

Exertional heat stroke: nutritional considerations

Jason K. W. Lee^{1,2,3,4,5,6,7,8}  | Beverly Tan^{1,8} | Henry B. Ogden^{9,10} |
Shaun Chapman^{9,11} | Michael N. Sawka¹²

¹Human Potential Translational Research Program, Yong Loo Lin School of Medicine, National University of Singapore, Singapore

²Heat Resilience and Performance Centre, Yong Loo Lin School of Medicine, National University of Singapore, Singapore

³Department of Physiology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore

⁴N.1 Institute for Health, National University of Singapore, Singapore

⁵Global Asia Institute, National University of Singapore, Singapore

⁶Institute for Digital Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore

⁷Singapore Institute for Clinical Sciences, Agency for Science, Technology and Research (A*STAR), Singapore

⁸Campus for Research Excellence and Technological Enterprise (CREATE), Singapore, Singapore

⁹Army Recruit Health and Performance Research, Headquarters of Army Recruiting and Initial Training Command, Upavon, Pewsey, UK

¹⁰Department of Sport, Health and Wellbeing, Plymouth Marjon University, Plymouth, UK

¹¹Cambridge Centre for Sport and Exercise Sciences, School of Psychology and Sport Science, Anglia Ruskin University, Cambridge, UK

¹²School of Biological Sciences, Georgia Institute of Technology, Atlanta, GA, USA

Correspondence

Jason Kai Wei Lee, FACSM, Human Potential Translational Research Program, Yong Loo Lin School of Medicine, National University of Singapore, 2 Medical Drive, #04-20, Singapore 117593.

Email: pshjkw@nus.edu.sg

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Abstract

Exertional heat stroke (EHS) is a life-threatening illness and an enduring problem among athletes, military servicemen and -women, and occupational labourers who regularly perform strenuous activity, often under hot and humid conditions or when wearing personal protective equipment. Risk factors for EHS and mitigation strategies have generally focused on the environment, health status, clothing, heat acclimatization and aerobic conditioning, but the potential role of nutrition is largely underexplored. Various nutritional and dietary strategies have shown beneficial effects on exercise performance and health and are widely used by athletes and other physically active populations. There is also evidence that some of these practices may dampen the pathophysiological features of EHS, suggesting possible protection or abatement of injury severity. Promising candidates include carbohydrate ingestion, appropriate fluid intake and glutamine supplementation. Conversely, some nutritional factors and low energy availability may facilitate the development of EHS, and individuals should be cognizant of these. Therefore, the aims of this review are to present an overview of EHS along with its mechanisms and pathophysiology, discuss how selected nutritional considerations may influence EHS risk focusing on their impact

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on the key pathophysiological processes of EHS, and provide recommendations for future research. With climate change expected to increase EHS risk and incidence in the coming years, further investigation on how diet and nutrition may be optimized to protect against EHS would be highly beneficial.

KEYWORDS

exercise, heat stress, supplements

1 | INTRODUCTION

Excessive heat exposure can impose significant physiological strain and potentially result in heat-related illnesses. Heat stroke is the most severe manifestation of heat-related illnesses that can result in morbidity and mortality (Bouchama et al., 2022). Classic heat stroke results from passive environmental heat exposure and typically occurs in vulnerable and compromised populations (e.g., infants and elderly), whereas exertional heat stroke (EHS) impacts individuals engaged in physical activity in cool to hot environments (Epstein & Yanovich, 2019). Athletes, military servicemen and -women, and occupational labourers (e.g., firefighters, construction and agricultural workers) who regularly perform strenuous activities, often during high-heat stress conditions, are populations who report the highest prevalence of EHS (Epstein & Yanovich, 2019).

EHS is a leading cause of sudden non-traumatic death among athletes (Hosokawa et al., 2021; Kucera et al., 2020). Between 1995 and 2020, a total of 70 football players in the USA died of EHS (Kucera et al., 2020). Furthermore, the incidence of near-fatal EHS during endurance events in warm weather was reportedly 10 times greater than that for serious cardiac events (Yankelson et al., 2014). In military and occupational settings, the US armed forces reported 475 cases of EHS in 2020, while at least 285 heat-related deaths occurred among construction workers between 1992 and 2016 (Dong et al., 2019; US Armed Forces, 2021). Notably, the high prevalence and incidence of chronic kidney disease and kidney injury among agricultural workers may render this population more vulnerable to heat stress (Butler-Dawson et al., 2019; Johnson et al., 2019). As global mean temperatures and humidity and the number of extreme weather events continue to rise due to climate change, the incidence and risk of heat stroke is expected to increase as more individuals become exposed to dangerous levels of heat stress (Ebi et al., 2021).

Various risk factors for EHS and effective strategies for prevention and mitigation are available (Pryor et al., 2020). These typically focus on environmental conditions, health status, clothing, heat acclimatization and aerobic conditioning, but the potential role of nutrition is seldom considered, despite its importance in overall health. Thus, we will discuss how nutrition can influence the development of EHS, specifically in relation to its potential impact on the underlying mechanisms of EHS.

