



Exertional heat stroke: pathophysiology and risk factors

Christian K Garcia,¹ Liliana I Renteria,² Gabriel Leite-Santos,² Lisa R Leon,¹ Orlando Laitano ¹

For numbered affiliations see end of article.

Correspondence to: Dr Orlando Laitano, Department of Applied Physiology and Kinesiology, University of Florida, Gainesville, FL, USA; orlando.laitano@UFL.edu

Cite this as: *BMJMED* 2022;1:e000239. doi:10.1136/bmjmed-2022-000239

Received: 27 April 2022

Accepted: 6 September 2022

ABSTRACT

Exertional heat stroke, the third leading cause of mortality in athletes during physical activity, is the most severe manifestation of exertional heat illnesses. Exertional heat stroke is characterised by central nervous system dysfunction in people with hyperthermia during physical activity and can be influenced by environmental factors such as heatwaves, which extend the incidence of exertional heat stroke beyond athletics only. Epidemiological data indicate mortality rates of about 27%, and survivors display long term negative health consequences ranging from neurological to cardiovascular dysfunction. The pathophysiology of exertional heat stroke involves thermoregulatory and cardiovascular overload, resulting in severe hyperthermia and subsequent multiorgan injury due to a systemic inflammatory response syndrome and coagulopathy. Research about risk factors for exertional heat stroke remains limited, but dehydration, sex differences, ageing, body composition, and previous illness are thought to increase risk. Immediate cooling remains the most effective treatment strategy. In this review, we provide an overview of the current literature emphasising the pathophysiology and risk factors of exertional heat stroke, highlighting gaps in knowledge with the objective to stimulate future research.

Introduction

Heat stroke is classified into two separate endotypes, referred to as classic heat stroke and exertional heat stroke (EHS). Classic heat stroke is induced by heat exposure in the absence of physical exertion.¹ EHS is induced by vigorous physical activity performed normally, but not always,² in hot or humid environments.¹⁻³ The term "heat stroke" suggests the presence of stroke-like symptoms associated with warm environments and hyperthermia (normally characterised by increases greater than 2.5°C from resting values). EHS is characterised by central nervous system (CNS) dysfunction (eg, delirium, convulsions, or coma) with the possibility of follow-on organ or tissue damage in people with hyperthermia. The prevention of EHS is currently more effective than any treatment strategy.

Understanding the pathophysiology and the risk factors that lead to EHS is important for the correct diagnosis and the choice of mitigation strategies. Here, we provide an overview of the pathophysiology of the disorder and discuss the potential risk factors that contribute to its incidence.

Sources and selection criteria

The following electronic databases were searched for articles published from the inception of the databases until July 2022: Medline (accessed by PubMed), Cochrane Wiley (Central Register of Controlled Trials), and LILACS. In addition, the reference lists of relevant published studies were searched manually. To identify relevant publications, the combined search term (exploded versions of the medical subject headings) were used: ("heat illness" OR "heat stroke" OR "exertional heat stroke" OR "heat exhaustion") AND ("heat injury" OR "hot temperature" OR "extreme heat" OR "thermoregulation" OR "warm environment" OR "heat stress") AND ("dehydration" OR "water stress" OR "water-electrolyte imbalance" OR "fluid balance"). We prioritised peer reviewed original studies including case series and retrospective studies. In addition, we also included studies using both clinical (eg, human participants) and preclinical models (eg, animal models). We did not include unpublished data from thesis or dissertations.

Incidence of exertional heat stroke

The precise incidence of EHS is underestimated, but large incidence is observed among warfighters, athletes, labourers, and those engaging in recreational exercise. Problems with classification of the disorder contributes to the lack of a clear reported incidence. Most studies include EHS under the umbrella term of exertional heat illness. Exertional heat illness is classified as a spectrum of severity and includes heat exhaustion, heat injury, and heat stroke,⁴ which can be severe if untreated and are all characterised by hyperthermia.⁵ To differentiate heat injury from heat exhaustion, tissue or organ injury must be present, although it might quickly resolve in patients that are rapidly treated. A recent systematic review performed in a military cohort reported incidence of exertional heat illness ranging from 0.2 to 10.5 per 1000 person years and prevalence ranging from 0.3% to 9.3%.⁶ In addition, long distance road races reported an EHS incidence ranging between 1.6 and 2.13 per 1000 finishers without mortality.^{7,8}

Another factor that interferes with the precise incidence of EHS is the criteria often used to define the disorder clinically. Previous definitions of EHS have used the cut-off core temperature of >40°C. The use of a threshold core temperature to define the disorder is considered inaccurate.⁹ Athletes can collapse at a wide range of core temperatures,^{2,10} and the measurements can be inaccurate if taken at peripheral body sites or after cooling has already occurred. The use of a threshold core temperature can lead to a misdiagnosis, suggesting that reliance on other

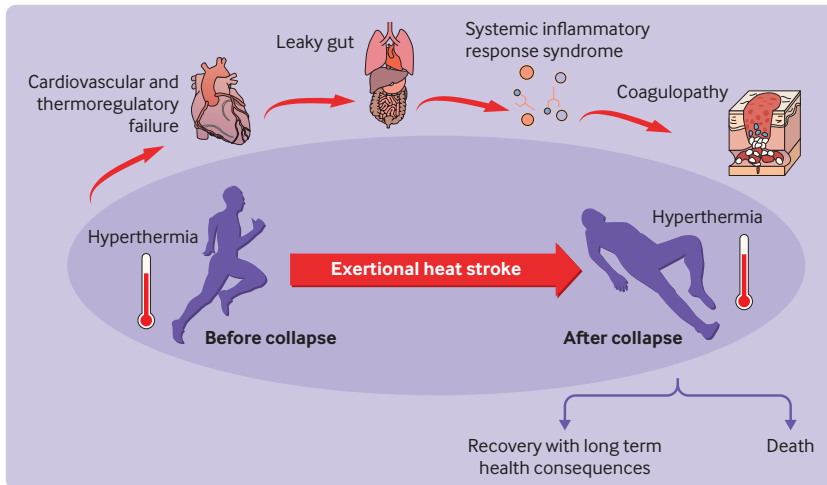


Figure 1 | Summary of the main pathophysiological factors participating in exertional heat stroke. During exercise (before collapse), hyperthermia ensues due to an inability of the cardiovascular system to sustain thermoregulation. Shifts in blood flow leads to increased intestinal permeability, causing leakage of intestinal content into the systemic circulation, a response is known as the leaky gut hypothesis. Intestinal content and hyperthermia lead to the systemic inflammatory response syndrome, which promotes a disseminated intravascular coagulation characterising the coagulopathy. Most of these responses remain after collapse or until the victim is adequately cooled and regains consciousness. The two most common outcomes of exertional heat stroke are death or recovery with long term negative consequences to health. Figure based on original graphical scheme prepared using Servier medical art (smart.servier.com)

pathological manifestations (ie, CNS dysfunction) is warranted and likely more accurate. Immediate cooling, regardless of core temperature, should always be the main priority on collapse because reliance on a specific core temperature could delay (or fail to prescribe) medical intervention and cause long term organ damage.¹¹ Although less likely, false positive cases are possible because core temperatures $>40^{\circ}\text{C}$ can occur without CNS impairment.¹²⁻¹³ Thus, CNS dysfunction is likely to define EHS with more sensitivity or specificity.

Pathophysiology

In this article, we will discuss four aspects of EHS pathophysiology: thermoregulatory or cardiovascular limitations, the so-called leaky gut hypothesis and endotoxaemia, inflammation and systemic inflammatory response syndrome, and coagulopathy and disseminated intravascular coagulation (figure 1).

