Applied Physiology, Nutrition, and Metabolism

OPEN ACCESS | Research Article

The effect of consuming a sucrose-containing sports drink on acute kidney injury risk during a 4 h simulated occupational heat stress

Maxime Jeanovitch Lignier[a], Hayden W. Hess[a,b], Jessica A. Freemas[a], Blair D. Johnson[a,c], David Hostler[b], and Zachary J. Schlader[a,c]

[a]Department of Kinesiology, Indiana University School of Public Health – Bloomington, Bloomington, IN, USA; [b]Center for Research and Education in Special Environments, Department of Exercise and Nutrition Sciences, University at Buffalo, Buffalo, NY, USA; [c]Nutrition and Exercise Research Center, Indiana University School of Public Health – Bloomington, Bloomington, IN, USA

Corresponding author: **Zachary J. Schlader** (email: zschlade@iu.edu)

Abstract

Occupational heat stress increases acute kidney injury risk. Drinking a soft drink sweetened with high fructose corn syrup further elevates this acute kidney injury risk. However, the impact of sucrose, another fructose-containing sweetener, on acute kidney injury risk remains unexplored. We tested the hypothesis that drinking a sucrose-containing sports drink increases acute kidney injury risk when compared to drinking a sugar-free sports drink during 4 h of simulated occupational heat stress. Ten healthy adults consumed a sucrose-containing or sugar-free sport drink ad libitum during 4 h exposures to wet bulb globe temperatures of ∼28 °C. Thirty min of work and 30 min of rest were completed each hour. Work involved treadmill walking at a fixed rate of metabolic heat production (sucrose-containing: 6.0 ± 1.2 W/kg, sugar-free: 5.5 ± 0.9 W/kg, $p = 0.267$). The product of urinary insulin-like growth factor-binding protein 7 and tissue inhibitor of metalloproteinase-2, normalized to urine specific gravity ($[IGFBP7{\cdot}TIMP\text{-}2]_{USG}$), provided an acute kidney injury risk index. Mean core (intestinal: $n = 13$, rectal: $n = 7$) temperature (sucrose-containing: 37.5 ± 0.1 °C, sugar-free: 37.5 ± 0.3 °C; $p = 0.914$), peak core temperature (sucrose-containing: 37.8 ± 0.2 °C, sugar-free: 37.9 ± 0.3 °C; $p = 0.398$), and percent changes in body mass (sucrose-containing: −0.5 ± 0.4%, sugar-free: −0.3 ± 0.6%; $p = 0.386$) did not differ between groups. $[IGFBP7{\cdot}TIMP\text{-}2]_{USG}$ increased in both groups (time effect: $p = 0.025$) with no drink ($p = 0.675$) or interaction ($p = 0.715$) effects. Peak change $[IGFBP7{\cdot}TIMP\text{-}2]_{USG}$ did not differ between sucrose-containing (median 0.0116 [−0.0012, 0.1760] $(ng/mL)^2/1000$) and sugar-free (median 0.0021 [0.0003, 0.2077] $(ng/mL)^2/1000$; $p = 0.796$). Sucrose-containing sports drink consumption during simulated occupational heat stress does not modify acute kidney injury risk when compared to sugar free-sport drink consumption.

Key words: fructose, sucrose, polyol-fructokinase, hyperthermia, dehydration, AKI

Introduction

With global warming, the severity and the frequency of heat waves are forecasted to continue increasing in the coming years (Redner and Petersen 2006; Wassel 2009). Outdoor workers often engage in physically demanding work and are regularly subjected to hot environmental conditions, which would put them at a greater risk of experiencing hyperthermia and dehydration (Ioannou et al. 2022). Hyperthermia, dehydration, and physical work can all independently cause a reduction in kidney function and elevate the risk of acute kidney injury (AKI), as assessed via elevations in biomarkers of AKI (Junglee et al. 2013; Laws et al. 2016; McDermott et al. 2018; Chapman et al. 2020).

Studies conducted in rodents (Roncal Jimenez et al. 2014) and humans (Chapman et al. 2020) demonstrate that drinking water to offset body fluid losses due to sweating reduces the risk of AKI when doing physical work in the heat. The mechanism by which fluid replacement attenuates AKI risk is likely two-fold: (1) Better preservation of renal perfusion (via lower core temperatures and maintenance of plasma volume) and (2) Lower sodium reabsorption in the kidneys, the latter of which reduces ATP usage (Masoud et al. 2024), which has been shown to be a primary mechanism by which heat stress increases AKI risk (Sato et al. 2019).

To replace the electrolytes lost in sweat, occupational hydration recommendations recommend that workers consume sport drinks containing electrolytes when work duration in the heat exceeds 2 h (Jacklitsch et al. 2016). Sodium reabsorption in the kidneys has an energy cost (due to reliance on the Na^+/K^+ pump) and ingesting a sports drink could reduce the need to reabsorb sodium (Krisher et al. 2020; Masoud et al. 2024). That said, most sports drinks contain sugar to enhance intestinal fluid absorption (via glucose co-transportation), promote energy repletion and/or for taste

Table 1. Participant characteristics.

	Sucrose-containing	Sugar-free	*p*-value
Gender, *n*	5 women, 5 men	5 women, 5 men	—
Age, years	27 ± 5	28 ± 5	0.737
Height, cm	174 ± 9	172 ± 10	0.629
Weight, kg	72.7 ± 12.8	77.0 ± 16.8	0.524
Body mass index, kg/m^2	24.0 ± 3.3	25.8 ± 3.9	0.295
Body surface area, m^2	1.9 ± 0.2	1.9 ± 0.3	0.766

Note: Unpaired *t* test was used to examine differences between sucrose-containing and sugar-free for all variables. Data are presented as means ± SD. Data are $n = 10$ in each group.

(Baker and Jeukendrup 2014). Importantly, sugar containing drinks may exacerbate the risk of AKI due to the high energy cost of fructose metabolism in the kidneys caused by activation of the polyol-fructokinase pathway (Chapman et al. 2019; Schlader et al. 2019; Masoud et al. 2024). As such, rehydrating with a soft drink (or soft drink like) beverage sweetened with high fructose corn syrup (HFCS) (55%–60% fructose and 40%–45% glucose) has been shown to elevate AKI risk in both rodents (García-Arroyo et al. 2016) and humans (Chapman et al. 2019). However, more recent work has indicated that AKI risk during simulated occupational heat stress did not differ when rehydrating with a sports drink sweetened with HFCS compared to rehydrating with water containing a noncaloric sweetener (Atkins et al. 2024). In explanation of their findings, the authors highlighted that there may be an absolute fructose threshold that, unless it is reached, fructose does not exert a meaningful impact on heat-induced AKI risk, which could occur alongside or independent of the ratio of fructose to glucose. That said, this previous study employed only 2 h of simulated occupational heat stress. Thus, these findings may not reflect longer duration occupational heat stress scenarios, which likely exerts a larger challenge to the kidneys. Moreover, it is unknown if similar findings translate to commercially available sports drinks primarily sweetened with sucrose—a disaccharide containing 50% glucose and 50% fructose. Therefore, the purpose of this study was to test the hypothesis that drinking a sucrose-containing sports drink increases AKI risk to a greater extent during 4 h of simulated occupational heat stress when compared to drinking a sugar-free sports drink.