2 | EXERTIONAL HEAT STROKE

2.1 | Definition

Though one of the oldest recognized medical conditions, a universally accepted definition of EHS is still lacking (Laitano et al., 2019). EHS is commonly characterized by signs and symptoms of marked central nervous system disturbances (e.g., delirium, stupor, combativeness, unconsciousness) with high deep-tissue temperatures (usually, but not always, $>40^{\circ}\text{C}$) resulting from strenuous exercise, often in hot/humid environments (Roberts et al., 2021). Clinical signs of organ (e.g., kidney, liver) and tissue (e.g., gut, muscle) damage are also commonly observed (Bouchama et al., 2022). As a medical emergency, EHS can lead to multiple-organ failure and even death without early identification and rapid reversal of hyperthermia (Filep et al., 2020). Although most EHS victims survive, EHS can have long-term sequelae and adverse health effects (Wallace et al., 2007). Recent epidemiological data from heat stroke survivors show a ~ 2.5 times and 4.4 times increased risk of cardiovascular and kidney disease, respectively, during a 14-year follow-up (Tseng et al., 2019; Wang et al., 2019). Permanent neurological dysfunction has also been observed in $\sim 30\%$ of EHS survivors (Lawton et al., 2019; Yang et al., 2017). EHS is sometimes preventable and if victims undergo immediate cooling, the pathology can be markedly reduced (Filep et al., 2020; Roberts et al., 2021).

High motivation (e.g., during competitions) and peer or organizational pressure are theoretical risk factors of EHS as it can drive individuals to override internal cues (e.g., excessive fatigue, dizziness, nausea) to modify work rate or cease exercise and instead continue exerting themselves (Corbett et al., 2018; Epstein & Yanovich, 2019; Stacey et al., 2015). Other common risk factors include environmental conditions (e.g., high ambient heat and/or humidity), lack of heat acclimatization, low physical fitness and high body mass index (Westwood et al., 2021). However, EHS can impact low-risk persons who are apparently practicing sound heat mitigation procedures (Gardner & Kark, 2001; Stacey et al., 2015). EHS often occurs under conditions that the victim has been exposed to many times before or while others are concurrently exposed to the same condition without incident, which suggests that these victims were inherently more vulnerable that day and/or some unique event or illness triggered the heat injury (Carter et al., 2007).

2.2 | Physiology and pathophysiological features

During physical work in the heat, the most significant physiological burden is cardiovascular support of high skin blood flow for heat dissipation while compensatory mechanisms attempt to maintain adequate blood pressure to perfuse tissues (Rowell, 1974). Warm to hot skin is associated with a greater cutaneous vasodilatation (skin blood flow) and venous compliance (skin blood volume), which displaces blood away from the central circulation augmenting cardiovascular strain (Kenefick et al., 2010). As ambient temperature increases, sweat evaporation becomes the primary heat-loss mechanism during exercise, resulting in high rates of sweat loss. If excessive fluid losses are not replaced, the reduced plasma volume (with hyperosmolality from dehydration) further elevates thermal (body temperature) and cardiovascular strain (Sawka et al., 2015). As a result, splanchnic and renal blood flow are reduced by strenuous exercise, severe heat stress and dehydration (Rowell, 1974). When these compensatory responses are insufficient, skin, muscle and even brain blood flow are compromised, augmenting hyperthermia and increasing the risk of EHS (Périard et al., 2021).

The greater the exercise intensity and/or heat stress, the greater the hyperthermia, as evidenced by body core temperature (T_c) and organ and skeletal muscle temperatures (Lee et al., 2010; Sawka et al., 2011). Furthermore, faster running pace (greater exercise intensity) is associated with an increased risk of EHS (Breslow et al., 2021; Grundstein et al., 2019). Active skeletal muscle and organ/tissue temperatures often exceed T_c values during physical exercise (Jay et al., 2007; Nybo et al., 2002). Excessively high tissue temperatures (heat shock: $>41^\circ\text{C}$) can produce direct tissue injury; the magnitude and duration of the heat shock influence whether cells respond by adaptation (acquired thermal tolerance), injury or death (apoptotic or necrotic). Heat shock, ischaemia, and systemic inflammatory responses can result in cellular dysfunction, disseminated intravascular coagulation and multiorgan dysfunction syndrome (Bouchama et al., 2022).

Figure 1 provides a conceptual progression of 'normal' physiological responses to exertional-heat stress that progresses to pathophysiological responses and culminate in EHS. When these physiological perturbations are excessive, they will induce pathological events including increased intestinal permeability, endotoxaemia, exaggerated acute phase response and systemic inflammatory response syndrome (SIRS), coagulopathy, and cell death (Bouchama et al., 2022; Sawka et al., 2011). Of particular concern is intestinal barrier damage accentuating endotoxin leakage and potentiating liver damage, endotoxaemia, SIRS and sepsis (Lim, 2018). Another possibility is that liver damage and/or exercise-induced immunosuppression may promote endotoxaemia (Laitano et al., 2019). Furthermore, reduced cerebral blood flow, combined with hyperthermia, abnormal local metabolism and coagulopathy, can lead to dysfunction of the central nervous system. Heat-induced brain abnormalities include cerebral oedema, Purkinje cell damage, loss of grey and white matter discrimination, and microhaemorrhages (Laitano et al., 2019).

New Findings

- **What is the topic of this review?**

The potential role of nutrition in exertional heat stroke.

- **What advances does it highlight?**

Certain nutritional and dietary strategies used by athletes and workers may exert a protective effect the pathophysiological processes of exertional heat stroke, whereas others may be detrimental. While current evidence suggests that some of these practices may be leveraged as a potential countermeasure to exertional heat stroke, further research on injury-related outcomes in humans is required.