Thermoregulatory and cardiovascular limitations

It seems reasonable to hypothesise that EHS is primarily due to impaired thermoregulation, because patients often display severe hyperthermia at the time of collapse. A person's ability to thermoregulate is closely linked to the ability of the cardiovascular system to cope with central and peripheral blood flow demands to support metabolic and thermoregulatory requirements.¹⁴⁻¹⁵ During vigorous exercise, heat is produced by skeletal muscle contractions

at rates that are 15-18 times greater than the basal metabolic rate.¹⁶ Most of this heat is transferred from the muscles to the blood and carried to the body core. Theoretically, if no thermoregulatory mechanisms are activated, metabolic heat production of this magnitude would raise core temperature from 37°C to 42°C in only about 25 minutes.¹⁶ This magnitude of endogenous heat production could overcome the thermoregulatory mechanisms of heat dissipation and induce EHS, even in a temperate environment.² Given that cellular tolerance to heat is in the range of $40-45^{\circ}\text{C}$,¹⁷ this magnitude of heat would result in cellular and organ damage. Effective thermoregulatory pathways must be active to provide means for heat loss to prevent EHS during severe or prolonged physical activity.

The most effective thermoregulatory mechanism, at least during exercise performed on land and in the heat, is the evaporation of sweat.¹⁸ Sweat production is initiated either by the activation of the central temperature receptors or by elevation of skin temperature,¹⁹ both of which trigger the activation of the eccrine sweat glands. Evaporation of sweat depends on the vapour pressure gradient between the skin and air,²⁰ such that thermoregulation is normally impaired in humid environments. However, evaporation can still occur even if the skin and air are both saturated with water, provided the air is cooler than the skin. A thermoregulatory failure underlying EHS would signify a suppressed ability to dissipate heat coupled with high rates of heat storage, which would result in a marked elevation in core temperature. One argument against the hypothesis of a thermoregulatory failure underlying EHS is that during exercise in hot environments, core body temperature values of $40-42^{\circ}\text{C}$ are not uncommon in athletes who are fit and acclimatised to heat.^{12-13 21-23} These individuals show no signs or symptoms of EHS. Reports indicate that people with EHS might collapse during activities that were previously completed safely.²⁴ In addition, high grade fever exceeds 40°C without morbidity.²⁵⁻²⁶ Therefore, although a thermoregulatory limitation could participate in the EHS pathophysiology to some extent, it does not entirely explain the manifestation. Since thermoregulation and cardiovascular responses are so tightly intertwined, an overwhelmed cardiovascular system might have a key role in EHS pathophysiology.

During muscle contraction, metabolic heat production increases in an intensity dependent manner.²⁷⁻²⁹ During exercise in the heat or when wearing encapsulated clothing, individuals gain extra heat from the environment to the body or the trapping of heat within the clothing ensemble.³⁰⁻³¹ To sustain exercise, cardiac output must match the demands for blood flow. Blood flow to active muscles is required to meet the oxygen demands for muscular activity, while blood flow to skin is required to meet the demands of thermoregulation.¹⁴ Vasodilation

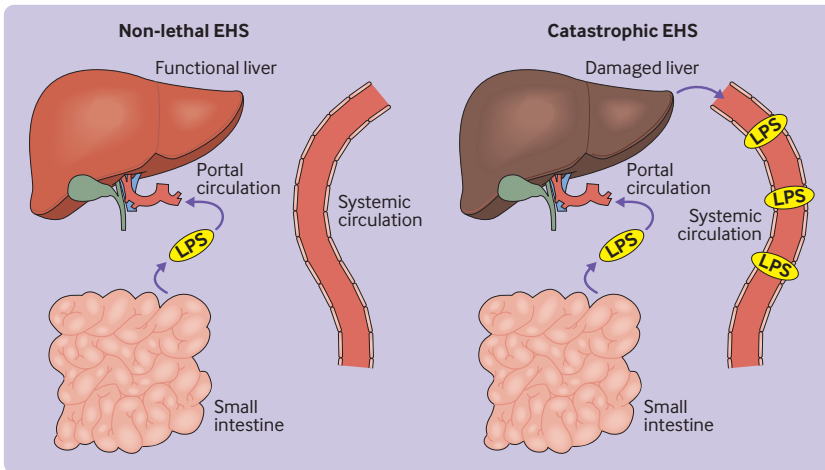


Figure 2 | Working hypothesis for the leaky gut response during exertional heat stroke (EHS). In non-lethal EHS, the liver effectively clears endotoxins. In catastrophic EHS, particularly with severe liver damage, endotoxin leaks into the circulation and causes sepsis. LPS=lipopolysaccharide. Figure based on original graphical scheme prepared using Servier medical art (smart.servier.com)

and increased skin blood flow increase the amount of blood pooled in peripheral vessels, which reduces central blood volume. Splanchnic and renal blood flow are reduced by both vigorous exercise and severe heat stress. Reductions in gut and renal blood flow are generally thought to facilitate shifts in cardiac output to the skin and exercising muscle to maintain blood pressure and allow continued exercise.^{32 33} When these adjustments are inadequate during exercise in hot environments at high metabolic rates (>75% of maximal oxygen consumption (VO_2 max)), skin, muscle, and brain blood flow are compromised and contribute to severity of exertional heat illness.^{1 34–36} These cardiovascular alterations lead to a diversity of outcomes including altered gut permeability that can have consequences to EHS pathophysiology.

Leaky gut hypothesis and endotoxaemia

Increased intestinal permeability, also known as the leaky gut hypothesis, suggests that bacteria and toxins leak from the gut lumen, where they are normally contained via tight junctions, through the intestinal wall into the portal and general circulation. Several reports have documented increased intestinal permeability during exercise with^{37–39} and without heat stress.⁴⁰ As blood flow in the splanchnic circulation declines, skin blood flow increases for heat dissipation and gut epithelial membranes undergo nitrosative and oxidative stress, due to ischaemia reperfusion.⁴¹ These processes degrade tight junction integrity and are thought to facilitate endotoxin leakage into the portal circulation.

The leaky gut hypothesis has been linked to EHS pathophysiology because of observations that in patients with extreme EHS, high levels of lipopolysaccharide (a cell wall component

of Gram negative bacteria) are observed. Under normal circumstances, the liver reticuloendothelial system clears endotoxin so that it does not reach the general circulation.⁴² In extreme heat stress conditions, dysfunction or damage to the liver could compromise the ability of the reticuloendothelial system to function. Only under these catastrophic conditions of liver failure or damage does endotoxaemia occur. Endotoxaemia and liver necrosis were observed in a football player who died of EHS at a body core temperature of 40.6°C.⁴³ In primates, circulating endotoxin was markedly increased under classic heat stroke conditions once body core temperatures exceeded the fatal level of 43.0°C.⁴⁴ Although liver damage was not assessed in this study, it is typically detectable at body core temperatures ranging from about 42°C to 43°C.^{45–47}

Studies using endotoxin neutralisation in several species have shown protective effects of antibiotics and endotoxin tolerance against heat stroke mortality, but once again these studies looked at catastrophic models with high mortality rates and core temperatures exceeding the threshold where liver injury would be expected.^{44 48 49} On the other hand, a murine model of classic heat stroke that induced body core temperature as high as 42.7°C did not show detectable circulating endotoxin despite considerable gut histological injury.^{50 51} This lack of endotoxin was most likely due to the absence of liver damage, which supports the hypothesis that liver dysfunction might be required for endotoxaemia. Chung et al⁵² failed to show elevated endotoxin in patients with heat stroke. The liver has a critical role in recovery from EHS, as demonstrated in preclinical mouse models owing to the formation and release of acute phase proteins that support the immune system in repairing organ damage.⁵³ In [figure 2](#), we summarise the hypothesis for the leaky gut and endotoxaemia contributions to EHS pathophysiology with and without liver dysfunction.

Inflammation and systemic inflammatory response syndrome

Systemic inflammatory response syndrome is a dysregulated defence response of the body to a noxious stressor to localise and eliminate the source of the insult.⁵⁴ The syndrome involves the release of acute phase proteins, cytokines, and chemokines, which are direct mediators of widespread autonomic, endocrine, haematological, and immunological alterations in the host. The dysregulated inflammation can lead to a pro-inflammatory cascade resulting in organ dysfunction and even death.