Methods

Ethical approval

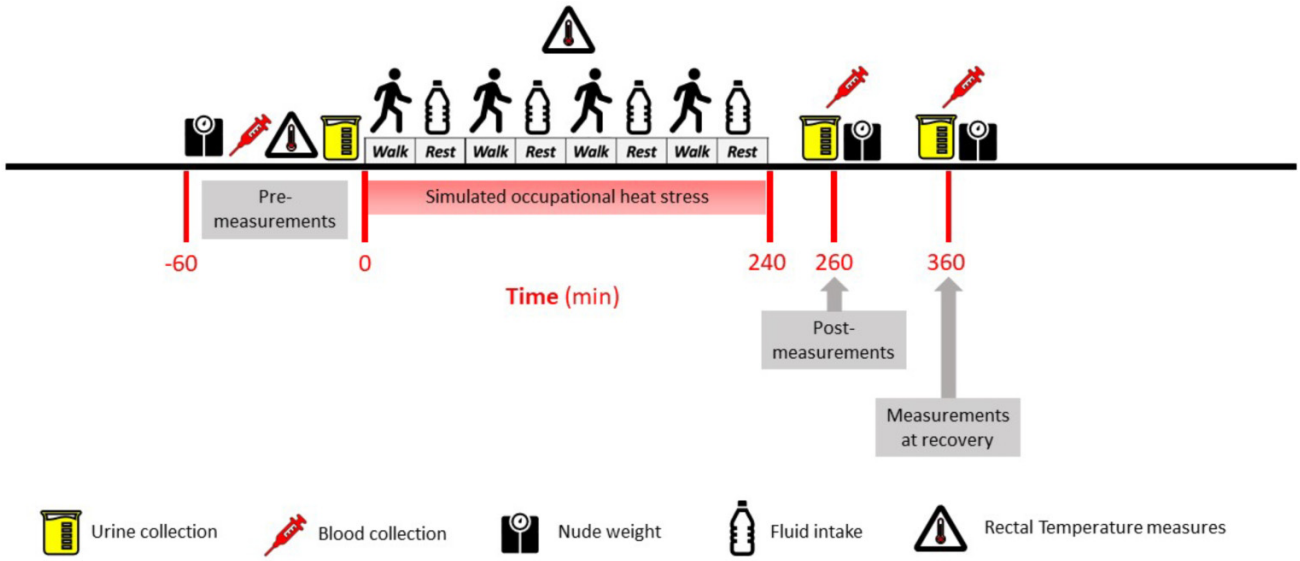
This retrospective analysis involves data collected as part of two studies approved by the Institutional Review Board at Indiana University (IRB#s: 1902420140 and 2004319694) and conformed to the Declaration of Helsinki. Each participant was fully informed of the experimental procedures and possible risks before giving their written consent. The data presented here were collected as part of two previously published studies (Freemas et al. 2023; Hess et al. 2023), but not all data have been presented previously. The present study tested a unique hypothesis, which was made possible because the two studies employed the same methods except that in one of the studies participants drank a sugar-free sports drink (Gatorade Zero) (Freemas et al. 2023) and in the other they drank a sucrose-containing sports drink (Gatorade G2) (Hess et al. 2023).

Participants

To determine sample size, effect size was calculated from the differences in urinary neutrophil gelatinase associated lipocalin (NGAL), an AKI risk biomarker, between soft drink rehydration and water rehydration trials in our previous work (Chapman et al. 2019). Urinary NGAL was used as the variable to determine the sample in the current study because urinary NGAL is a marker of AKI risk (Schaub and Parikh 2016). Notably, we have found urinary NGAL to be strongly and positively correlated ($r = 0.745$, $p < 0.001$, unpublished observations) with our primary outcome variable, the product of urinary IGFBP7 and TIMP-2 ([IGFBP7 · TIMP-2]). Further details regarding the primary outcome variable are provided below. Using this effect size ($f = 0.365$), $\alpha = 0.05$, $1 - \beta = 0.80$, and a moderate correlation coefficient between repeated measures ($r = 0.3$), the calculated total sample size needed to detect a significant within–between interaction using a mixed-model Analysis of variance (ANOVA) (the a priori primary analysis) was 20 participants, 10 in each group (G*Power 3.1.9.7). Thus, this study involved an analysis of twenty healthy adults, ten participants in the sugar-free group and ten in the sucrose-containing group. Each participant only completed one study. These participants were specifically selected so that they were matched for gender, age, height, weight, body surface area, and the rate of metabolic heat production. Participant selection was made before statistical analysis of AKI risk. This was determined a priori. Importantly, unpublished data from our laboratory indicate that with this effect size and sample size we would expect to identify differences between conditions in our primary outcome variable ([IGFBP7 · TIMP-2]) of ~0.54 (ng/mL)^2/1000.

Participant characteristics can be found in Table 1. All participants reported being physically active, nonsmokers, and free from any known cardiovascular, renal, metabolic, neurological, or gastrointestinal disease. Women were not pregnant and self-reported to be normally menstruating. Women in the sucrose-containing group were tested at any point during their menstrual cycle. Women in the sugar-free group were in their early follicular phase.

Fig. 1. Schematic representation of the experiment.



Experimental protocol

The timeline of the experimental visit can be found in Fig. 1. In all instances, participants arrived at the laboratory after abstaining from exercise and caffeine for 12 h, alcohol for 24 h, and food for 2 h. Participants were encouraged to maintain their normal diet and to arrive at the laboratory well hydrated. Upon arrival at the laboratory participants voided their bladder and euhydration was confirmed (i.e., urine specific gravity (USG) $\leq$ 1.020). After urine collection, participants in the sucrose-containing group drank 363 $\pm$ 62 mL of cool tap water (0.5% of body mass) and participants in the sugar-free group consumed 250 mL of cool tap water. Participants were then instrumented with a heart rate monitor. Following 20 min of supine rest, pre-exercise measurements of heart rate, blood pressure, and core temperature were collected. The first venous blood sample was then collected, and participants voided their bladder. They then measured their nude body weight and donned long work pants and a long-sleeved shirt, a short-sleeve cotton undershirt, and athletic shoes.