3 | NUTRITION AND EHS RISK

A large proportion of athletes, military personnel and working adults utilize nutritional supplements and dietary strategies to optimize health and performance (Knapik et al., 2016, 2021; Mishra et al., 2021). Specific recommendations for the application of these interventions have been promoted by the International Olympic Committee, American College of Sports Medicine and Union of European Football Associations (Collins et al., 2021; Maughan et al., 2018; Thomas et al., 2016). Contextual factors have huge importance on the guidance provided in sports nutrition position statements; however, to date there has been limited guidance for nutritional countermeasures that could help prevent EHS during arduous physical activity. Furthermore, certain supplements and dietary practices may increase EHS risk and should be cautioned against (Westwood et al., 2021). The major pathophysiological features of EHS that are likely modifiable by nutrients and diet are cardiovascular stability, hydration, intestinal permeability and microbial translocation, cellular thermotolerance, systemic inflammation and/or immune activation, and central drive (Figure 1). The following section provides an overview of selected nutritional factors (excluding pharmaceuticals) that may have protective (Table 1) or harmful (Table 2) effects on EHS pathophysiology.

3.1 | Protective strategies

3.1.1 | Carbohydrate

Carbohydrate is the main macronutrient in the western diet, with international health authorities widely recommending 45–75% of habitual energy intake from carbohydrate (Buyken et al., 2018). Sport nutrition guidelines recommend consuming 30–90 g h⁻¹ of carbohydrates

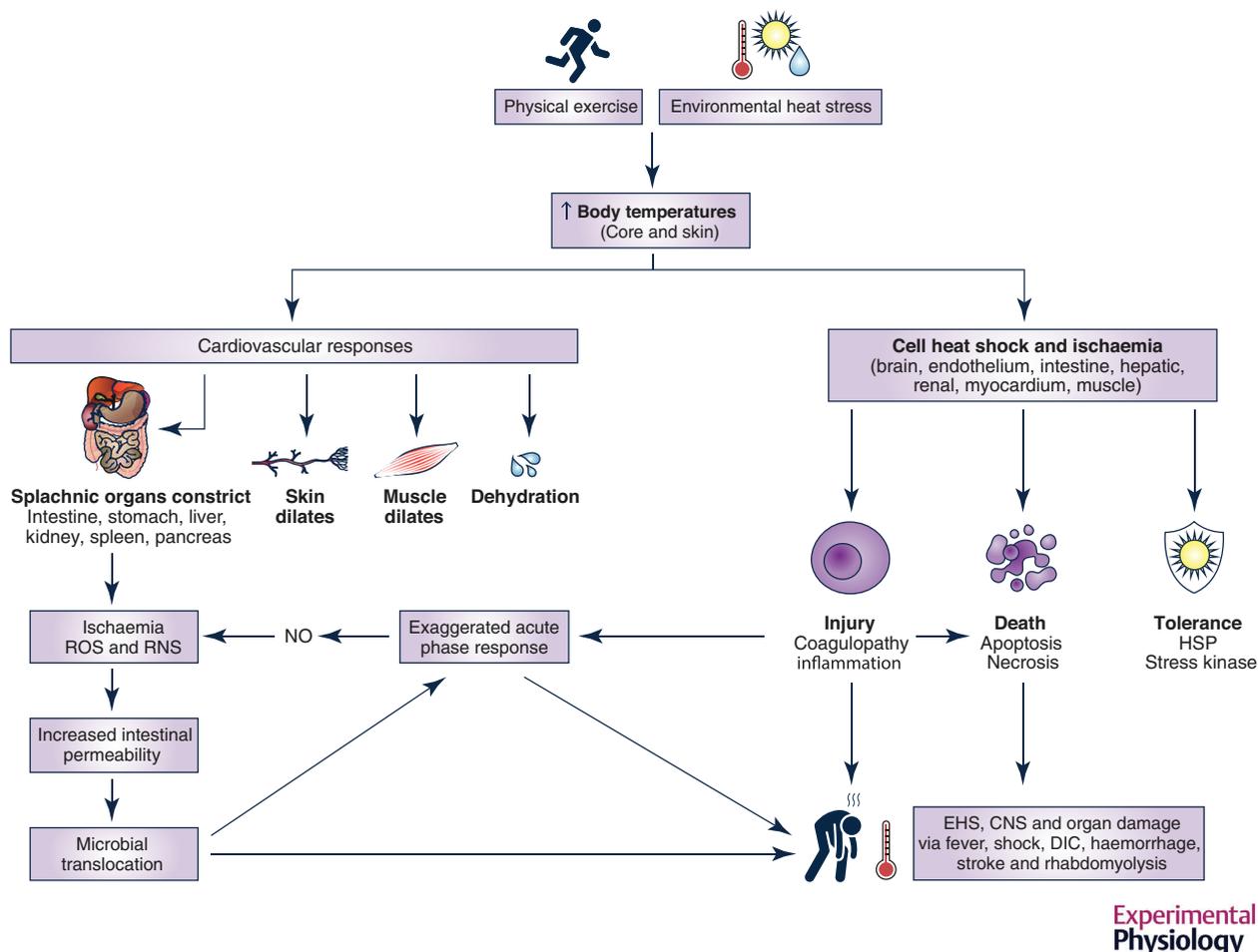


FIGURE 1 Conceptual pathogenesis of the progression from ‘normal’ exercise heat stress to exertional heat stroke. CNS, central nervous system; DIC, disseminated intravascular coagulation; ROS, reactive oxygen species; RNS, reactive nitrogen species; NO, nitric oxide; HSP, heat-shock protein. (Adapted from Sawka et al., 2012)

during exercise lasting ≥ 90 min to optimize performance and recovery (Jeukendrup, 2014).