Preclinical models of classic heat stroke and EHS show a robust inflammatory response that ensues after collapse, which mimics mechanisms observed

in patients.^{55–57} In both male and female mice with EHS,^{53 58 59} levels of plasma interleukin 6 peaked at 0.5 hours after loss of consciousness.^{58 59} Induction of interleukin 6 in severe hyperthermia is thought to come from either endotoxaemia or hyperthermia and the actions of this cytokine can differ depending on its circulatory concentration. Sustained elevation of circulating interleukin 6 during recovery from classic heat stroke has been correlated with poor outcome in primates and humans.^{55–57} Mice with interleukin 6 gene knockout showed increased mortality, indicating protective effects at a basal level. Interleukin 6 injection in mice with classic heat stroke led to protection from organ injury.⁶⁰ Whether these possible dual actions of interleukin 6 also exist for EHS remains unknown.

One possibility for induction of the systemic inflammatory response syndrome after EHS (or classic heat stroke) is that the endotoxaemia via the so-called leaky gut triggers an inflammatory response after its binding to toll-like receptors, a class of proteins that have a crucial role in immune signalling by recognising pathogen and damage associated molecular patterns.⁶¹ Evidence of endotoxaemia is only present in catastrophic EHS events (figure 2), the leaky gut is unlikely to explain the inflammatory response observed on collapse in survivors of EHS. A secondary source for the inflammatory response could be hyperthermia. Hyperthermia increases interleukin 6 mRNA content in myofibres, in part by heat shock factors, although the response in other organ levels has not yet been determined.⁶² This response is relevant because interleukin 6 regulates the hepatic acute phase response during recovery from EHS.⁵³ In summary, EHS is accompanied by a strong inflammatory response that leads to systemic inflammatory response syndrome and multi-organ damage. The triggers for these responses are endotoxaemia (in catastrophic EHS) and probably hyperthermia.

Coagulopathy and disseminated intravascular coagulation

Coagulation is the process of changing the physical state of the blood from liquid to semi-solid. In vertebrates, coagulation is an evolutionary conserved mechanism that maintains haemostasis, in cases of blood vessel damage, by preventing bleeding.⁶³ Overall, coagulation has four stages of clot formation, including constriction of the blood vessel, formation of a temporary platelet plug, activation of the coagulation cascade, and formation of the final clot. The system is tightly regulated by the complex interaction of 20 pro-coagulation factors, including fibrinogen, thrombin, prothrombin, von Willebrand factors, among others.⁶⁴ When the system is under equilibrium, the clotting formation process is balanced by fibrinolysis, which is the enzymatic breakdown of the fibrin in blood clots.⁶⁵ Once vascular repair is achieved, the fibrinolytic factors plasminogen and

tissue plasminogen activator are attracted by the clot through lysine residues of fibrin and start clot digestion. Disturbances in these haemostatic processes lead to several problems, including thrombosis and disseminated intravascular coagulation.⁶⁶

Disseminated intravascular coagulation can be classified into hyperfibrinolytic coagulation, which will lead to thrombotic events, or hypofibrinolytic coagulation, which leads to excessive bleeding.⁶⁷ Disseminated intravascular coagulation has been reported in patients with EHS. For example, a 38-year-old male recreational athlete presented in the emergency room with a history of sudden loss of consciousness during a 10 km run. He did not have a history of cardiovascular or respiratory disease and did not have similar loss of consciousness episodes previously. His level of fibrin degradation product, small pieces of protein that stay in the circulation when a blood clot dissolves, was substantially elevated at 0.8 mg/L (normal <0.05 mg/L). Prothrombin time and activated partial thromboplastin time, indicators of the time required for clot formation in a blood sample, were 29.7 seconds (normal time 12.3 seconds) and 33.5 seconds (control time 26.38 seconds), respectively.⁶⁸ He also presented bilateral intracerebral bleeding, consistent with hypofibrinolytic disseminated intravascular coagulation.

Treatment strategies for disseminated intravascular coagulation in EHS have not been established, and the time course changes in coagulofibrinolytic markers have not been thoroughly evaluated. The triggers of disseminated intravascular coagulation during heat stroke events are difficult to determine. In a baboon model of classic heat stroke, inhibition of tissue factor/factor VIIa, which has an activating role in the clotting formation cascade, attenuated disseminated intravascular coagulation.⁶⁹ The authors concluded that a pathway dependent on tissue factor/factor VIIa initiates coagulation activation in this model. Whether the same factor is responsible for the initiation of disseminated intravascular coagulation in EHS or whether the response holds true in other mammals remains unknown.

Risk factors

No sound evidence indicates which risk factors increase EHS predisposition, but several factors have been implicated. In figure 3, we highlight the risk factors discussed in this review.

Dehydration

No direct evidence indicates that dehydration has a causative role in EHS. But to hypothesise that it will be a risk factor is logical, given the known impact of dehydration on human physiology.^{70 71} Blood plasma consists of about 90% water. During exercise, because of increased metabolic demand and sweat production, plasma volume decreases,

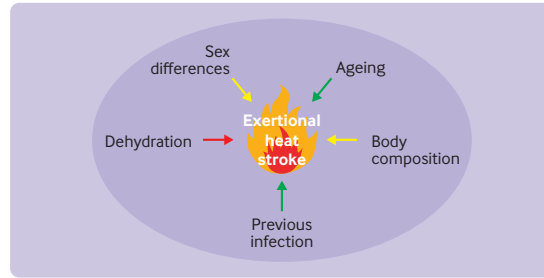


Figure 3 | Potential risk factors affecting exertional heat stroke. Arrow colours represent level of evidence for each risk factor: green=strong; yellow=moderate; red=anecdotal

which increases plasma osmolality and blood viscosity, which are associated with increased reactive oxygen species production.⁷² The increased osmolality induces a pull of water from intracellular stores to extracellular stores to overcome the impact from exercise. The greater viscosity from decreased plasma volume causes cardiac drift, leading to greater cardiac strain.⁷³ When decreases in plasma volume are drastic enough to decrease blood pressure, it can diminish cerebral blood flow and cause syncope.⁷⁴ By exercising in the heat, sweat rates escalate to increase evaporative heat loss from the paired metabolic heat produced from exercise and the external environmental heat. The detriments of dehydration are exacerbated when individuals begin exercise in a hypohydrated state,⁷⁵ which is frequent in athletes.^{76–78} In a crossover study of 17 male soldiers, Sawka et al compared heat strain between euhydrated and hypohydrated individuals with about 8% dehydration after walking for 180 minutes at 49°C and 20% humidity.⁷⁹ The hypohydrated state was more responsible for heat intolerance than aerobic fitness. In the hypohydrated condition, the heart rate was higher, sweat rate was lower, and participants showed lower tolerance for temperature change (observed through exhaustion occurring at lower rectal temperature) even after heat acclimation.⁷⁹ Therefore, dehydration could potentially enhance the risk of EHS via hyperthermia. While the role of dehydration in increased intestinal permeability has been hypothesised,⁸⁰ more studies are needed to support this idea with EHS.

Body composition

Obesity is associated with decreased cardiovascular fitness and impaired microvascular function at the skin, potentially leading to impaired thermoregulatory responses.⁸¹ Impaired skin microvascular function could lead to a diminished ability to produce sweat that matches evaporative heat loss demands. However, an association between skin blood flow and overall thermoregulation is absent.⁸² In a clinical trial involving independent groups (n=9 per group), Dervis et al reported that individuals with higher fat mass have impaired sudomotor responses leading to

a decreased ability to thermoregulate.⁸³ When heat production induced by exercise was fixed, individuals with low body fat had a higher sweat rate than those with high body fat. The fact that both groups exercised at the same heat production relative to lean body mass could explain these findings. The lower lean body mass in the high fat group resulted in a lower absolute heat production and thus a lower evaporative requirement. This diminished sudomotor response could have contributed to the measured core temperature in the Dervis study being greater in the high body fat group after 60 minutes of activity than the low body fat group. Overall, the main message of Dervis study was that, once the effects of heat production and mass were accounted for, a lower average specific heat capacity of body tissues in the high fat group led to a disproportionate mean elevation in core temperature. The findings also reinforce that the thermoregulatory responses of groups with different adiposity levels should not be compared using a fixed heat production.

