR reflect abnormal “leakage” of high molecular weight proteins in blood (such as albumin) through the glomerular basement membrane. On average, the greatest increase in uACR occurred on mid-season Day 1 and was small (2 mcg/mg creatinine). The median uACR at the end of Day 1 was not increased compared

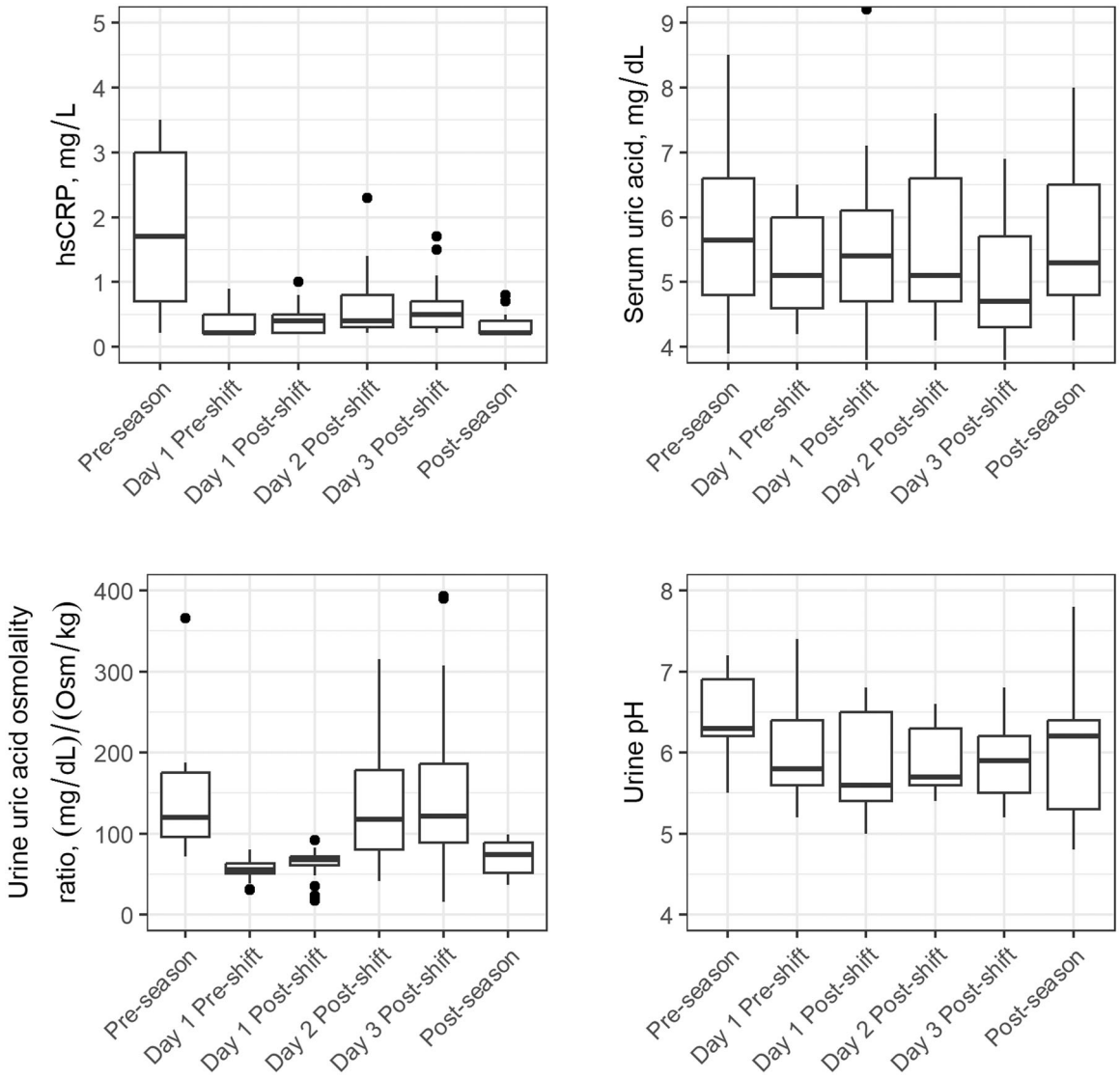

FIGURE 3 | Changes in biomarkers related to inflammation and uric acid across the 2019 fire season among 19 wildland firefighters. Days 1–3 occurred during a mid-season fire incident. Some outliers are not shown (for hsCRP during the pre- and post-season study intervals, for the uric acid osmolality ratio during the pre-season study interval, and for pH during the mid-season study interval) to better display the change in the median and interquartile range. Serum uric acid during the pre-season study interval is missing for one participant. hsCRP, high-sensitivity C-reactive protein.

to the pre- and post-season medians. However, moderately increased albuminuria (uACR ≥ 30 mcg/mg), which resolved, was observed among one participant at the end of Day 1. An increase in the urine albumin osmolality ratio was also observed. Nonetheless, the change in $eGFR_{cys}$ on Day 1 of the mid-season study interval was not correlated with the Day 1 change in or values of uACR or the urine albumin osmolality ratio. Thus, our findings suggest the observed decrease in $eGFR_{cys}$ on Day 1 was not associated with glomerular damage.

The pattern of results for biomarkers of tubular injury (NGAL, KIM-1) varied depending on whether the results accounted for urine concentration and whether this was based on urine creatinine or urine osmolality. However, the ratios of both NGAL and KIM-1 to urine osmolality increased (on average) during the mid-season study interval, but not across the fire season. These temporary increases may indicate acute kidney stress, during which the risk of AKI is increased [38, 65].

4.3 | Biomarkers of Dehydration and Hydration Status