Following pre-exercise measurements, participants entered the environmental chamber set to elicit a wet bulb globe temperature (WBGT) of ~28 °C (sucrose-containing: 34 $\pm$ 0 °C dry bulb temperature, 48 $\pm$ 1% relative humidity; sugar-free: 34 $\pm$ 0 °C dry bulb temperature, 54 $\pm$ 1% relative humidity). These environmental conditions are commonly encountered by outdoors workers in the Southeast U.S. (Chapman et al. 2021*a*) (Table 2). Participants then completed a 4 h occupational heat stress simulation, corresponding to approximately half a typical workday. Participants walked on a treadmill for 30 min per hour with an intensity corresponding to a target absolute rate of metabolic heat production ($\dot{H}$prod) of ~430 W. Based on the Compendium of Physical Activities (Ainsworth et al. 2011), this $\dot{H}$prod is the average workload encountered in outdoor occupational settings that are regularly exposed to heat stress. The employed 1:1 work-rest ratio is in accordance with NIOSH guidelines for the employed WBGT and $\dot{H}$prod (Jacklitsch et al. 2016). Throughout each rest period, participants remained seated on a mesh chair inside the environmental chamber. Participants were permitted to drink fluids ad libitum throughout. The sucrose-containing group participants were given a flavor preferred sucrose-containing sport drinks (Gatorade G2) whereas the sugar-free group participants were given a flavor preferred sugar free sports drink (Gatorade Zero). In all instances, the temperature of the drinks was 10–15 °C. Gatorade G2 had a measured osmolality of 255 $\pm$ 3 mOsm/kg whereas Gatorade Zero had a measured osmolality of 56 $\pm$ 2 mOsm/kg. The calculated total fructose load for the sucrose-containing group averaged 50 $\pm$ 17 g, while the sugar-free group did not consume any fructose. After the simulated occupational heat stress, participants weighed themselves nude, voided their bladder, and then rested supine for 20 min before a venous blood sample was collected. Participants then rested for another ~60 min before urine and venous blood sampling was repeated.

Table 2. Average metabolic heat production and WBGT.

	Sucrose-containing	Sugar-free	*p*-value
$\dot{H}$prod, W	429 $\pm$ 51	414 $\pm$ 55	0.539
$\dot{H}$prod, W/kg	6.0 $\pm$ 1.2	5.5 $\pm$ 0.9	0.267
WBGT, °C	28 $\pm$ 0	28 $\pm$ 1	0.135

Note: Unpaired *t* test was used to examine differences between sucrose-containing and sugar-free for all variables. Data are presented as means $\pm$ SD. Data are $n = 10$ in each group. $\dot{H}$prod: Rate of metabolic heat production, WBGT: wet bulb globe temperature.

Instrumentation and measurements

Core temperature was measured continuously using a telemetry pill (HQ Inc.) swallowed approximately 6–8 h before each experimental trial ($n = 7$ for sucrose-containing and

$n = 6$ for sugar-free) or a rectal temperature probe inserted approximately 10 cm beyond the sphincter ($n = 3$ for sucrose-containing and $n = 4$ for sugar-free). Heart rate was continuously measured using a Polar (Bethpage, NY) heart rate monitor. Blood pressure was measured manually at rest and during exercise throughout the occupational heat stress simulation every 15 min. Mean arterial pressure was calculated as diastolic pressure plus 1/3 pulse pressure. USG was measured using refractometry (Atago, Tokyo, Japan). Urine volume divided by the time (minutes) between each bladder void was used to determine urine flow rate.

Serum and urinary creatinine in the sucrose-containing group was measured using human creatinine ELISA kits (Eagle Bioscience, Inc.). In the sugar-free group, serum and urinary creatinine was measured using a COBAS INTEGRA 400 + Analyzer (Roche Diagnostics). Creatinine clearance was calculated as urinary creatinine divided by serum creatinine multiplied by urine flow rate. Because creatinine was measured using different methods in the sugar-free and sucrose-containing groups, these data are presented as the absolute change from pre- to account for potential differences at pre-. Given these limitations, the serum and urinary creatinine and the creatinine clearance data are presented as supplemental data.

Insulin-like growth factor-binding protein 7 (IGFBP7) and tissue inhibitor metalloproteinase 2 (TIMP-2) were measured in urine using separate commercially available (RayBiotech Life) human IGFBP7 and TIMP-2 ELISA kits. The product of urinary IGFBP7 and TIMP-2 ([IGFBP7 · TIMP-2]) provided an index of AKI risk because it is approved by US Food and Drug Administration as an indicator of AKI risk in critically ill patients (Endre and Pickering 2014), which has recently been translated for use in the context of occupational heat stress (Chapman et al. 2021*b*; Hess et al. 2023). To account for differences in urine concentration, [IGFBP7 · TIMP-2] was normalized to USG (Cone et al. (2009)) (e.g., $[\text{IGFBP7} \cdot \text{TIMP-2}]_{\text{USG}}$) and is presented both over time and as the peak change (Δ) from pre-. Normalization of [IGFBP7 · TIMP-2] to USG has the advantage of correcting the biomarkers for urine concentration while maintaining the units, which aids interpretation. IGFBP7 and TIMP-2 were also reported separately normalized to USG ($\text{IGFBP7}_{\text{USG}}$ and $\text{TIMP-2}_{\text{USG}}$) and urine flow rate ($\text{IGFBP7}_{\text{UFR}}$ and $\text{TIMP-2}_{\text{UFR}}$) as has been done previously (Chapman et al. 2021*b*; Hess et al. 2022) to provide an index of the location of potential injury (e.g., IGFBP7 – proximal tubule; TIMP-2 – distal tubule (Emlet et al. 2017).

Whole body sweat rate was calculated from changes in nude body weight after correcting for fluid intake and urine output and dividing by the time of exposure. Absolute $\dot{H}$prod was estimated using indirect calorimetry (Parvo Medics, Salt Lake City, UT) (Cramer and Jay 2019) and is also presented as normalized to body mass (W/kg), which reduces between participant variability when comparing independent groups (Cramer and Jay 2019).

Sodium concentration in urine and plasma was measured using a commercially available system (Medica Corporation, Bedford, MA). Fractional excretion of sodium was calculated from the concentration of sodium in serum and urine and from the change in serum and urine creatinine concentration (Chapman et al. 2021*b*). Percent changes in plasma volume were calculated from changes in hemoglobin and hematocrit (Dill and Costill 1974). Plasma and urine osmolality were measured in duplicate via freezing-point depression osmometry (Advanced Instruments, Norwood, MA). Free water clearance was calculated as urine flow rate × (1 − (urine osmolality/plasma osmolality)). All blood and urine analyses were carried out in duplicate.