Adipose tissue itself is an insulator under cool conditions (about 21°C) such that high adiposity might result in decreased ability to dissipate heat and heightened risk of hyperthermia.⁸⁴ Sweat evaporation is partially determined by skin temperature and varies across the body.^{85–87} In a clinical trial with independent groups (n=20 per group), Chudecka et al observed a statistically significant difference in skin temperature between obese and normal weight women at the thighs and abdomen—locations where excess adipose tissue is typically found in women. These findings support the concept of adipose tissue acting as an insulator, making heat dissipation in those areas less likely and causing heat retention.⁸⁴ Yokota et al used a simulated heat model with six compartments (muscle, fat, vascular skin, avascular skin, core, and central blood in passive and active heat) that was based on human physiology and biophysics in male soldiers.⁸⁸ The simulated model suggested that short and lean men have the greatest thermoregulatory response while tall and fat men have disadvantage in hyperthermic environments. Therefore, short and lean men were expected to wear their body armour and perform their tasks in a hyperthermic environment for 18 minutes longer than tall and fat men before reaching a core temperature of 38.5°C—a temperature in which 25% of heat casualties occur.⁸⁹ This study was simply a predictive model based off collected physiological and anthropometric data in male soldiers. Yokota et al validated this same model in women. Similar to the male data, female soldiers who were short and lean were expected to cope better with required activities in hyperthermic conditions than tall-fat women.⁹⁰ The researchers then had the women do the previously simulated situation and found the measured results to be consistent with the predicted results. Both Yokota studies support the idea that increased adipose

tissue increases insulation, although the anatomical location of these extra fat stores and the properties of the clothing worn might also be factors.

One aspect to consider is that cutaneous blood vessels pass through the subcutaneous fat layer, thus vasodilated skin allows warm blood to bypass the subcutaneous fat layer, regardless of its thickness.^{91 92} The lower density of fat tissue can alter the surface area for heat dissipation, although this effect is likely small. Ultimately, regardless of the mechanism, greater body surface area probably contributes to an increased core temperature and decreased heat loss, making exertional heat illness and EHS more probable. Finally, another factor associated with obesity that might explain a greater susceptibility to EHS is inflammation. Increased adiposity is well known to cause chronic inflammation and metabolic disease,⁹³ which are thought to be predisposing EHS risk factors.

Sex differences

Thermoregulatory differences exist between male and female individuals at high ambient temperatures in active conditions.^{94 95} In military populations, heat illnesses are more prevalent in women, but EHS is most common in men.⁹⁶ Behavioural, hormonal, morphological, and physiological differences can be difficult to dissociate between the sexes. From a morphological perspective, variations in surface area and body composition affect thermoregulatory efficiency. Overall, male and female mammals differ in size. Absolute mass and surface area tend to be greater in male mammals whereas surface area-to-mass ratio and body fat tend to be greater in female mammals. The implications of these morphological differences between sexes to EHS responses remain unclear.⁹⁷ In a preclinical model of EHS,⁹⁸ female mice outperformed male mice by about 40%.⁵⁹ This finding was unexpected given that this preclinical model consists of forced wheel running in uncompensable heat (37.5°C environmental temperature and 40% relative humidity) and the greater surface area-to-mass ratio in female mice.

Behavioural responses driven by endocrine stimuli could account for the higher incidence of EHS in men. Testosterone has a role in certain behaviours, including aggression and dominance,⁹⁹ which could justify men's tendency to ignore the protective physical signs and symptoms of heat illness. A clinical trial of 10 men and 10 women confirmed that, during exercise, women use thermal behaviour to a greater extent than men.¹⁰⁰ When looking at sex specific differences, menstrual cycle fluctuations in oestrogen, progesterone, and the ratio between the two result in oscillating core temperatures,¹⁰¹ although the influence of menstrual cycle in thermoregulation has been limited. At least during hot and dry conditions, the menstrual cycle phase does not appear to modulate whole body heat loss during exercise.¹⁰² Oral contraceptives could affect the core temperature due to the manipulation of these sex hormones,¹⁰³

however, the effect of these drugs on EHS has not been studied.

Responses to thermal stress between the sexes are primarily a result of decreased rates of metabolic heat production in female individuals.⁹⁵ This decrease in metabolic heat production is presumably associated with cutaneous vascular conductance and sudomotor activity.^{104 105} Female individuals tend to show lower sudomotor activity at a similar heat load than male individuals, resulting in differences in temperature regulation and sweat production.⁹⁴ However, in a clinical trial, Kazman et al¹⁰⁴ compared men's (n=55) and women's (n=20) responses to a heat tolerance test. All women were in the follicular phase of the menstrual cycle (ie, the longest step in the menstrual cycle, lasting from the first day of a period to ovulation, when oestrogen levels are high and progesterone levels are low). In this study, women were more heat intolerant than men, as defined by a core temperature over 38.5°C, failure to plateau in body temperature, or a heart rate over 150 bpm. Thus, sex was thought to predict heat intolerance. However, a linear regression analysis found body fat percentage and VO₂ max were more accurate predictors and negated the effect of sex. These findings also suggested thermal strain is less important than cardiovascular strain regarding performance in the heat.¹⁰⁴ However, the heat tolerance test lacks sensitivity and specificity owing to its stringent terminal criteria and cannot account for fluctuations in temperature above 38.5°C^{106 107} and it is associated with a high fail rate of false positives.¹⁰⁷

Oestrogen and progesterone fluctuations in the oestrous cycle result in variations in core temperature with women in the luteal phase (eg, high progesterone, lower oestrogen) showing 0.3-0.5 °C increase in core temperature compared with the follicular phase (eg, high oestrogen, low progesterone). Even with this variation in temperature, thermoregulatory responses did not differ throughout the estrous cycle phases. On the other hand, in a clinical trial of four women aged 20-35 years, Horvath et al observed differences in core temperature at rest that were attenuated during combined heat and exercise.¹⁰⁸ More studies are warranted to determine the influence of sex hormones on EHS susceptibility.

Ageing

Although EHS is more prevalent in young cohorts, ageing can be considered a risk factor because it is known to hinder several thermoregulatory and cardiovascular responses. Ageing in humans is accompanied by a decrease in sudomotor function, cardiovascular function, immune function, and behavioural thermoregulation.¹⁵ These factors contribute to the increased risk of heat related morbidity and mortality.¹⁰⁹ Elderly people typically have a higher incidence of classic heat stroke than EHS because of decreased activity levels, and many older individuals also have pre-existing cardiovascular insufficiencies, as observed by a lower

VO₂max, which has a negative effect on the ability to adequately respond to heat.¹¹⁰

Increased levels of physical activity on ageing mitigates the negative physiological alterations associated with ageing. Many factors might contribute to this impact of increased levels of physical activity, such as improved cardiovascular fitness, reduced weight, and improved immunity. The sudomotor system begins to decline considerably at age 40 years, beginning with the lower limbs and followed by the back, abdomen, upper limbs, and then head.¹¹¹ The resultant decline in sweat rate is due to decreased functionality of sweat glands, and not the number of sweat glands. An age related decline in sweating limits the ability to dissipate internal (metabolic) and external (ambient) sources of heat gain causing hyperthermia and potentially collapse. With the increasing incidence of EHS beyond athletics, it is likely that humans performing daily tasks, such as lawn mowing and gardening, might be at risk of developing EHS and the impact of ageing must be taken into consideration.