Several biomarkers of dehydration were assessed, but a gold standard does not exist [66]. The ACSM [45] considers a first-morning urine specific gravity ≥ 1.020 or osmolality ≥ 700 mOsm/kg indicative of hypohydration. Accordingly, our results suggest many participants were hypohydrated at the beginning of the mid-season study interval, although the pre-shift urine samples were not necessarily first morning samples. Yet, specific gravity and osmolality measurements of spot urine samples may not accurately reflect a person's true hydration status because the measurements can be influenced by recent fluid intake before equilibration [67]. Instead, cross-shift changes in body weight may be the best marker of dehydration during this study interval [66], although these changes may be underestimated because of the potential for unevaporated sweat in clothing post-shift. The ACSM [45] and National Athletic

TABLE 4 | Correlation of biomarkers with the change in $eGFR_{cys}$ across Day 1 of the mid-season study interval, Wildland Firefighter Exposure and Health Effect Study, 2019.

Biomarker[a]	ΔeGFR$_{cys}$[b] τ	ΔeGFR$_{cys}$[b] p value[c]
Glomerular injury		
uACR		
Pre-shift	0.01	0.97
Post-shift	−0.20	0.24
Δ[d]	−0.05	0.78
Albumin-osmolality ratio		
Pre-shift	0.04	0.84
Post-shift	−0.19	0.27
Δ	−0.04	0.84
Tubular injury		
NGAL-osmolality ratio		
Pre-shift	−0.04	0.84
Post-shift	0.05	0.78
Δ	0.05	0.78
KIM-1-osmolality ratio		
Pre-shift	0.04	0.84
Post-shift	−0.17	0.33
Δ	−0.19	0.27
Dehydration		
Weight		
Δ	0.29	0.09
Serum osmolality		
Pre-shift	−0.04	0.84
Post-shift	−0.12	0.49
Δ	0.09	0.63
Urine osmolality		
Pre-shift	0.08	0.68
Post-shift	−0.23	0.19
Δ	−0.23	0.19
Urine specific gravity		
Pre-shift	0.15	0.40
Post-shift	−0.18	0.29
Δ	−0.26	0.12
Inflammation		
hsCRP		
Pre-shift	−0.25	0.18
Post-shift	−0.57	**0.001**
Δ	−0.43	**0.02**
Mechanisms involving uric acid		
Serum uric acid		
Pre-shift	0.09	0.60
Post-shift	−0.01	0.97
Δ	−0.32	0.06
Urine uric acid osmolality ratio		
Pre-shift	0.04	0.84
Post-shift	0.24	0.16
Δ	0.08	0.68
Urine pH		
Pre-shift	−0.24	0.17
Post-shift	0.06	0.73
Δ	0.30	0.07