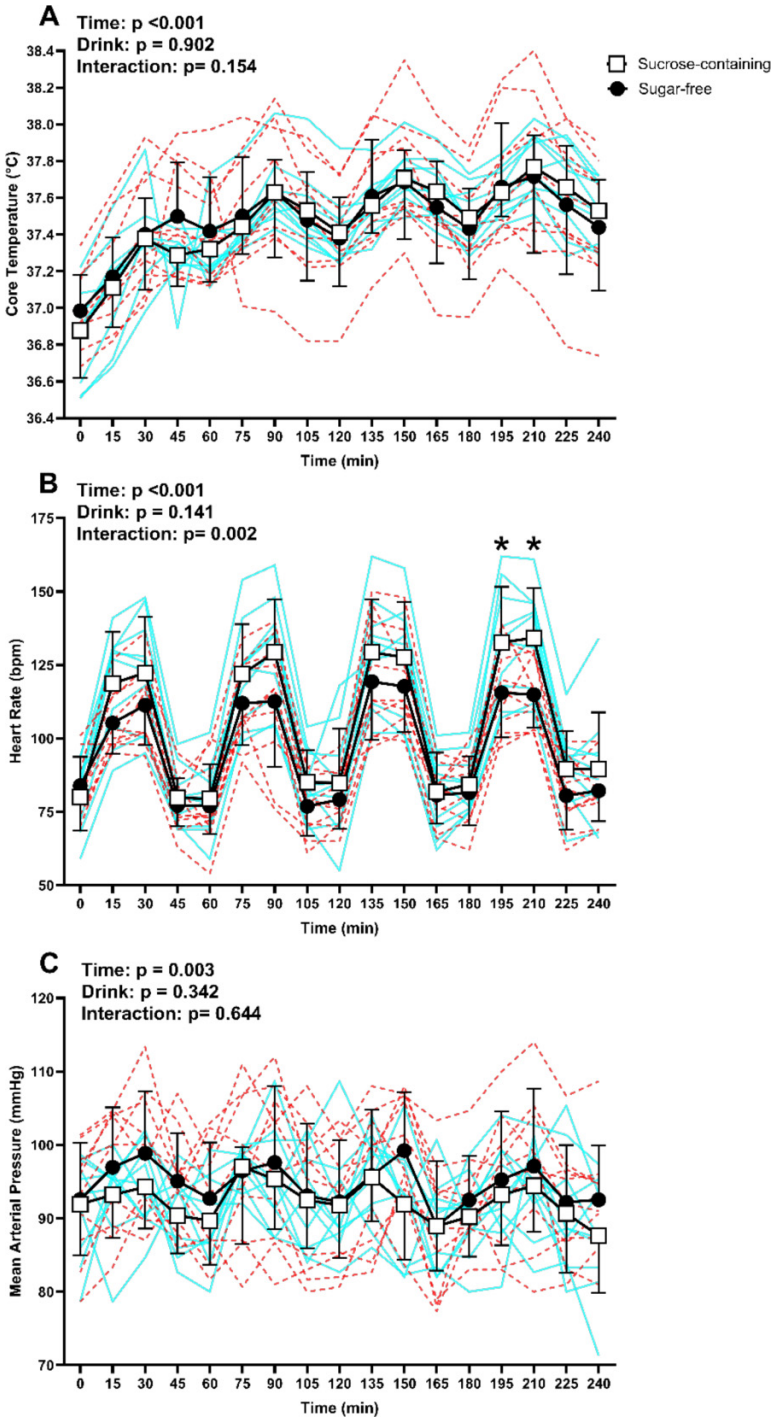
Data and statistical analysis

All data were collected pre- and post-occupational heat stress and during the recovery period except for rectal temperature, heart rate, and blood pressure, which were measured at rest and then every 15 min throughout the 4 h simulated occupation heat stress period. Participant characteristics (e.g., age, height, weight, etc.), mean WBGT, $\dot{H}$prod, peak core temperature, mean core temperature, percent changes in body weight, and sweat rate during simulated occupational heat stress were compared between groups using unpaired t-tests. Inspection of the residuals indicated that fluid intake and peak Δ $[\text{IGFBP7} \cdot \text{TIMP-2}]_{\text{USG}}$ data were not normally distributed. These data were not log transformed due to the prevalence of negative peak Δ $[\text{IGFBP7} \cdot \text{TIMP-2}]_{\text{USG}}$ data. Rather, these data were analyzed using non-parametric Mann–Whitney tests. Moreover, the residuals for all IGFBP7 and TIMP-2, and $[\text{IGFBP7} \cdot \text{TIMP-2}]_{\text{USG}}$ data over time were not normally distributed. In these instances, data were $\log_{10}$ transformed prior to analysis, which normalized the residuals. Data collected over time were analyzed using two-way linear mixed models with one between (drink) and one within (time) factor. When the assumption of sphericity was violated, the Geisser-Greenhouse correction was applied. Post hoc multiple comparisons were performed when a significant interaction effect was found using Sidak's test, which adjusts for multiple comparisons. A priori statistical significance was set at $p \leq 0.05$. Data are presented as individual values and mean ± SD or median (interquartile range) for not normally distributed data. For data analyzed using parametric statistical tests, pairwise comparisons are reported as the mean difference and the 95% confidence interval. For data analyzed using non-parametric statistical tests, pairwise comparisons are reported as the Hodges–Lehmann difference and the 95% confidence interval. Data were analyzed with GraphPad Prism software (version 10.2.1).

Results

Core temperature, heart rate, and mean arterial pressure data can be found in Fig. 2. Core temperature increased over time in both groups ($p < 0.001$) (Fig. 2A), but the increase in core temperature did not differ between drinks ($p = 0.902$) and no interaction effect was found ($p = 0.154$). Mean core temperature was 37.5 ± 0.1 °C for the sucrose-containing group and 37.5 ± 0.3 °C for the sugar-free group. The mean difference between the groups was 0.0 [−0.2, 0.2] °C ($p = 0.914$). Peak core temperature was 37.8 ± 0.2 °C for the sucrose-containing group and 37.9 ± 0.3°C for the sugar-free group. The mean difference between the groups was 0.1 [−0.1, 0.3] °C ($p = 0.398$). Heart rate increased over time (main

Fig. 2. Core temperature (A), heart rate (B), and mean arterial pressure (C) in the sucrose-containing and sugar-free groups during simulated occupational heat stress. Pre- resting data upon entry into the chamber is 0 min. Timepoints 60, 120, 180, and 240 min are end rest while timepoints 30, 90, 150, and 210 min are end exercise. Blue lines represent individual data points for sucrose-containing. Red lines represent individual data points for sugar-free. *Sucrose-containing significantly different from sugar-free ($p \leq 0.0435$). Data are presented as means ± SD and were analyzed using a two-way linear mixed model with one between (drink) and one within (time) factor. When a significant interaction was identified pairwise comparisons were carried out using Sidak's test.



effect of time: $p < 0.001$), and while there was no effect of drinks ($p = 0.141$), a significant interaction effect was observed ($p = 0.002$) (Fig. 2B). There was a significant effect of time in both groups ($p = 0.003$) for mean arterial pressure, there were no differences between drinks ($p = 0.342$) and no interaction effect ($p = 0.644$) (Fig. 2C).