Previous illness

When an organism has an immunological challenge, the innate and adaptive immune systems are activated. Innate immunity represents non-specific immunological defenses that are activated immediately after antigens appear. Adaptive immunity is an antigen specific immune response that requires recognition of the antigen and development of immune cells specific to destroying that antigen. Heat stress and EHS have been shown to degrade gut integrity and stimulate the immune system.^{112 113} The degradation in gut integrity is implicated in a catastrophic immune response known as systemic inflammatory response syndrome.¹¹⁴ Heat exposure induces a set of proteins that modulate the immune response to resolve systemic inflammatory response syndrome. Cytokines are immune modulators that have a dynamic nature and have been associated with fatalities from heat stroke. However, as previously mentioned with interleukin 6, some cytokines have been implicated in both proinflammatory and anti-inflammatory functions, which could be a function of their concentration or the surrounding milieu in which they are functioning.¹¹⁵ Because of the vast array of cytokines and their diverse functions, understanding which specific set of cytokines can reduce or accentuate the effects of EHS has been difficult, and is likely to involve a coordinated response among several different cytokines.^{62 116} Another important set of immunological cells involved in heat stroke are lymphocytes.^{117 118} In classic heat stroke, T regulatory cells have been shown decrease in number and in immunosuppressive function.¹¹⁷ When lymphocyte production is compromised, heat stroke severity is exacerbated.¹¹⁸ Other factors might also come into play when determining how EHS or heat stress modulate the immune response, such as thermosensors, pre-existing conditions, previous illnesses,¹¹⁹ and epigenetic consequences.^{120 121}

Innate immunity is altered in individuals with comorbidities and pre-existing conditions, thus increasing the potential for exertional heat illness and, if left untreated, death. Diabetes mellitus has been shown to disrupt immune responses that are critical to staving off fungi, toxins, parasites, viruses, and bacteria. The mechanisms that are suppressed in patients with diabetes mellitus include dysfunction of immune cells, decreases in cytokine production, dysfunction in phagocytosis, and a decreased ability to eliminate microbials.¹²² These effects are prevalent owing to the hyperglycaemic environment in patients with diabetes mellitus.¹²³ In terms of heat stress, hyperglycaemic environments are strongly associated with reductions in skin blood flow and sudomotor function, potentially incapacitating evaporative heat loss.^{124 125} Another deleterious effect of hyperglycaemic is the loss of nitric oxide availability, contributing to vascular complications.¹²⁶ Based on the available evidence, a possible interplay could exist between the cardiovascular system, immune system, and diabetes—which complicates how to treat this condition and determine who is most vulnerable and why.

Emerging treatments and studies

Despite all the progress in our understanding of EHS, effective treatment strategies are still limited. Whole body cooling remains the most effective treatment to manage EHS victims on collapse.¹²⁷ A recent review of the literature highlighted the most effective forms of cooling which include immersion in iced or cold water, cold water dousing, tarp assisted immersion in ice or cold water, towels or sheets soaked in iced or cold water, cold water immersion in portable water impermeable bags, and water spray or mister or high powered fan with water spray.¹²⁷ Effective drug strategies to treat patients with EHS do not exist and common drugs, such as dantrolene sodium (primarily used to treat disorders related with skeletal muscle spasticity and malignant hyperthermia¹²⁸) have failed.^{129 130} Future studies of potential drug interventions to treat EHS are necessary.

This review highlights gaps in our knowledge to stimulate future research in the field of EHS. Important gaps in knowledge include the contributions of sex hormones to EHS susceptibility, whether dehydration is a risk factor for EHS, the role of endotoxemia in non-lethal EHS pathophysiology, the time course of changes in coagulofibrinolytic markers in EHS, and the impact of oral contraceptives on EHS risk. Research studies partitioning the contributions of different physiological systems¹³¹ and risk factors to EHS are required to advance knowledge on the precise sequence of events leading to EHS and the underlying mechanisms mediating organ damage.

Conclusions

EHS pathophysiology is complex and involves an interaction of thermoregulatory and cardiovascular factors that lead to systemic inflammatory response

syndrome. In catastrophic EHS events, systemic inflammatory response syndrome is likely initiated by endotoxaemia when the hepatic system fails to clear bacteria effectively. Coagulopathy is also present in the pathophysiology and manifests through disseminated intravascular coagulation, resulting in thrombosis or bleeding (or both). Risk factors discussed in this review include dehydration, sex differences, ageing, body composition, and previous illness. The reason why some people are more susceptible to EHS than others warrants further research.

QUESTIONS FOR FUTURE RESEARCH

- ⇒ What are the contributions of sex hormones to susceptibility exertional heat stroke (EHS)?
- ⇒ Is dehydration a risk factor for EHS?
- ⇒ Can endotoxaemia be involved in non-lethal EHS pathophysiology?
- ⇒ What is the time course of changes in coagulofibrinolytic markers in EHS?
- ⇒ What is the impact of oral contraceptives on EHS risk?

PATIENT INVOLVEMENT

No patients were asked for input in the creation of this article.

AUTHOR AFFILIATIONS

¹Department of Applied Physiology and Kinesiology, University of Florida, Gainesville, FL, USA

²Department of Nutrition and Integrative Physiology, Florida State University, Tallahassee, FL, USA

Twitter Orlando Laitano @olaitano

Contributors OL and LRL prepared the figures; CKG, LIR, GL-S, and OL drafted the manuscript; OL and LRL edited and revised the manuscript; CKG, LIR, GL-S, LRL, and OL approved final version of the manuscript. OL is the guarantor.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial, or not-for-profit sectors.

Competing interests We have read and understood the BMJ policy on declaration of interests and declare the following interests: none.

Provenance and peer review Commissioned; externally peer reviewed.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

ORCID iD

Orlando Laitano <http://orcid.org/0000-0003-2768-1427>

REFERENCES

- 1 Bouchama A, Abuyassin B, Lehe C, et al. Classic and exertional heatstroke. *Nat Rev Dis Primers* 2022;8:8. doi:10.1038/s41572-021-00334-6