The influence of acute carbohydrate availability on EHS risk has never been directly examined in either humans or animals, although carbohydrate is well understood to protect intestinal permeability, skeletal muscle injury, systemic cytokinaemia, innate immune function and perceived physical exertion in response to general aerobic exercise. Many studies report 30–108 g h⁻¹ of liquid carbohydrate (i.e., glucose, sucrose, sucrose + glucose, or maltodextrin + fructose) increases splanchnic perfusion and protects intestinal permeability in response to 1–2 h moderate-intensity aerobic exercise (Flood et al., 2020; Jonvik et al., 2019; Snipe et al., 2017). It is also well established that 30–60 g h⁻¹ of carbohydrate attenuates the rise in some plasma cytokines (interleukin (IL)-1ra, IL-6 and IL-10) during exercise (Nieman et al., 2003). Conversely, low pre-exercise carbohydrate availability increases cytokine secretion (Nieman et al., 2003). Several days on a low (<20% total energy intake) versus high (>60% total energy intake) carbohydrate diet increases plasma cytokines and blunts leukocyte function during fasted exercise, whereas such effects are reduced after ingestion of a pre-exercise mixed-macronutrient meal (Bishop

et al., 2001). From a whole-body integrated perspective, carbohydrate ingestion during exertional-heat stress does not influence T_c elevation during physical exercise, despite being a more efficient energy substrate than fat (Jentjens et al., 2006).

Overall, 30–90 g h⁻¹ carbohydrate ingestion during subclinical exercise favourably impacts intestinal permeability, plasma cytokine concentrations and leukocyte function, which could protect against EHS. Alternatively, carbohydrate supplementation may elevate EHS risk by increasing central drive, lowering perceived physical exertion and extending exercise capacity in the heat (Carter et al., 2003). Ingestion of large doses of carbohydrate, particularly gels, bars and high-osmolality beverages, can cause vomiting and/or diarrhoea during exercise, which, without adequate fluid replacement to prevent dehydration, can exacerbate EHS risk (de Oliveira & Burini, 2014).

3.1.2 | Hydration

Adequate hydration is essential for optimizing physiological and cell function, and both cognitive and physical performance with heat stress

TABLE 1 Summary of nutritional strategies that may help protect against exertional heat stroke (EHS), their mechanisms of action and considerations

Dietary intervention or supplement	Dosing	Potential mechanisms of protection against EHS	Considerations
Carbohydrate	30–90 g h ⁻¹ during physical activity	<ul style="list-style-type: none"> • ↓ Intestinal permeability (Butler-Dawson et al., 2019; Gan et al., 2022; King et al., 2016) • ↓ Cytokinaemia (Bouchama et al., 2022; Ogden et al., 2021) • ↑ Leukocyte function (Bouchama et al., 2022) 	<ul style="list-style-type: none"> • ↑ Central drive and ↓ perceived effort may increase EHS risk (Carter et al., 2007) • Large doses may induce GI symptoms (Dong et al., 2019)
Hydration	Euhydration before exercise, individualized drinking plan during activity (Butler-Dawson et al., 2019)	<ul style="list-style-type: none"> • ↑ Cardiovascular stability (Mountjoy et al., 2018; Viribay et al., 2020) • ↓ Intestinal and blood–brain barrier permeability (Davison et al., 2016; Wittbrodt & Millard-Stafford, 2018) • ↓ Acute kidney injury (Chatterjee et al., 2005) 	<ul style="list-style-type: none"> • Avoid pre-exercise alcohol (Epstein & Yanovich, 2019; Impey et al., 2018) • Avoid over-drinking during exercise (Hosokawa et al., 2021)
Glutamine	0.3–0.9 g kg ⁻¹ , >6 h before exercise for ≥1 day	<ul style="list-style-type: none"> • ↑ Intracellular HSP70 (Zuhl et al., 2015, Zuhl et al., 2014) • ↓ Intestinal permeability (Roberts et al., 2021; Zuhl et al., 2015; Zuhl et al., 2014) 	<ul style="list-style-type: none"> • Higher doses may induce GI symptoms (Parker et al., 2018) • No beneficial effect at low doses (Peel et al., 2021; Roberts et al., 2021)
Bovine colostrum	20 g day ⁻¹ for 14 days	<ul style="list-style-type: none"> • ↓ Intestinal permeability and epithelial injury (de Oliveira & Burini, 2014; McQuillan et al., 2018) 	<ul style="list-style-type: none"> • Less effective with greater exertional-heat stress (Montain & Coyle, 1992; Nybo et al., 2002)
Antioxidants (flavonoids, curcumin, ascorbic acid)	<ul style="list-style-type: none"> • May ↓ intestinal permeability and microbial translocation, but findings are inconsistent (Bailes et al., 2002; Landry & Landry, 2003; Lim & Lim, 2018; Trangmar & Gonzalez-Alonso, 2017) • More evidence is required 		
Probiotics	<ul style="list-style-type: none"> • No beneficial effects in humans (Nieman et al., 2007; Rowell & Rowell, 1974; Sanders, 2008; Sonna et al., 2007) • May ↑ endotoxaemia and cytokinaemia (Grgic et al., 2021) • More evidence is required 		
Arginine	<ul style="list-style-type: none"> • No beneficial effects in humans (Burke & Burke, 2021) • More evidence is required 		

GI, gastrointestinal; HSP, heat-shock protein.