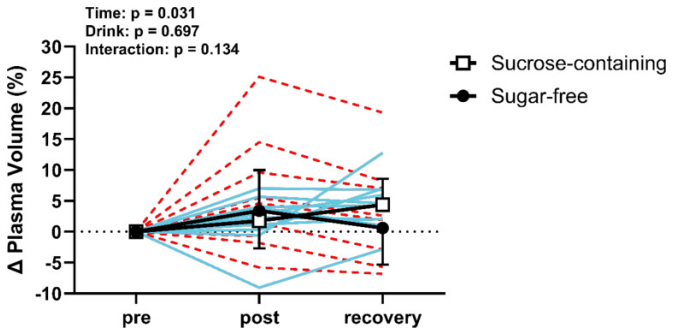
Markers of hydration status can be found in Table 3. Median fluid intake was 1530 (1199, 2040) mL for the sucrose-

Table 3. Fluid balance measures.

	Sucrose-containing	Sugar-free	*p*-value
Fluid intake, mL	1530 (1199, 2040)	1644 (1515, 1966)	0.481
Δ body mass, %	−0.5 ± 0.4	−0.3 ± 0.6	0.386
Sweat rate, L/h	0.2 ± 0.1	0.3 ± 0.1	0.073

Note: Unpaired *t* test was used to examine differences between sucrose-containing and sugar-free for the change in body mass and sweat rate. The Mann–Whitney test was used for fluid intake data. Unless stated below data are presented as means ± SD. Fluid intake data are presented as median (interquartile range). Data are $n = 10$ in each group. Δ indicates change from pre-.

Fig. 3. Percent changes in plasma volume in the sucrose-containing group and the sugar-free group at pre-, post- and at recovery following simulated occupational heat stress. Blue lines represent individual data points for sucrose-containing. Red lines represent individual data points for sugar-free. Data are presented as means ± SD and were analyzed using a two-way linear mixed model with one between (drink) and one within (time) factor. For sugar-free, $n = 9$ at pre- and post- and $n = 8$ at recovery. Δ indicates change from pre-.



containing group and 1644 (1515, 1966) mL for the sugar-free group, with a Hodges–Lehmann difference of 198 [−296, 650] mL (p = 0.481). The mean difference in sweat rate between groups was 0.1 [−0.0, 0.2] L/h ($p = 0.073$). Thus, the percent changes in body mass did not differ significantly between both groups ($p = 0.386$, mean difference in percent changes in body mass 0.2 [−0.3, 0.7]%).

Percent changes in plasma volume are presented in Fig. 3. There was a significant main effect of time ($p = 0.031$), but no significant main effect of drink ($p = 0.697$) or interaction effect ($p = 0.134$)

Markers of kidney function can be found in Table 4. There was a significant main effect of time for the fractional excretion of sodium ($p = 0.001$), but no significant main effect of drink ($p = 0.156$) or interaction effect ($p = 0.877$). There was no significant main effect of time ($p = 0.114$), drink ($p = 0.555$), or interaction effect ($p = 0.808$) on free water clearance. There was a significant main effect of time on urine flow rate ($p = 0.004$), but no significant main effect of drink ($p = 0.320$) or interaction effect ($p = 0.620$). There was no significant time effect ($p = 0.285$) or drink effect ($p = 0.730$) for serum osmolality. There was however a significant interaction effect ($p = 0.009$). Post hoc analysis showed sucrose-containing to be significantly lower than sugar-free at pre- ($p = 0.038$) but serum osmolality did not differ between groups at any other timepoint ($p \geq 0.232$). There was a significant main effect of time ($p = 0.028$) but no significant drink ($p = 0.499$) or interaction ($p = 0.843$) effect for urine osmolality. There was no significant main effect of time ($p = 0.054$), drink ($p = 0.599$), or interaction effect ($p = 0.817$) on urine specific gravity.

Biomarkers of AKI risk can be found in Fig. 4. For $IGFBP7_{UFR}$ there was a significant main effect of time ($p = 0.001$), but no significant main effect of drink ($p = 0.521$) or interaction effect ($p = 0.418$) (Fig. 4A). For $IGFBP7_{USG}$, there was a significant main effect of time ($p = 0.025$), but no significant main effect of drink ($p = 0.292$) or interaction effect ($p = 0.698$) (Fig. 4B). When considering $TIMP\text{-}2_{UFR}$, there was a significant main effect of time ($p < 0.001$), but no significant main effect of drink ($p = 0.393$) or interaction effect ($p = 0.528$) (Fig. 4C). Similarly, for $TIMP2_{USG}$ there was a significant main effect of time ($p = 0.030$), but no significant main effect of drink ($p = 0.810$) or interaction effect ($p = 0.714$) (Fig. 4D).

$[IGFBP7 \cdot TIMP2]_{USG}$ and Peak Δ $[IGFBP7 \cdot TIMP\text{-}2]_{USG}$ can be found in Fig. 5. $[IGFBP7 \cdot TIMP2]_{USG}$ demonstrated a significant main effect of time ($p = 0.025$), but no significant main effect of drink ($p = 0.675$) or interaction effect ($p = 0.715$) (Fig. 5A). For Peak Δ $[IGFBP7 \cdot TIMP\text{-}2]_{USG}$ the median was 0.0116 (−0.0012, 0.1760) $(ng/mL)^2/1000$ for sucrose-containing and 0.0021 (0.0003, 0.2077) $(ng/mL)^2/1000$ for sugar-free, with a Hodges–Lehmann difference of 0.0007 [−0.1990, 0.0325] $(ng/mL)^2/1000$ ($p = 0.796$) (Fig. 5B).

Discussion

This study investigated the effects of consuming a sucrose-containing sports drink and a sugar-free sports drink on AKI risk when performing physical work in the heat for 4 h. Previous studies demonstrate that rehydrating with a soft drink sweetened with HFCS heightens AKI risk when working in the heat (García-Arroyo et al. 2016; Chapman et al. 2019). More recent evidence has shown that rehydrating with a sports drink sweetened with HFCS does not modify AKI risk during 2 h of physical work in the heat (Atkins et al. 2024). Whether this finding translated to a longer duration of simulated occupational heat stress, as often encountered by outdoor workers, remains unknown. Moreover, to our knowledge, no study has examined the effect of a sport drink containing sucrose, a disaccharide containing 50% glucose and 50% fructose, on AKI risk during occupational heat stress. In light of this previous work, we hypothesized that drinking a sucrose-containing sport drink would increase AKI risk compared to drinking a sugar-free sports drink during 4 h of simulated occupational heat stress. The data presented here do not support our hypothesis, as demonstrated by no significant differences in $[IGFBP7 \cdot TIMP\text{-}2]_{USG}$ between the sucrose-containing and sugar-free groups throughout simulated occupational heat stress (Fig. 5). Consistent with this finding, there were no differences in measures of kidney function (e.g., creatinine clearance, free water clearance, fractional excretion of sodium) between these two groups (Table 4). Therefore, drinking a sucrose-containing sports drink is unlikely to worsen the risk of AKI during occupational heat stress compared to drinking a sugar-free sport drink.

Table 4. Markers of kidney function during simulated occupational heat stress.