- 2 Roberts WO. Exertional heat stroke during a cool weather marathon: a case study. *Med Sci Sports Exerc* 2006;38:1197–203. doi:10.1249/01.mss.0000227302.80783.of
- 3 Laitano O, Oki K, Leon LR. The role of skeletal muscles in exertional heat stroke pathophysiology. *Int J Sports Med* 2021;42:673–81. doi:10.1055/a-1400-9754
- 4 Costrini AM, Pitt HA, Gustafson AB, et al. Cardiovascular and metabolic manifestations of heat stroke and severe heat exhaustion. *Am J Med* 1979;66:296–302. doi:10.1016/0002-9343(79)90548-5
- 5 Exertional heat illness in adolescents and adults: Epidemiology, thermoregulation, risk factors, and diagnosis - UpToDate. Available: https://www.uptodate.com/contents/exertional-heat-illness-in-adolescents-and-adults-epidemiology-thermoregulation-risk-factors-and-diagnosis?sectionName=Heat%20syncope%20and%20exercise%20associated%20collapse&topicRef=17235&anchor=H25338600&source=see_link#H25338600 [Accessed 12 Jan 2022].
- 6 Alele FO, Malau-Aduli BS, Malau-Aduli AEO, et al. Epidemiology of exertional heat illness in the military: a systematic review of observational studies. *Int J Environ Res Public Health* 2020;17:E7037. doi:10.3390/ijerph17197037
- 7 Breslow RG, Shrestha S, Feroe AG, et al. Medical tent utilization at 10-km road races: injury, illness, and influencing factors. *Med Sci Sports Exerc* 2019;51:2451–7. doi:10.1249/MSS.0000000000002068
- 8 Demartini JK, Casa DJ, Stearns R, et al. Effectiveness of cold water immersion in the treatment of exertional heat stroke at the Falmouth road race. *Med Sci Sports Exerc* 2015;47:240–5. doi:10.1249/MSS.000000000000409
- 9 Laitano O, Leon LR, Roberts WO, et al. Controversies in exertional heat stroke diagnosis, prevention, and treatment. *J Appl Physiol* 2019;127:1338–48. doi:10.1152/jappphysiol.00452.2019
- 10 Broessner G, Beer R, Franz G, et al. Case report: severe heat stroke with multiple organ dysfunction - a novel intravascular treatment approach. *Crit Care* 2005;9:R498–501. doi:10.1186/cc3771
- 11 Roberts WO, Armstrong LE, Sawka MN, et al. ACSM expert consensus statement on exertional heat illness: recognition, management, and return to activity. *Curr Sports Med Rep* 2021;20:470–84. doi:10.1249/JSR.0000000000000878
- 12 Maron MB, Wagner JA, Horvath SM. Thermoregulatory responses during competitive marathon running. *J Appl Physiol Respir Environ Exerc Physiol* 1977;42:909–14. doi:10.1152/jappphysiol.1977.42.6.909
- 13 Racinais S, Moussay S, Nichols D, et al. Core temperature up to 41.5°C during the UCI road cycling world Championships in the heat. *Br J Sports Med* 2019;53:426–9. doi:10.1136/bjsports-2018-099881
- 14 González-Alonso J, Crandall CG, Johnson JM. The cardiovascular challenge of exercising in the heat. *J Physiol* 2008;586:45–53. doi:10.1113/jphysiol.2007.142158
- 15 Cramer MN, Gagnon D, Laitano O, et al. Human temperature regulation under heat stress in health, disease, and injury. *Physiol Rev* 2022;102:1907–89. doi:10.1152/physrev.00047.2021
- 16 Nadel ER, Wenger CB, Roberts MF, et al. Physiological defenses against hyperthermia of exercise. *Ann N Y Acad Sci* 1977;301:98–109. doi:10.1111/j.1749-6632.1977.tb38190.x
- 17 Ritchie KP, Keller BM, Syed KM, et al. Hyperthermia (heat shock)-induced protein denaturation in liver, muscle and lens tissue as determined by differential scanning calorimetry. *Int J Hyperthermia* 1994;10:605–18. doi:10.3109/02656739409022441
- 18 Gagnon D, Crandall CG. Sweating as a heat loss thermoeffector. *Handb Clin Neurol* 2018;156:211–32. doi:10.1016/B978-0-444-63912-7.00013-8
- 19 Romanovsky AA. Skin temperature: its role in thermoregulation. *Acta Physiol* 2014;210:498–507. doi:10.1111/apha.12231
- 20 Havenith G. Heat balance when wearing protective clothing. *Ann Occup Hyg* 1999;43:289–96.
- 21 Byrne C, Lee JKW, Chew SAN, et al. Continuous thermoregulatory responses to mass-participation distance running in heat. *Med Sci Sports Exerc* 2006;38:803–10. doi:10.1249/01.mss.0000218134.74238.6a
- 22 Ely BR, Ely MR, Chevront SN, et al. Evidence against a 40 degrees C core temperature threshold for fatigue in humans. *J Appl Physiol* 2009;107:1519–25. doi:10.1152/jappphysiol.00577.2009
- 23 Sawka MN, Knowlton RG, Critz JB. Thermal and circulatory responses to repeated bouts of prolonged running. *Med Sci Sports Exerc* 1979;11:177–80.
- 24 Carter R, Chevront SN, Sawka MN. A case report of idiosyncratic hyperthermia and review of U.S. Army heat stroke hospitalizations. *J Sport Rehabil* 2007;16:238–43. doi:10.1123/jsr.16.3.238
- 25 Ogoina D, Fever OD. Fever, fever patterns and diseases called 'fever'—a review. *J Infect Public Health* 2011;4:108–24. doi:10.1016/j.jiph.2011.05.002
- 26 Robinson S. Temperature regulation in exercise. *Pediatrics* 1963;32:691–702. doi:10.1542/peds.32.4.691
- 27 González-Alonso J, Quistorff B, Krstrup P, et al. Heat production in human skeletal muscle at the onset of intense dynamic exercise. *J Physiol* 2000;524 Pt 2:603–15. doi:10.1111/j.1469-7793.2000.00603.x