TABLE 2 Summary of ergogenic aids and their potential adverse effect on exertional heat stroke (EHS) pathophysiology

Ergogenic supplement/aid	Dosing	Potential harmful effects on EHS risk
Sodium bicarbonate (Grgic et al., 2021)	0.2–0.5 g kg ⁻¹ before exercise	<ul style="list-style-type: none"> • May induce diarrhoea and/or vomiting, potentially leading to dehydration
Oral menthol (mouth-rinsing) (Bermon et al., 2017)	0.1–0.5 g l ⁻¹	<ul style="list-style-type: none"> • ↓ Thermal sensation may increase the risk of exceeding safe T_c levels
Dietary nitrate (beetroot) (Mishra et al., 2021)	200–300 mg before exercise or for >3 days	<ul style="list-style-type: none"> • May induce GI discomfort (nausea) • May ↑ T_c responses to exercise-heat stress (Lawton et al., 2019; Moore et al., 2014)
Creatine	20 g day ⁻¹ for 5 days, then 3–5 g day ⁻¹ (McKenna et al., 2017)	<ul style="list-style-type: none"> • No adverse effects on exercise-heat tolerance or hydration status (Maughan et al., 2018) • Unlikely a concern for EHS

GI, gastrointestinal; T_c, body core temperature.

(Périard et al., 2021; Wittbrodt & Millard-Stafford, 2018). However, sweat losses during physical activity often outpace fluid intake, leading to a progressive loss of body water or dehydration that, if substantial, exacerbates physiological strain and if excessive can predispose to EHS and possible death (Adolph, 1947; Périard et al., 2021).

Hydration is often considered as an important strategy to alleviate the risk of EHS (Racinais et al., 2015). Proper fluid and electrolyte intake during physical work/exercise to avoid excessive dehydration, especially in hot conditions, may protect against EHS by mitigating hyperthermia, sustaining cardiovascular stability and supporting organ and tissue perfusion (Montain & Coyle, 1992; Trangmar & Gonzalez-Alonso, 2017). Maintaining euhydration (normal level of total body water) was also shown to attenuate exercise-associated increases in intestinal permeability, blood-brain barrier permeability and acute kidney injury, compared with dehydration (Chapman et al., 2020; Costa et al., 2019; Watson et al., 2006). In heat-exposed sugarcane cutters, an association between dehydration and a higher incidence of acute kidney injury was found, whereas hydration interventions appeared somewhat protective (Butler-Dawson et al., 2019; Glaser et al., 2020).

Although adequate rehydration during exertional-heat stress is beneficial, the role of dehydration in many EHS cases is unclear. Dehydration was not found to be a contributing factor in 83% of military EHS cases, while marked dehydration (~ 5% body mass loss) has been reported in endurance runners competing in warm/humid climates without ill effects (Carter et al., 2005; Tan et al., 2021). Nonetheless, individuals should ensure they begin physical work/exercise in a euhydrated state. Prior alcohol consumption should also be avoided, as it may increase intestinal permeability as well as induce diuresis (Elamin et al., 2014; Hobson & Maughan, 2010). Regarding fluid and electrolyte replacement strategies during physical activity, an individualized approach based on contextual and personal factors would likely be optimal (Burke, 2021). Caution should also be exercised to avoid drinking in excess of sweat losses (gain in body mass) which may lead to exercise-associated hyponatraemia (Hew-Butler et al., 2017).

3.1.3 | Glutamine

Glutamine is a conditionally essential nutrient, where supplementation prevents nutritional deficiency during extreme physiological stress (Wischmeyer et al., 2014). Although required for several important regulatory functions (e.g., cell proliferation, acid-base regulation, intracellular heat-shock protein expression), general sports nutrition guidelines do not presently recommend glutamine to athletic populations (Bermon et al., 2017).

The influence of glutamine on EHS risk has not been directly examined in humans, though glutamine supplementation reduces mortality from classic heat stroke in rats. These effects that were attributed to increased cellular heat-shock protein expression across multiple organs and blunted intestinal permeability (Singleton & Wischmeyer, 2006). In humans, glutamine consumed either over 7 days or as a single acute bolus (0.9 g kg⁻¹) 2 h before exertional-

heat stress enhanced intracellular heat-shock protein 70 (HSP70) concentrations (in peripheral blood mononuclear cells) and blunted intestinal permeability (Pugh et al., 2017; Zuhl et al., 2014, 2015). However, this supplementation strategy is poorly tolerated in some individuals (Ogden et al., 2020). Lowering the glutamine dose to ≤ 0.3 g kg⁻¹ improves tolerance, but has no meaningful protective effects (Ogden et al., 2021; Pugh et al., 2017). Available data do not indicate any influence of glutamine supplementation on T_c elevation during aerobic exercise in humans (Ogden et al., 2021; Pugh et al., 2017; Zuhl et al., 2014).

Ignoring tolerance constraints associated with high-dose glutamine supplementation, a multi-day supplementation protocol that ceases >6 h prior to exertional-heat stress could offer some protective benefits. Whether glutamine supplementation influences the development of cellular thermotolerance with heat acclimation is an important question that warrants clarification.

3.1.4 | Bovine colostrum

Bovine colostrum is the milk produced by the mammary glands of dairy cows during the initial 24–48 h following birth. It is a rich natural source of macro- and micronutrients, immunoglobulins, hormones and peptides with anti-microbial, immune modulatory and/or growth-factor activity (Playford & Weiser, 2021). Bovine colostrum has received recognition in sports nutrition guidelines as an emerging supplement that may support immune health (Bermon et al., 2017).