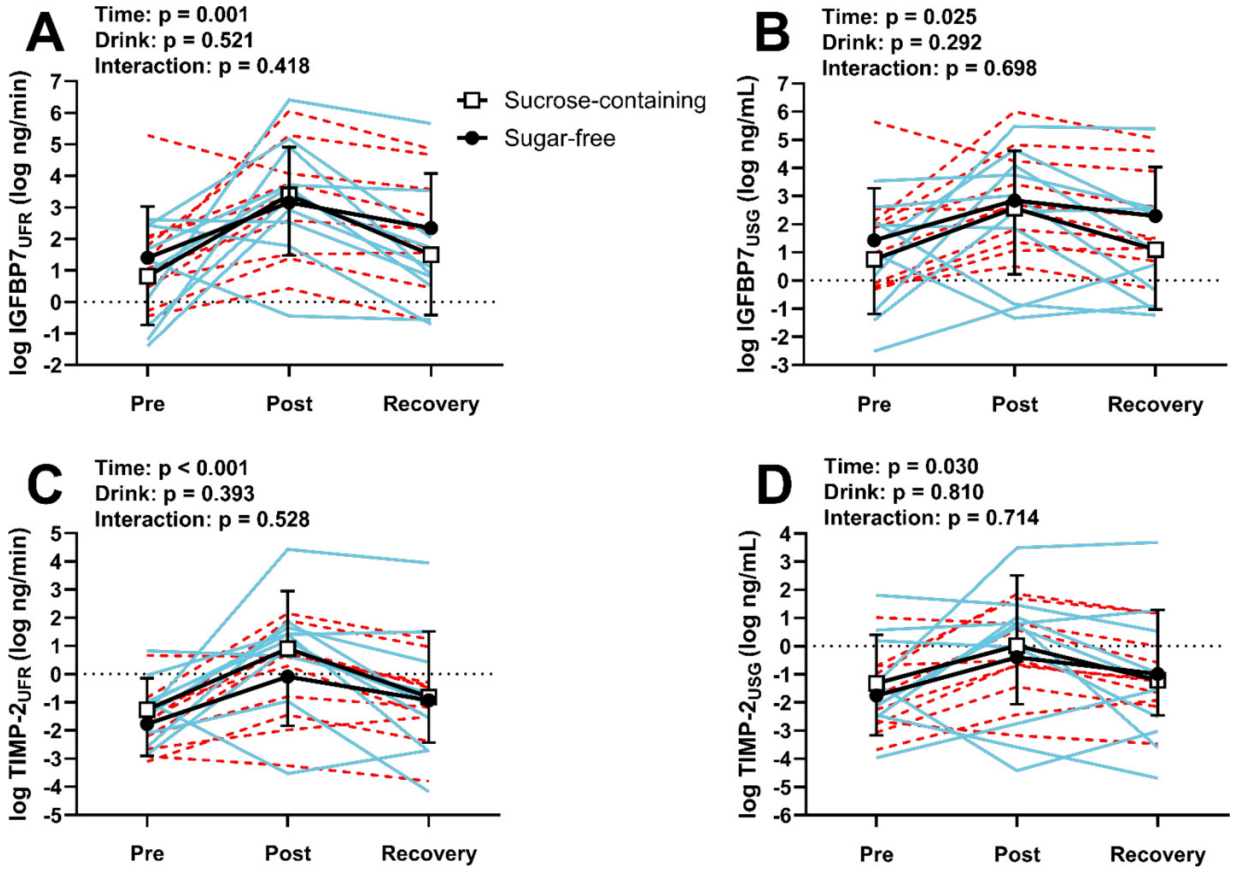
	Pre	Post	Recovery	*p*-values
Fractional excretion of sodium,%				Time: $p = 0.001$
Sucrose-containing	1.0 ± 0.5	0.5 ± 0.2	0.8 ± 0.5	Drink: $p = 0.156$
Sugar-free	1.2 ± 0.5	0.6 ± 0.3	1.0 ± 0.6	Interaction: $p = 0.877$
Free water clearance, mL/min				Time: $p = 0.114$
Sucrose-containing	2.1 ± 3.1	0.7 ± 2.5	1.9 ± 3.5	Drink: $p = 0.555$
Sugar-free	3.3 ± 3.1	1.1 ± 3.1	1.9 ± 3.8	Interaction: $p = 0.808$
Urine flow rate, mL/min				Time: $p = 0.004$
Sucrose-containing	4.8 ± 3.1	1.8 ± 2.3	4.5 ± 3.6	Drink: $p = 0.320$
Sugar-free	6.3 ± 2.9	3.3 ± 3.1	4.6 ± 3.5	Interaction: $p = 0.620$
Serum osmolality, mOsm/kg				Time: $p = 0.285$
Sucrose-containing	289 ± 3*	290 ± 5	289 ± 4	Drink: $p = 0.730$
Sugar-free	292 ± 4	288 ± 4	289 ± 2	Interaction: p = 0.009
Urine osmolality, mOsm/kg				Time: $p = 0.028$
Sucrose-containing	253 ± 194	408 ± 234	270 ± 250	Drink: $p = 0.499$
Sugar-free	200 ± 181	328 ± 231	251 ± 180	Interaction: $p = 0.843$
Urine specific gravity				Time: $p = 0.054$
Sucrose-containing	1.006 ± 0.005	1.011 ± 0.008	1.007 ± 0.008	Drink: $p = 0.599$
Sugar-free	1.006 ± 0.005	1.009 ± 0.006	1.007 ± 0.005	Interaction: $p = 0.817$

Note: Data are presented as means ± SD and were analyzed using a two-way linear mixed model with one between (drink) and one within (time) factor. When a significant interaction was identified pairwise comparisons were carried out using Sidak's test. *Sucrose-containing significantly different from sugar-free ($p = 0.0380$). Unless stated below, $n = 10$ for each group at all timepoints. Fractional excretion of sodium: $n = 9$ at post and recovery for sucrose-containing, $n = 8$ at recovery for sugar-free. Free water clearance: $n = 9$ at post for sucrose-containing, and $n = 9$ at pre and recovery for sugar-free. Serum osmolality: $n = 9$ at post for sucrose-containing and $n = 9$ at pre and recovery for sugar-free. Urine specific gravity: $n = 9$ at post for sucrose-containing. Δ indicates change from pre-.