- 28 Hill AV. The heat produced in contracture and muscular tone. *J Physiol* 1910;40:389–403. doi:10.1113/jphysiol.1910.sp001377
- 29 Hill AV, Hartree W. The four phases of heat-production of muscle. *J Physiol* 1920;54:84–128. doi:10.1113/jphysiol.1920.sp001913
- 30 Launstein ED, Miller KC, O'Connor P, et al. American football uniforms elicit thermoregulatory failure during a heat tolerance test. *Temperature* 2021;8:245–53. doi:10.1080/23328940.2020.1855958
- 31 Nye NS, O'Connor FG. Exertional Heat Illness Considerations in the Military. In: Adams WM, Jardine JF, eds. *Exertional heat illness: a clinical and evidence-based guide*. Cham: Springer International Publishing, 2020: 181–209.
- 32 Rowell LB. Human cardiovascular adjustments to exercise and thermal stress. *Physiol Rev* 1974;54:75–159. doi:10.1152/physrev.1974.54.1.75
- 33 Rowell LB. *Human circulation regulation during physical stress*. Oxford University Press, 1986.
- 34 Leon LR, Bouchama A. Heat stroke. *Compr Physiol* 2015;5:611–47. doi:10.1002/cphy.c140017
- 35 Nybo L, Rasmussen P, Sawka MN. Performance in the heat-physiological factors of importance for hyperthermia-induced fatigue. *Compr Physiol* 2014;4:657–89. doi:10.1002/cphy.c130012
- 36 Sawka MN, Leon LR, Montain SJ, et al. Integrated physiological mechanisms of exercise performance, adaptation, and maladaptation to heat stress. *Compr Physiol* 2011;1:1883–928. doi:10.1002/cphy.c100082
- 37 Pires W, Veneroso CE, Wanner SP, et al. Association between exercise-induced hyperthermia and intestinal permeability: a systematic review. *Sports Med* 2017;47:1389–403. doi:10.1007/s40279-016-0654-2
- 38 Soares ADN, Costa KA, Wanner SP, et al. Dietary glutamine prevents the loss of intestinal barrier function and attenuates the increase in core body temperature induced by acute heat exposure. *Br J Nutr* 2014;112:1601–10. doi:10.1017/S0007114514002608
- 39 Walter E, W Watt P, Gibson OR, et al. Exercise hyperthermia induces greater changes in gastrointestinal permeability than equivalent passive hyperthermia. *Physiol Rep* 2021;9:e14945. doi:10.14814/phy2.14945
- 40 Costa RJS, Snipe RMJ, Kitic CM, et al. Systematic review: exercise-induced gastrointestinal syndrome-implications for health and intestinal disease. *Aliment Pharmacol Ther* 2017;46:246–65. doi:10.1111/apt.14157
- 41 Oliver SR, Phillips NA, Novosad VL, et al. Hyperthermia induces injury to the intestinal mucosa in the mouse: evidence for an oxidative stress mechanism. *Am J Physiol Regul Integr Comp Physiol* 2012;302:R845–53. doi:10.1152/ajpregu.00595.2011
- 42 Nolan JP. The role of intestinal endotoxin in liver injury: a long and evolving history. *Hepatology* 2010;52:1829–35. doi:10.1002/hep.23917
- 43 Graber CD, Reinhold RB, Bream JG, et al. Fatal heat stroke. circulating endotoxin and gram-negative sepsis as complications. *JAMA* 1971;216:1195–6. doi:10.1001/jama.216.7.1195
- 44 Gathiram P, Gaffin SL, Brock-Utne JG, et al. Time course of endotoxemia and cardiovascular changes in heat-stressed primates. *Aviat Space Environ Med* 1987;58:1071–4.
- 45 Kew M, Bersohn I, Seftel H, et al. Liver damage in heatstroke. *Am J Med* 1970;49:192–202. doi:10.1016/s0002-9343(70)80075-4
- 46 Bowers WD, Hubbard RW, Leav I, et al. Alterations of rat liver subsequent to heat overload. *Arch Pathol Lab Med* 1978;102:154–7.
- 47 Chao TC, Sinniah R, Pakiam JE. Acute heat stroke deaths. *Pathology* 1981;13:145–56. doi:10.3109/00313028109086837
- 48 Bynum G, Brown J, Dubose D, et al. Increased survival in experimental dog heatstroke after reduction of gut flora. *Aviat Space Environ Med* 1979;50:816–9.
- 49 DuBose DA, Basamania K, Maglione L, et al. Role of bacterial endotoxins of intestinal origin in rat heat stress mortality. *J Appl Physiol Respir Environ Exerc Physiol* 1983;54:31–6. doi:10.1152/jappl.1983.54.1.31
- 50 Leon LR, DuBose DA, Mason CW. Heat stress induces a biphasic thermoregulatory response in mice. *Am J Physiol Regul Integr Comp Physiol* 2005;288:R197–204. doi:10.1152/ajpregu.00046.2004
- 51 Leon LR, Blaha MD, DuBose DA. Time course of cytokine, corticosterone, and tissue injury responses in mice during heat strain recovery. *J Appl Physiol* 2006;100:1400–9. doi:10.1152/jappphysiol.01040.2005
- 52 Chung NK, Shabbir M, Lim CL. Cytokine levels in patients with previous heatstroke under heat stress. *Mil Med* 1999;164:306–10.
- 53 Iwaniec J, Robinson GP, Garcia CK, et al. Acute phase response to exertional heat stroke in mice. *Exp Physiol* 2021;106:222–32. doi:10.1113/EP088501
- 54 Chakraborty RK, Burns B. *Systemic inflammatory response syndrome*. Treasure Island (FL): StatPearls Publishing, 2022. <http://www.ncbi.nlm.nih.gov/books/NBK547669/>
- 55 Bouchama A, al-Sedairy S, Siddiqui S, et al. Elevated pyrogenic cytokines in heatstroke. *Chest* 1993;104:1498–502. doi:10.1378/chest.104.5.1498
- 56 Hammami MM, Bouchama A, Al-Sedairy S, et al. Concentrations of soluble tumor necrosis factor and interleukin-6 receptors in heatstroke and heatstress. *Crit Care Med* 1997;25:1314–9. doi:10.1097/00003246-199708000-00017
- 57 Bouchama A, Ollivier V, Roberts G, et al. Experimental heatstroke in baboon: analysis of the systemic inflammatory response. *Shock* 2005;24:332–5. doi:10.1097/01.shk.0000180620.44435.9c
- 58 King MA, Leon LR, Mustico DL, et al. Biomarkers of multiorgan injury in a preclinical model of exertional heat stroke. *J Appl Physiol* 2015;118:1207–20. doi:10.1152/jappphysiol.01051.2014
- 59 Garcia CK, Mattingly AJ, Robinson GP, et al. Sex-Dependent responses to exertional heat stroke in mice. *J Appl Physiol* 2018;125:841–9. doi:10.1152/jappphysiol.00220.2018
- 60 Phillips NA, Welc SS, Wallet SM, et al. Protection of intestinal injury during heat stroke in mice by interleukin-6 pretreatment. *J Physiol* 2015;593:739–52; discussion 753. doi:10.1113/jphysiol.2014.283416
- 61 Kawasaki T, Kawai T. Toll-Like receptor signaling pathways. *Front Immunol* 2014;5:461. doi:10.3389/fimmu.2014.00461
- 62 Welc SS, Clanton TL, Dineen SM, et al. Heat stroke activates a stress-induced cytokine response in skeletal muscle. *J Appl Physiol* 2013;115:1126–37. doi:10.1152/jappphysiol.00636.2013
- 63 Rallapalli PM, Orengo CA, Studer RA, et al. Positive selection during the evolution of the blood coagulation factors in the context of their disease-causing mutations. *Mol Biol Evol* 2014;31:3040–56. doi:10.1093/molbev/msu248
- 64 Palta S, Saroa R, Palta A. Overview of the coagulation system. *Indian J Anaesth* 2014;58:515–23. doi:10.4103/0019-5049.144643
- 65 Chapin JC, Hajjar KA. Fibrinolysis and the control of blood coagulation. *Blood Rev* 2015;29:17–24. doi:10.1016/j.blre.2014.09.003
- 66 Matsumoto H, Takeba J, Umakoshi K, et al. Successful treatment for disseminated intravascular coagulation (DIC) corresponding to phenotype changes in a heat stroke patient. *J Intensive Care* 2019;7:2. doi:10.1186/s40560-019-0359-3
- 67 Iba T, Connors JM, Levi M, et al. Heatstroke-induced coagulopathy: biomarkers, mechanistic insights, and patient management. *EClinicalMedicine* 2022;44:101276. doi:10.1016/j.eclinm.2022.101276
- 68 Sonkar SK, Soni D, Sonkar GK. Heat stroke presented with disseminated intravascular coagulation and bilateral intracerebral bleed. *BMJ Case Rep* 2012;2012. doi:10.1136/bcr-2012-007027. [Epub ahead of print: 19 Oct 2012].
- 69 Bouchama A, Al-Mohanna F, Assad L, et al. Tissue factor/factor VIIa pathway mediates coagulation activation in induced-heat stroke in the baboon. *Crit Care Med* 2012;40:1229–36. doi:10.1097/CCM.0b013e3182387bef
- 70 de Melo-Marins D, Farinha JB, Boeno FP, et al. The impact of dehydration and hyperthermia on circulatory glutathione metabolism after exercise in the heat with insights into the role of erythrocytes. *Life* 2021;11:1144. doi:10.3390/life11111144
- 71 Chevront SN, Kenefick RW. Dehydration: physiology, assessment, and performance effects. *Compr Physiol* 2014;4:257–85. doi:10.1002/cphy.c130017
- 72 King MA, Clanton TL, Laitano O, Hyperthermia LO. Hyperthermia, dehydration, and osmotic stress: unconventional sources of exercise-induced reactive oxygen species. *Am J Physiol Regul Integr Comp Physiol* 2016;310:R105–14. doi:10.1152/ajpregu.00395.2015
- 73 Coyle EF, González-Alonso J. Cardiovascular drift during prolonged exercise: new perspectives. *Exerc Sport Sci Rev* 2001;29:88–92. doi:10.1097/00003677-200104000-00009
- 74 Leyk D, Hoitz J, Becker C, et al. Health risks and interventions in exertional heat stress. *Dtsch Arztebl Int* 2019;116:537–44. doi:10.3238/arztebl.2019.0537
- 75 Maughan RJ, Shirreffs SM. Dehydration and rehydration in competitive sport. *Scand J Med Sci Sports* 2010;20 Suppl 3:40–7. doi:10.1111/j.1600-0838.2010.01207.x
- 76 Volpe SL, Poule KA, Bland EG. Estimation of prepractice hydration status of national collegiate athletic association division I athletes. *J Athl Train* 2009;44:624–9. doi:10.4085/1062-6050-44.6.624
- 77 Osterberg KL, Horswill CA, Baker LB. Pregame urine specific gravity and fluid intake by National Basketball association players during competition. *J Athl Train* 2009;44:53–7. doi:10.4085/1062-6050-44.1.53
- 78 Maughan RJ, Watson P, Evans GH, et al. Water balance and salt losses in competitive football. *Int J Sport Nutr Exerc Metab* 2007;17:583–94. doi:10.1123/ijsnem.17.6.583
- 79 Sawka MN, Young AJ, Latzka WA, et al. Human tolerance to heat strain during exercise: influence of hydration. *J Appl Physiol* 1992;73:368–75. doi:10.1152/jappl.1992.73.1.368
- 80 Roca Rubio MF, Eriksson U, Brummer RJ, et al. Sauna dehydration as a new physiological challenge model for intestinal barrier function. *Sci Rep* 2021;11:15514. doi:10.1038/s41598-021-94814-0
- 81 de Jongh RT, Serné EH, IJzerman RG, et al. Impaired microvascular function in obesity. *Circulation* 2004;109:2529–35. doi:10.1161/01.CIR.0000129772.266476f