The influence of bovine colostrum on EHS risk has never been directly examined in either humans or animals, but does impact several processes involved in the pathophysiology of EHS in human subclinical exercise models, particularly intestinal permeability. Two weeks of bovine colostrum supplementation (20 g day⁻¹) had clear beneficial effects on small intestinal permeability and epithelial injury in response to 20 min of high-intensity running under mild heat strain, but had little or no impact during more pronounced heat strain (Davison et al., 2016; March et al., 2019; McKenna et al., 2017). Similarly, 7 days of supplementation at a higher dose (1.7 g kg day⁻¹) did not improve small intestinal epithelial injury or plasma inflammatory cytokine profile (IL-6, IL-8 or IL-10) after 75 min exercise in a 30°C ambient environment in humans, but offered good protection of intestinal permeability in a rat model of classic heat stroke (Morrison et al., 2014; Prosser et al., 2004). Finally, 5 weeks of bovine colostrum (10 g day⁻¹) had no influence on serum IL-6, IL-10, tumour necrosis factor- α (TNF- α), interferon- γ or IL-12p40 concentrations following a 40 km cycling time trial in temperate conditions (Shing et al., 2007). Available data do not indicate any influence of bovine colostrum supplementation on T_c elevation from physical exercise in humans (Davison et al., 2016; March et al., 2019; McKenna et al., 2017; Morrison et al., 2014; Shing et al., 2007).

Whilst evidence does not currently support the use of bovine colostrum to mitigate the risk of EHS by protecting intestinal integrity or attenuating cytokinaemia, further research is still warranted focusing on specific doses, timings and product formulations in relation to bioactivity.

3.1.5 | Antioxidants

Large concentrations of reactive oxygen species (ROS) and reactive nitrogen species (RNS) – unstable molecules with a missing electron which can damage various cellular components – are produced during arduous exercise by skeletal muscle and leukocytes (King et al., 2016). Antioxidants are chemical compounds and enzymes that exist as a natural means of quenching excessive ROS/RNS. Proponents of antioxidant supplementation argue that dietary intervention is required to prevent oxidative stress, though evidence is inconclusive on whether excessive production in response to exercise is even detrimental to human health (Bermon et al., 2017). Circumstances in which antioxidant supplementation could be recommended are in preventing nutritional deficiencies and during severe exertional-heat stress (King et al., 2016). To date, certain antioxidants have shown some protective effects from classic heat stroke in rats and subclinical exertional-heat stress in humans, though results are inconsistent.

Quercetin is a flavonoid polyphenol that is highly concentrated in many fruits and vegetables. In rats, quercetin administration (15–30 mg kg⁻¹) 1 h before heat stroke increased intracellular antioxidant capacity across several organs, which had a favourable effect on multi-organ injury, systemic pro-inflammatory cytokines, peak T_c and survival rate (Chen et al., 2014; Lin et al., 2017). At larger doses (~400 mg kg⁻¹), however, quercetin inhibited cellular thermotolerance without influencing plasma cytokine concentrations, overall increasing mortality (Lam et al., 2013; Yan et al., 2017). Inconsistent results with quercetin supplementation have also been reported in humans. For example, 3 weeks of quercetin (1 g day⁻¹) had no influence on plasma cytokine responses to 3 h of moderate-intensity cycling, but a single 2 g dose blunted intestinal permeability, microbial translocation and plasma TNF- α following 40 min of exertional-heat stress (Kuennen et al., 2011; Nieman et al., 2007). One recent human study reported that 7 days' supplementation with anthocyanin-rich blackcurrant extract, another flavonoid antioxidant, protected intestinal permeability in response to exertional-heat stress; however, these benefits did not extend to blunted microbial translocation or systemic inflammation (Lee et al., 2022).

Curcumin is the principal curcuminoid of turmeric and is a popular spice. In rats, curcumin supplementation at increasing doses (50, 100 and 200 mg kg⁻¹) for 7 days prior to classic heat stroke attenuated intestinal microbial translocation in a dose-dependent manner (Li et al., 2020). In humans, 3 days of curcumin supplementation (0.5 g day⁻¹) blunted intestinal injury in response to 1 h of exertional-heat stress, but had no meaningful influence on plasma cytokine concentrations (Szymanski et al., 2018).

Ascorbic acid (vitamin C) is an essential vitamin. The impact of ascorbate acid on oxidative stress-related diseases is widely considered to be marginal because of its poor oral bioavailability and rapid clearance (Padayatty et al., 2004). In mice, parenteral administration of ascorbic acid (100–500 mg kg⁻¹) immediately following onset of classic heat stroke drastically improved 24-h survival rates and markedly attenuated heat stroke-induced systemic inflammation, coagulation, oxidative tissue injury and multiple-

organ injury (Chang et al., 2016). In humans, oral ascorbic acid supplementation (1 g) blunted intestinal microbial translocation when ingested 2 h before graded-intensity exercise to fatigue, but a similar dose supplemented over 7 days did not influence plasma cytokines in response to running in the heat (Ashton et al., 2003; McNulty et al., 2004). Available data do not indicate any influence of antioxidant supplementation on T_c elevation from physical exercise (Cheuvront et al., 2009; Kuennen et al., 2011; McNulty et al., 2004; Szymanski et al., 2018).

Overall, inconsistent data are presented for the influence of antioxidant supplementation on EHS risk, which can be attributed to differences in the supplementation regime (i.e., type, timing and dose), severity of heat strain and selected outcome measures.