Both the sucrose-containing and sugar-free groups demonstrated an increase in $[IGFBP7 \cdot TIMP\text{-}2]_{USG}$ with simulated occupational heat stress (Fig. 5). Increases in $[IGFBP7 \cdot TIMP\text{-}2]_{USG}$ were due to elevations in both IGFBP7 and TIMP-2, a finding that persisted independent of normalization of the urinary biomarkers to USG or UFR (Fig. 4). These findings are in accordance with previous work examining AKI risk during physical work in the heat over 2–4 h (Chapman et al. 2020; Hess et al. 2023). Our participants performed intermittent exercise in an ~28 °C WBGT environment, which was sufficient to cause hyperthermia as reflected by the increases in core temperatures (Fig. 2A). We did not measure renal blood flow during the simulated occupational heat stress in this study, but it is well established that exercise (i.e., physical work) leads to a reduction in renal blood flow (Barclay et al. 1947; Kenney and Zappe 1994), with such reductions being due to sympathetic activation, and the activation of the renin-angiotensin system, and the release of vasopressin (Tidgren et al. 1991; Chapman et al. 2021*b*). It is also well established that hyperthermia can independently decrease renal blood flow (Radigan and Robinson 1949), with dehydration further reducing blood flow to the kidneys (Smith et al. 1952). Furthermore, dehydration increases sodium reabsorption, which is ATP dependent (Doucet 1988; Schlader et al. 2019) The fractional excretion of sodium decreased with simulated occupational heat stress in the present study (Table 4), which is suggestive of increased sodium reabsorption. Thus, reductions in renal blood flow (particularly to the renal cortex) and increases in sodium reabsorption can increase renal ATP depletion (Sato et al. 2019), which has been hypothesized to increase AKI risk (Schlader et al. 2019). The participants in our study remained hydrated throughout the exposure as highlighted by their increase in plasma volume from pre- (Fig. 3) and the small reduction in body mass (Table 3). This suggests that dehydration likely had little influence on AKI risk in the present study, and that hyperthermia and physical work were the predominant factors in the observed $[IGFBP7 \cdot TIMP\text{-}2]_{USG}$ increase.

Despite the increased $[IGFBP7 \cdot TIMP\text{-}2]_{USG}$, no differences from pre- were found for several kidney function markers (e.g., creatinine clearance, free water clearance). Reductions in creatinine clearance were to be expected when exercising in the heat (Radigan and Robinson 1949) but such reductions can be attenuated if dehydration is prevented (Smith et al. 1952). The finding that our participants remained well-hydrated may explain the lack of change in creatinine clearance and other markers of kidney function. This suggests that the elevated AKI risk assessed by the increase in $[IGFBP7 \cdot TIMP\text{-}2]_{USG}$ may not reflect reductions in kidney function per se. It is worth noting, however, that some other markers of reduced kidney function were observed (e.g., reduced urine flow rate, reduced fractional excretion of sodium). We contend, however, that these responses are primarily physiological in nature and do not reflect dysfunction per se. Interestingly, in opposition to the observations of Atkins et al. (2024), we observed a reduction in urine flow rate. We think this could be explained by the longer duration of simulated occupational heat stress used in our study (4 h vs. 2 h) in which the kidneys are under stress. Nevertheless, we observed increases in AKI risk, but changes in

Fig. 4. $IGFBP7_{UFR}$ (A), $IGFBP7_{USG}$ (B), $TIMP2_{UFR}$ (C), $TIMP_{USG}$ (D) in the sucrose-containing group and the sugar-free group at pre-, post- and at recovery following simulated occupational heat stress. Blue lines represent individual data points for sucrose-containing. Red lines represent individual data points for sugar-free. Data are presented as means ± SD and were analyzed using a two-way linear mixed model with one between (drink) and one within (time) factor. Data were log transformed before analysis. $n = 10$ for each group and all timepoints, except for Figs. 4B and4D where $n = 9$ at post- in sucrose-containing. IGFBP7—Insulin-like growth factor-binding protein 7, TIMP-2—tissue inhibitor metalloproteinase 2, USG—urine specific gravity, UFR—urine flow rate.

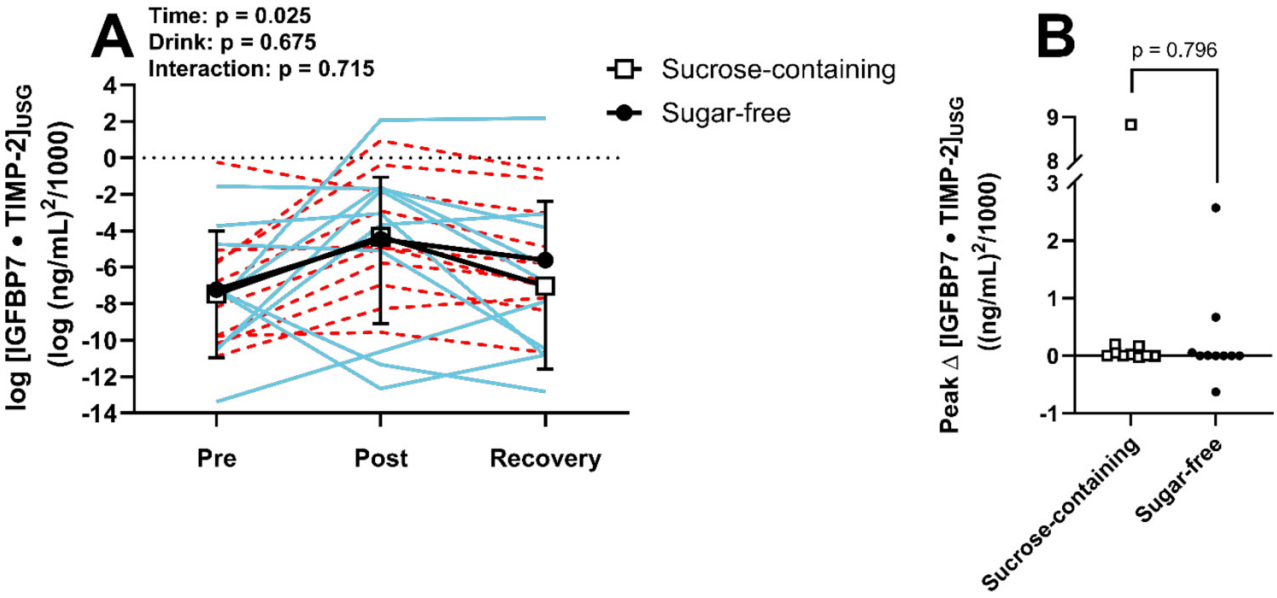


$[IGFBP7 \cdot TIMP\text{-}2]_{USG}$ did not parallel reductions in kidney function.

While both groups had a significant increase in $[IGFBP7 \cdot TIMP\text{-}2]_{USG}$, the increase did not differ between sucrose-containing and sugar-free groups (Fig. 5). There were also no differences in IGFBP7 and TIMP-2 independently, and this persisted whether they were normalized to USG or to UFR (Fig. 4). This is in contradiction with previous studies showing that soft drink consumption in the heat elevates AKI risk in humans (Chapman et al. 2019) and rodents (García-Arroyo et al. 2016). Our findings, however, concur with the study of Atkins et al. (2024), which found no differences in AKI risk when rehydrating with a sport drink sweetened with HFCS compared to rehydrating with water containing a noncaloric sweetener. Ingestion of fructose could lead to heightened vasopressin release (Song et al. 2017) and/or the activation of the energy dependent polyol-fructokinase pathway (García-Arroyo et al. 2016) which could exacerbate the depletion of ATP in the kidneys (Roncal-Jimenez et al. 2016; Chapman et al. 2019). Atkins et al. (2024) theorized that there may be a fructose load threshold that needs to be reached before any significant differences in AKI risk can be seen during or following occupational heat stress. To this point, it was highlighted that previous studies administered a total load of 276 g of fructose (Chapman et al. 2019), whereas Atkins et al. (2024) administered a more moderate amount of fructose (~145 g total). In our study, the calculated fructose load was ~50 g, which is ~3× less than that in Atkins et al. (2024) and ~6× less than previous studies in which participants drank soft drinks sweetened with HFCS (Chapman et al. 2019). Thus, the relatively small fructose load could explain the lack of differences between our groups.