Abbreviations: $eGFR_{cys}$, estimated glomerular filtration rate obtained using the 2012 CKD-EPI cystatin C equation; hsCRP, high sensitivity C-reactive protein; KIM-1, kidney injury molecule 1; NGAL, neutrophil gelatinase-associated lipocalin; uACR, urine albumin creatinine ratio.
[a]Biomarker result pre-shift or post-shift on Day 1 of the mid-season study interval, or the change in the biomarker result across Day 1 (post-shift minus pre-shift) of the mid-season study interval.
[b]Change in $eGFR_{cys}$ across Day 1 (post-shift minus pre-shift) of the mid-season study interval.
[c]Bold text indicates $p < 0.05$.
[d]Change in biomarker result across Day 1 (post-shift minus pre-shift) of the mid-season study interval.

Trainers' Association [46] recommend fluid replacement to avoid dehydration resulting in a loss in body weight of 2% or more. More than half of the participants (10 of 19) had a cross-shift loss in body weight of this magnitude on Day 1 of the mid-season study interval, indicative of dehydration, when the greatest decrease in $eGFR_{cys}$ was observed. The correlation analysis indicated that the changes in weight and $eGFR_{cys}$ on Day 1 were correlated, although this finding was not statistically significant.

4.4 | Biomarkers Related to Inflammation and Uric Acid

Proposed mechanisms of kidney effects of arduous work with hyperthermia and dehydration include inflammation and elevated uric acid concentrations with or without the formation of urate crystals in urine [4, 37, 40, 41]. Low urine pH may also play a role because uric acid is less soluble in acidic urine, which increases the risk of urate crystals [41, 68]. A mild, statistically significant increase in the levels of hsCRP (a marker of inflammation) was observed during the mid-season study interval. In addition, negative moderate correlations were observed between the change in eGFR on Day 1 of the mid-season study interval and both the change in hsCRP on Day 1 and the concentration of hsCRP at the end of Day 1. These findings are consistent with inflammation playing a role in the observed decrease in $eGFR_{cys}$. The findings were somewhat weaker for uric acid. The urine uric acid to urine osmolality ratio increased across the mid-season study interval, but the change in $eGFR_{cys}$ on Day 1 was not correlated with the change in the urine uric acid to osmolality ratio. Non-statistically significant correlations were observed between the change in $eGFR_{cys}$ on Day 1 and the change in serum uric acid and urine pH.

4.5 | Heat Stress and HRIs

The primary a priori exposure of concern in our study was occupational heat stress. Heat stress is a combination of the heat gained from the environment and the metabolic heat generated during physical exertion minus the heat loss due to skin evaporation [69, 70]. The maximum WBGT measurement during this study was 24.5°C (76.1°F), suggesting that the environmental heat load was not a significant factor during the mid-season study interval. Due to logistical considerations, the metabolic heat generated (i.e., signs of heat strain such as core body temperature or heart rate) was not measured among study participants. In addition, the available data on time spent performing various job tasks was insufficient to accurately estimate the proportion of worktime spent engaged in sedentary, light, moderate, and high physical activity. However, the job tasks performed by Type 1 WFFs during fire suppression (job tasks similar to those performed by the study participants), have been reported in other studies to average 7.5 kilocalories per minute (kcals/min), with ranges from 4 to 10 kcal/min, suggesting moderate to heavy workloads and significant metabolic heat stress [2, 19–22, 70]. A previous study has also found direct associations between job tasks with increased physical demand and increases in core body temperatures among WFFs [30]. An increase in core body temperature and a biomarker of AKI risk (i.e., the product of insulin-like growth factor-binding protein 7 [IGFBP7] and tissue inhibitor metalloproteinase 2 [TIMP-2]) has been observed with physical exertion at a WBGT of 24.1°C (75.4°F) [71]. Furthermore, the metabolic heat from physical exertion can lead to HRIs at WBGTs observed in our study, although the risk is greater at higher WBGTs [72–74]. Except for the chaps worn by those using and assisting with the chainsaws, the clothes worn by crew members were well-suited to remove heat by evaporation and convection [69, 70].