3.1.6 | Probiotics

Probiotics are live microorganisms that, when administered in adequate amounts, confer a health benefit to the host. Probiotics are best known for microbiome management in the intestinal tract, though they are said to also support healthy immune, central nervous system and endocrine function (Sanders, 2008). Therefore, the consumption of probiotic supplements and/or fortified food products has become popular in athletes during periods of intensified training, competition or ill-health (Möller et al., 2019). Several recent meta-analyses conclude that probiotics do not support intestinal health in the general population, though more promising evidence has been published using specific probiotic formulations (Parker et al., 2018). The key pathways for how probiotics could mitigate EHS risk include inhibition of pathogenic bacterial overgrowth by competition for binding sites on mucins and/or epithelial cells, increased neutralizing of mucosal immunoglobulin and antimicrobial protein secretion, increased electrolyte and water absorption, and reduced intestinal permeability (Armstrong et al., 2018).

The influence of probiotics on EHS risk has not been directly examined in humans, though probiotic supplementation (*Bacillus licheniformis*) was reported to reduce mortality in rats. Mechanistically, *Bacillus licheniformis* lowered peak heat strain, increased intestinal tight-junction protein expression, and alleviated multiple-organ injury (intestine, kidney, liver and skeletal muscle) and systemic cytokinaemia (Li et al., 2021). This conclusion is consistent with two earlier rat studies involving subclinical passive hyperthermia (peak $T_c = 40.3 \pm 0.2^\circ\text{C}$) and exhaustive exercise (peak $T_c = 39.3 \pm 0.3^\circ\text{C}$), where 2 days of *Bacillus subtilis* supplementation (108 colony-forming units (CFU) day⁻¹) entirely prevented morphological intestinal injury, microbial translocation and cytokinaemia (Ducray et al., 2020; Moore et al., 2014). Less favourable results have been reported in humans, where various probiotic formulas have failed to influence intestinal permeability, hepatic injury, microbial translocation, cytokinaemia and T_c in response to sub-clinical exercise (Mooren et al., 2020; Pugh et al., 2019, 2020; Shing et al., 2014). In one study, 7-day supplementation with an increased dose of *Lactobacillus casei* (45×10^{11} CFU day⁻¹) actually worsened plasma endotoxin and TNF- α concentrations in

response to 2 h of moderate-intensity running in a 34°C ambient environment (Gill et al., 2016).

Prebiotics are non-digestible dietary components that have beneficial effects for the host through affecting the growth and/or activity of the intestinal microbiota. To date, no research has been undertaken on the impact of prebiotic supplementation on physiological responses relevant to EHS.

In summary, several weeks of probiotic supplementation has little influence on any pathophysiological feature of EHS in humans, though research in rats has returned more positive outcomes. It is not possible to elucidate whether inconsistent results are attributable to differences between probiotic formulations, species or research design. Future research should replicate the exact probiotic intervention demonstrated in rats to human exertional-heat stress.

3.1.7 | Arginine

Arginine is also a conditionally essential nutrient, where supplementation prevents nutritional deficiency in response to extreme physiological stress (Drover et al., 2011). Arginine is required for several important regulatory functions, including nitrogen transport, urea synthesis and creatine synthesis. Supplementation with arginine has become an increasingly popular strategy to improve aerobic exercise performance, though specific nutritional guidelines do not currently exist (Viribay et al., 2020).

The influence of arginine on EHS risk has not been directly examined in humans. In rodents, arginine may both increase and reduce mortality from classic heat stroke, depending on the dose and timing of administration. Intravenous injection of arginine (30–120 g kg⁻¹) either 1 h before or following the onset of heat stroke increased mortality, whereas 120 g kg⁻¹ injected 2–4 h following heat stroke initiated the repair pathway (e.g., HSP70, p53, Th2 cytokines) and prevented mortality (Chatterjee et al., 2005; Chen et al., 2008; Poduval et al., 2003). Favourable results are likely attributable to a shift in arginine metabolism towards arginase with a concomitant decrease in the expression of inducible nitric oxide synthase (Chatterjee et al., 2005). When administered prior to exhaustive exertional-heat stress (130 g day⁻¹ for 7 days), arginine blunted intestinal permeability and microbial translocation in mice (Costa et al., 2014).

There is currently a lack of relevant data examining the influence of arginine supplementation on clinically relevant outcome measures in humans, except for one study reporting no influence of 14 days' supplementation on intestinal permeability following a 42.2-km marathon (Buchman et al., 1999). When ingested before exercise, other nitric oxide precursors like sodium nitrate and beetroot juice have little impact on intestinal permeability, but may accelerate the exercise-induced T_c elevation via reduced cutaneous vasodilatation (Jonvik et al., 2019; Kuennen et al., 2015; McQuillan et al., 2018).

At present, acute pre-administration of arginine, citrulline or dietary nitrate cannot be recommended as a strategy to help prevent EHS. The effects of post-exposure arginine in rodents are interesting,

though later stage clinical trials are required before recommendations are made.