We would be remiss not to address the potential importance of beverage osmolality as a factor modifying AKI risk during occupational heat stress. The soft drink used previously was extremely hyperosmotic (~834 mOsm/kg), resulting in a contraction in plasma volume (Chapman et al. 2019). A sport drink sweetened with HFCS has approximately half the osmotic load of a soft drink (~420 mOsm/kg; Atkins et al. 2024). Thus, a role for beverage osmolality in modifying AKI risk may be likely. Indeed, ingesting a hyperos-

Fig. 5. $[IGFBP7 \cdot TIMP2]_{USG}$ in the sucrose-containing group and the sugar-free group at pre-, post-, and at recovery following simulated occupational heat stress (A) and peak Δ $[IGFBP7 \cdot TIMP2]_{USG}$ in the sucrose-containing group and the sugar-free group (B). Blue lines represent individual data points for sucrose-containing. Red lines represent individual data points for sugar-free. $n = 10$ for each group and all timepoints except in A where $n = 9$ at post for sucrose-containing. (A) Data are presented as means $\pm$ SD and was analyzed using a two-way linear mixed model with one between (drink) and one within (time) factor. (B) Data are presented as medians and was analyzed using a Mann–Whitney test. Δ indicates change from pre-, IGFBP7—Insulin-like growth factor-binding protein 7, TIMP-2—tissue inhibitor metalloproteinase 2, USG—urine specific gravity.



motic beverage leads to plasma volume contraction as more water is drawn into the intestinal tract (Evans et al. 2009). Increases in plasma osmolality and reductions in plasma volume leads to the release of angiotensin II, via activation of the renin-angiotensin aldosterone system, and the release of vasopressin (Sparks et al. 2014). Angiotensin II release causes sodium reabsorption (Cogan 1990; Coppola and Frömter 1994), vasoconstriction in the renal afferent and efferent arterioles (Casellas et al. 1990; Ito et al. 1995), and the release of aldosterone (leading to more sodium reabsorption) (Spät and Hunyady 2004). Vasopressin increases water reabsorption (Danziger and Zeidel 2015) and induces vasoconstriction of the efferent kidney arterioles (Skorecki et al. 2011). In the present study, the sucrose-containing group consumed a nearly isosmotic spork drink (~255 mOsm/kg). Given that changes in plasma volume did not differ between sucrose-containing and sugar-free (Fig. 3), despite differing in beverage osmolality (255 mOsm/kg vs. 56 mOsm/kg, respectively), it is likely that the fluid regulatory response was not different between these two groups. This is supported by evidence that the fluid conservation responses did not differ between groups (Table 4). With this background, perhaps it is not surprising that AKI risk did not differ between sugar-free and sucrose-containing, despite differences in the fructose load, especially given that optimal rehydrating ability of iso- and hypo- osmotic beverages (Rowlands et al. 2022). That said, future research should examine the role of fructose, independent of beverage osmolality, on AKI risk during occupational heat stress.

Limitations

The present study was retrospective in nature and employed a between-subjects study design. We made all efforts to ensure that that the analysis was appropriately powered and the groups were well matched for individual characteristics, including $\dot{H}$prod (W/kg), which is beneficial with regards to making between group comparisons (Cramer and Jay 2014). For these reasons, we believe that this study provides a valid comparison of drinking a sucrose-containing sports drink to drinking a sugar-free sports drink during 4 h of simulated occupational heat stress. However, we acknowledge the limitations of the between-participant study design, as ideally, we would have employed a double-blind within-participant design. We employed a 4 h simulated occupational heat stress scenario. Thus, a limitation is that this duration is less than the 8–10 h work shift typical of outdoor workers. Moreover, this study did not consider the impact of consecutive workdays, which could potentially exacerbate the risk of AKI when consuming sports drinks. Furthermore, our participants were healthy younger adults. This population may not represent that of the typical outdoor worker, which may be older and have underlying medical conditions. Finally, we would be remiss not to acknowledge the potential for conscious or subconscious bias with regards to our participant selection. That said, we believe the potential for bias was limited by our a priori plan for participant selection, in which participants were matched without regards for AKI risk.

Conclusion

The present study provided no evidence that consuming a sucrose-containing sports drink during 4 h of simulated occupational heat stress modifies AKI risk when compared to consuming a sugar-free sport drink. Future studies should focus on longer duration occupational heat stress and better delineate the roles of fructose load and beverage osmolality as factors that may contribute to AKI risk. That said, to date, there is little evidence that consuming sugar containing sport drinks during occupational heat stress negatively impacts AKI risk.

Acknowledgements

We would like to thank the people for participating in our study. Supported by R01OH011528.

Article information

History dates

Received: 6 June 2024
Accepted: 15 September 2024
Accepted manuscript online: 15 October 2024
Version of record online: 2 December 2024

Notes

This paper is part of a collection entitled "The Physiology of Extreme Temperatures: From Cold to Hot and Hazard to Health". https://cdnsciencepub.com/topic/apnm-extreme-temperature.

Data availability

Raw data are available upon reasonable request to the corresponding author.

Author information

Author ORCIDs

Hayden W. Hess https://orcid.org/0000-0002-8432-7208
David Hostler https://orcid.org/0000-0002-7711-4001
Zachary J. Schlader https://orcid.org/0000-0003-3590-3958

Author contributions

Conceptualization: HWH, JAF, BDJ, DH, ZJS
Data curation: HWH, JAF, ZJS
Formal analysis: MJL, HWH, ZJS
Funding acquisition: DH, ZJS
Investigation: MJL, BDJ, DH, ZJS
Methodology: JAF, BDJ, DH, ZJS
Project administration: BDJ, ZJS
Resources: BDJ, ZJS
Software: ZJS
Supervision: BDJ, ZJS
Validation: MJL, ZJS
Visualization: MJL, ZJS
Writing – original draft: MJL
Writing – review & editing: MJL, HWH, JAF, BDJ, DH, ZJS

Competing interests

ZJS has received consultant fees from Otsuka Holdings Co., Ltd. Otherwise, no other potential conflicts of interest, financial or otherwise, are declared by the authors.

Funding information

This study was funded by a grant from the United States Centers for Disease Control and Prevention, National Institute of Occupational Safety and Health (grant number: R01OH011528).

Supplementary material

Supplementary data are available with the article at https://doi.org/10.1139/apnm-2024-0261.

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