Before this study, 14 (36%) participants reported experiencing heat stress while fighting fires. Few (< 5) WFFs reported ever being diagnosed by a health professional with HRI due to fighting fires. This small number may be the positive result of decades of work by the federal wildland fire service to address the safety culture within the wildland fire service [19]. On the other hand, this small number may reflect under-reporting of HRI due to several factors. First, most HRIs are relatively mild and resolve with rest. Second, while deployed, WFFs have limited access to healthcare providers. Third, Type 1 WFFs may consider HRI symptoms "part of the job." Finally, some WFFs might think that reporting an injury or illness might negatively influence their being rehired the next fire season [19]. Although heat stress and HRIs were not defined in the questionnaires, WFFs receive training about heat stress and HRIs throughout their employment.

4.6 | Limitations

A limitation of our study is that we did not evaluate exposure-response relationships using measures of heat stress or strain. Furthermore, our primary hypothesis was that WFFs experience decrements in kidney function from occupational heat stress. However, WFFs may also be at risk of AKI and CKD from exposure to air contaminants in wildland fire smoke. Associations have been observed between fine particulate matter (particles with an aerodynamic diameter $\leq 2.5\,\mu m$) from air pollution and a variety of kidney outcomes, including AKI, reductions in eGFR, and CKD [75, 76]. While much of the research has focused on particulate matter, associations have also been observed between exposure to other air contaminants and kidney outcomes [77]. Exposure concentrations to respirable particulate matter (particles with an aerodynamic diameter $\leq 4\,\mu m$) from wildland fire smoke among WFFs vary depending on work tasks and crew type [26, 78] and can exceed the recommended occupational exposure limit established for WFF by the National Wildfire Coordinating Group [78, 79]. However, exposure concentrations to respirable particulate matter were not measured in our study.

Other limitations of our study include the small sample size, especially during the mid-season study interval. This limited our ability to adjust for potential confounders. This was addressed, in part, by assessing within-subject change in biomarkers, which eliminates confounding by factors that are time-invariant within an individual. Another limitation was the lack of a comparison group or data on the cross-shift change in biomarkers at baseline, so that cross-shift changes during the mid-season study interval and baseline could be compared to account for normal circadian variation. However, we observed an increase in cystatin C and a corresponding decrease in $eGFR_{cys}$ across Day 1 of the mid-season study interval, whereas other data suggest that circadian variation would have led to a decrease in cystatin C and a corresponding increase in $eGFR_{cys}$ [80]. Additionally, many WFFs began working and physical training more than a week before the pre-season study interval. Thus, true "baseline" pre-season results were not obtained for all participants. This may have biased our cross-season results towards the null. Other limitations include the lack of data on serum creatine kinase, which is elevated in rhabdomyolysis, and fluid intake during the mid-season study interval. Finally, WFFs sometimes work when WBGTs are higher than were measured during the mid-season study interval. Thus, the mid-season study results may underestimate the potential for acute kidney effects. Nonetheless, in general, the mid-season incident was representative of other complex fires that occurred in the Great Basin region of the United States in July and August in recent years.