3.2 | Harmful factors

3.2.1 | Ergogenic aids

In 1994, the US Congress reduced the ability of the Food and Drug Administration (FDA) to regulate the manufacture and sale of nutritional products (US Public Law no. 103-417), resulting in potentially dangerous ingredients being included in nutritional supplements used by athletes and workers. Since 1994, an increased number of fatal EHSs in athletes has been reported with concern that use of dietary supplements may be responsible (Bailes et al., 2002). Indeed, the use of ephedrine-containing dietary supplements has been implicated as a contributing factor in previous EHS cases, including one fatality (Charatan, 2003; Oh & Henning, 2003). Ephedrine alkaloids may induce thermoregulatory dysfunction and adverse cardiovascular events while masking fatigue (Bailes et al., 2002; Landry, 2003). The FDA has since banned the sale of supplements containing ephedrine alkaloids (FDA, 2004). Of note, caffeine, a widely used (and legal) stimulant among athletes and adults, may also increase EHS risk as it reduces perception of effort, fatigue and pain, and may exacerbate T_c elevation during exercise in the heat (Guest et al., 2021; Peel et al., 2021). However, there is no evidence of caffeine directly contributing to EHS.

The International Olympic Committee has approved a list of dietary supplements with evidence for being ergogenic (Maughan et al., 2018). However, aside from their benefits on performance, some of these supplements have side effects that may make EHS more likely (Table 2). Sodium bicarbonate may induce diarrhoea and/or vomiting and potentially cause dehydration (Grgic et al., 2021). Gastrointestinal symptoms with dietary nitrate are also possible. Oral menthol (mouth rinsing) may increase EHS risk through reduced thermal sensation and misjudgement of one's internal thermal state (Barwood et al., 2020; Stevens et al., 2018). Creatine monophosphate was previously speculated to impair heat dissipation, exercise-heat tolerance, and induce fluid imbalance and renal damage, but these were subsequently not confirmed (Bailes et al., 2002; Gualano et al., 2012; Lopez et al., 2009). As such, creatine is unlikely a concern regarding EHS.

3.2.2 | Low energy availability

Low energy availability during training and competitions is common among athletes due to high energy expenditures and/or inadequate energy intake (Logue et al., 2020). The high energy demands of military training and occupational work, coupled with other constraints that limit energy intake, also often put soldiers and workers in an energy deficit (Christie, 2008; Gan et al., 2022). In recent years, the popularity of fasted or muscle glycogen-depleted training ('train low') has grown

in individuals looking to optimize aerobic training adaptations (Impey et al., 2018).

There is no evidence of a direct influence of energy status on EHS risk; however, prolonged deficits in energy and nutrient intakes may indirectly predispose to EHS through its negative effects on immune function and susceptibility to viral illness or infections (Mountjoy et al., 2018). Observational data in female athletes indicate an association between low energy availability, assessed via questionnaire, and a higher incidence of self-reported illness, including upper respiratory tract infections (Drew et al., 2018). In another study, an 18% reduction in the severity of energy deficit (via increased caloric intake) during 8 weeks of arduous military training attenuated the suppression of T-lymphocyte function and reduced the incidence of infections (Kramer et al., 1997). A recent or current viral illness or infection, in turn, can increase one's susceptibility to EHS (i.e., 'multiple-hit' hypothesis) (Sawka et al., 2011). EHS victims often report experiencing mild illness or infection several days prior to, or on the day of, the incident, especially those who unexpectedly succumb to EHS under seemingly low-risk conditions (Carter et al., 2007). The mechanism through which viral illness or infection increases EHS susceptibility is not fully understood, but may involve an exaggerated hyperthermic response to exertional-heat stress which can then trigger EHS, and/or elevated cytokine levels that blunt cellular thermotolerance to heat injury (Carter et al., 2007; Sonna et al., 2007).

However, the link between energy deficiency, immune function and infection is currently tenuous and requires further investigation (Walsh, 2019).

4 | CONCLUSIONS AND FUTURE DIRECTIONS

EHS poses a significant threat to the health and safety of physically active populations, which will be exacerbated by climate change. Risk factors and mitigation strategies for EHS have traditionally focused on the environment, health status, clothing, heat acclimatization and aerobic conditioning. However, the potential impact of diet and nutrition in protecting against or facilitating EHS is largely under-explored, yet an important area of research. There is evidence that some of the nutritional supplements and dietary strategies commonly used by athletes can influence the pathophysiological processes of EHS, either favourably or negatively. Regular carbohydrate ingestion during subclinical exertional-heat stress is the one approach shown to consistently dampen pathophysiological features of EHS, though verification is still required in actual EHS patients. Dehydration exacerbates physiological strain and if excessive may predispose one to EHS, whereas proper fluid-electrolyte replacement is protective. Preliminary evidence has shown some benefit of amino acid, bovine colostrum, probiotic and antioxidant supplements on EHS risk, yet inconsistent results currently make it difficult to provide conclusive recommendations. Conversely, certain ergogenic aids and low energy availability (via immune-suppressive effects) may predispose to EHS, but these hypotheses have yet to be tested.

Lastly, recommendations for further research include, but are not limited to, the following:

- Verify positive findings with both field and laboratory studies in humans.
- Investigate whether the results from rodent models of classic heat stroke persist in EHS.
- Conduct randomized-crossover studies to ascertain the efficacy of nutritional supplements, both in isolation and in combination, on EHS-related outcomes.
- Investigate the effects of diet and nutrition on EHS in youths, women, middle-aged and multi-ethnic populations.

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COMPETING INTERESTS

No potential conflicts or competing interests are disclosed.

AUTHOR CONTRIBUTIONS

All authors contributed to the conception or design of the manuscript; acquisition, analysis or interpretation of data; drafting or revising critically for intellectual content. All authors have read and approved the final version of this manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

ORCID

Jason K. W. Lee  <https://orcid.org/0000-0003-4042-795X>

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