5 | Conclusions

We observed a temporary decrease in kidney function among WFFs during a mid-season fire incident. Although the median decrease was not clinically significant, one participant developed AKI. Our findings suggest this decrease may be associated with inflammation and dehydration. We also observed temporary increases in several biomarkers of glomerular injury (uACR and urine albumin osmolality ratio) and tubular injury (ratios of urine NGAL and KIM-1 to urine osmolality). Additional research is warranted among a larger group of WFFs across a wider range of environmental conditions to confirm our findings; assess associations with measures or surrogates of occupational heat stress, fine particulate matter, and other contaminants in wildland fire smoke; and determine whether persistent, clinically relevant kidney injury and dysfunction

occur among WFFs over time. Our findings also indicate that dehydration was common across the first workday of the mid-season fire incident. This supports continued efforts to promote optimal hydration of WFFs, which may decrease their risk of acute kidney dysfunction and injury. The National Wildfire Coordinating Group recommends WFFs drink one to two cups of fluids before work, at least one quart per hour while working, and as much as possible during the lunch break, and continue fluid replacement after work [81]. Additional research is needed to inform recommendations on the types of fluids to drink because some data suggest fructose-sweetened drinks may increase the risk of heat-related AKI [4]. When heat stress criteria are exceeded, other steps to prevent HRIs include hourly work/rest cycles according to NIOSH and American Council of Governmental Industrial Hygienists guidelines [69, 70].

Author Contributions

Lynne E. Pinkerton participated in the design of the component of the Wildland Firefighter Exposure and Health Effect (WFFEHE) study that focused on biomarkers of kidney function and injury and wrote the first draft of the manuscript. Sara E. Luckhaupt consulted on the design of the study and edited the manuscript. Stephen Bertke conducted the analysis. Corey R. Butler and Christa R. Hale led the design of the overall WFFEHE study. Deborah Sammons and Christine Toennis participated in the planning and conducting of the field study and measured selected kidney biomarkers in urine. Alejandra Ramirez-Cardenas participated in investigation, project administration, programming, and writing – review and editing. All authors participated in the interpretation and presentation of results, approved the final manuscript, and agreed to be accountable for all aspects of the work.

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Disclosure

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention. Mention of any company name or product does not constitute endorsement by NIOSH/CDC. The findings and conclusions in this report are those of the authors and should not be construed to represent any official United States Department of Agriculture Forest Service or US Government determination or policy.

Ethics Statement

The study was approved by the National Institute for Occupational Safety and Health Institutional Review Board (Protocol #18-WSD-01).

Consent

All participants provided written informed consent.

Conflicts of Interest

Lynne E. Pinkerton currently works for Maximus Inc., which holds contracts with the CDC NIOSH for assistance, including the conduct of research studies. The other authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are not publicly available due to privacy restrictions. Limited data may be available upon request to NIOSH.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.
Supplemental-Figure-S1. **Supplemental-Figure-S2**. **Supplemental Table S1:** Biomarkers used to measure different aspects of kidney function and injury, Wildland Firefighter Exposure and Health Effect Study, 2018–2019. **Supplemental Table S2:** Characteristics of study participants by study interval, Wildland Firefighter Exposure and Health Effect Study, 2018–2019. **Supplemental Table S3:** Wildland firefighting work during the fire season of participation, Wildland Firefighter Exposure and Health Effect Study, 2019. **Supplemental Table S4:** Cross-season changes in biomarkers evaluated in supplemental analyses, Wildland Firefighter Exposure and Health Effect Study, 2018–2019. **Supplemental Table S5:** Cross-season changes in biomarkers by crew, Wildland Firefighter Exposure and Health Effect Study, 2018–2019. **Supplemental Table S6:** Changes in biomarkers evaluated in the main analyses across mid-season days 1–3, Wildland Firefighter Exposure and Health Effect Study, 2019a. **Supplemental Table S7:** Change in eGFRcys from the pre-season to mid-season study interval, Wildland Firefighter Exposure and Health Effect Study, 2019. **Supplemental Table S8:** Changes in biomarkers evaluated in supplemental analyses across mid-season days 1–3, Wildland Firefighter Exposure and Health Effect Study, 2019. **Supplemental Table S9:** Change in eGFRcys across day 1 of the mid-season study interval by non-steroidal anti-inflammatory agent (NSAIA) use and urine osmolality, Wildland Firefighter Exposure and Health Effect Study, 2019.