- 82 Cramer MN, Gagnon D, Crandall CG, *et al.* Does attenuated skin blood flow lower sweat rate and the critical environmental limit for heat balance during severe heat exposure? *Exp Physiol* 2017;102:202–13. doi:10.1113/EP085915
- 83 Dervis S, Coombs GB, Chaselink GK, *et al.* A comparison of thermoregulatory responses to exercise between mass-matched groups with large differences in body fat. *J Appl Physiol* 2016;120:615–23. doi:10.1152/jappphysiol.00906.2015
- 84 Chudecka M, Lubkowska A, Kempnińska-Podhorodecka A. Body surface temperature distribution in relation to body composition in obese women - ScienceDirect. Available: <https://www.sciencedirect.com/science/article/pii/S0306456514000461?via%3Dihub> [Accessed 13 Jan 2022].
- 85 Coull NA, West AM, Hodder SG, *et al.* Body mapping of regional sweat distribution in young and older males. *Eur J Appl Physiol* 2021;121:109–25. doi:10.1007/s00421-020-04503-5
- 86 Smith CJ, Havenith G. Body mapping of sweating patterns in male athletes in mild exercise-induced hyperthermia. *Eur J Appl Physiol* 2011;111:1391–404. doi:10.1007/s00421-010-1744-8
- 87 Smith CJ, Havenith G. Body mapping of sweating patterns in athletes: a sex comparison. *Med Sci Sports Exerc* 2012;44:2350–61. doi:10.1249/MSS.0b013e318267b0c4
- 88 Yokota M, Bathalon GP, Berglund LG. Assessment of male anthropometric trends and the effects on simulated heat stress responses. *Eur J Appl Physiol* 2008;104:297–302. doi:10.1007/s00421-007-0656-8
- 89 Sawka MN, Latzka WA, Montain SJ, *et al.* Physiologic tolerance to uncompensable heat: intermittent exercise, field vs laboratory. *Med Sci Sports Exerc* 2001;33:422–30. doi:10.1097/00005768-200103000-00014
- 90 Yokota M, Berglund LG, Bathalon GP. Female anthropometric variability and their effects on predicted thermoregulatory responses to work in the heat. *Int J Biometeorol* 2012;56:379–85. doi:10.1007/s00484-011-0441-6
- 91 Burse RL. Sex differences in human thermoregulatory response to heat and cold stress. *Hum Factors* 1979;21:687–99. doi:10.1177/001872087912210606
- 92 Havenith G, van Middendorp H. The relative influence of physical fitness, acclimatization state, anthropometric measures and gender on individual reactions to heat stress. *Eur J Appl Physiol Occup Physiol* 1990;61:419–27. doi:10.1007/BF00236062
- 93 Kawai T, Autieri MV, Scalia R. Adipose tissue inflammation and metabolic dysfunction in obesity. *Am J Physiol Cell Physiol* 2021;320:C375–91. doi:10.1152/ajpcell.00379.2020
- 94 Gagnon D, Kenny GP. Does sex have an independent effect on thermoenergetic responses during exercise in the heat? *J Physiol* 2012;590:5963–73. doi:10.1113/jphysiol.2012.240739
- 95 Gagnon D, Jay O, Lemire B, *et al.* Sex-Related differences in evaporative heat loss: the importance of metabolic heat production. *Eur J Appl Physiol* 2008;104:821–9. doi:10.1007/s00421-008-0837-0
- 96 Alele F, Malau-Aduli B, Malau-Aduli A, *et al.* Systematic review of gender differences in the epidemiology and risk factors of exertional heat illness and heat tolerance in the armed forces. *BMJ Open* 2020;10:e031825. doi:10.1136/bmjopen-2019-031825
- 97 Giersch GEW, Garcia CK, Stachenfeld NS, *et al.* Are there sex differences in risk for exertional heat stroke? a translational approach. *Exp Physiol* 2022. doi:10.1113/EP090402. [Epub ahead of print: 22 May 2022].
- 98 King MA, Alzahrani JM, Clanton TL, *et al.* A preclinical model of exertional heat stroke in mice. *J Vis Exp* 2021. doi:10.3791/62738. [Epub ahead of print: 01 07 2021].
- 99 Batrinos ML. Testosterone and aggressive behavior in man. *Int J Endocrinol Metab* 2012;10:563–8. doi:10.5812/ijem.3661
- 100 Vargas NT, Chapman CL, Sackett JR, *et al.* Thermal behavior differs between males and females during exercise and recovery. *Med Sci Sports Exerc* 2019;51:141–52. doi:10.1249/MSS.0000000000001756
- 101 Cagnacci A, Volpe A, Paoletti AM, *et al.* Regulation of the 24-hour rhythm of body temperature in menstrual cycles with spontaneous and gonadotropin-induced ovulation. *Fertil Steril* 1997;68:421–5. doi:10.1016/S0015-0282(97)00242-2
- 102 Notley SR, Dervis S, Poirier MP, *et al.* Menstrual cycle phase does not modulate whole body heat loss during exercise in hot, dry conditions. *J Appl Physiol* 2019;126:286–93. doi:10.1152/jappphysiol.00735.2018
- 103 Martin JG, Buono MJ. Oral contraceptives elevate core temperature and heart rate during exercise in the heat. *Clin Physiol* 1997;17:401–8. doi:10.1046/j.1365-2281.1997.04444.x
- 104 Kazman JB, Purvis DL, Heled Y, *et al.* Women and exertional heat illness: identification of gender specific risk factors. *US Army Med Dep J* 2015;58–66.
- 105 Gagnon D, Crandall CG, Kenny GP. Sex differences in postsynaptic sweating and cutaneous vasodilation. *J Appl Physiol* 2013;114:394–401. doi:10.1152/jappphysiol.00877.2012
- 106 Mitchell KM, Cheuvront SN, King MA, *et al.* Use of the heat tolerance test to assess recovery from exertional heat stroke. *Temperature* 2019;6:106–19. doi:10.1080/23328940.2019.1574199
- 107 Mitchell KM, Salgado RM, Bradbury KE, *et al.* Heat acclimation improves heat tolerance test specificity in a Criteria-dependent manner. *Med Sci Sports Exerc* 2021;53:1050–5. doi:10.1249/MSS.0000000000002545
- 108 Horvath SM, Drinkwater BL. Thermoregulation and the menstrual cycle. *Aviat Space Environ Med* 1982;53:790–4.
- 109 Millyard A, Layden JD, Pyne DB, *et al.* Impairments to thermoregulation in the elderly during heat exposure events. *Gerontol Geriatr Med* 2020;6:233372142093243. doi:10.1177/2333721420932432
- 110 Shibasaki M, Okazaki K, Inoue Y. Aging and thermoregulation. *J Phys Fit Sports Med* 2013;2:37–47. doi:10.7600/jpfsm.2.37
- 111 Inoue Y, Kuwahara T, Araki T. Maturation- and aging-related changes in heat loss effector function. *J Physiol Anthropol Appl Human Sci* 2004;23:289–94. doi:10.2114/jpa.23.289
- 112 Garcia CK, Sheikh LH, Iwaniec JD, *et al.* Effects of ibuprofen during exertional heat stroke in mice. *Med Sci Sports Exerc* 2020;52:1870–8. doi:10.1249/MSS.0000000000002329
- 113 Koch F, Thom U, Albrecht E, *et al.* Heat stress directly impairs gut integrity and recruits distinct immune cell populations into the bovine intestine. *Proc Natl Acad Sci U S A* 2019;116:10333–8. doi:10.1073/pnas.1820130116
- 114 Leon LR, Helwig BG. Heat stroke: role of the systemic inflammatory response. *J Appl Physiol* 2010;109:1980–8. doi:10.1152/jappphysiol.00301.2010
- 115 Heled Y, Fleischmann C, Epstein Y. Cytokines and their role in hyperthermia and heat stroke. *J Basic Clin Physiol Pharmacol* 2013;24:1–12. doi:10.1515/jbcp-2012-0040
- 116 King MA, Leon LR, Morse DA, *et al.* Unique cytokine and chemokine responses to exertional heat stroke in mice. *J Appl Physiol* 2017;122:296–306. doi:10.1152/jappphysiol.00667.2016
- 117 Hu J, Kang H-J, Liu C, *et al.* Response of regulatory T cells to classic heat stroke in mice. *Exp Ther Med* 2018;16:4609–15. doi:10.3892/etm.2018.6766
- 118 Tan Y, Liu X, Yu X, *et al.* Lack of lymphocytes exacerbate heat stroke severity in male mice through enhanced inflammatory response. *Int Immunopharmacol* 2021;101:108206. doi:10.1016/j.intimp.2021.108206
- 119 Dineen SM, Ward JA, Leon LR. Prior viral illness increases heat stroke severity in mice. *Exp Physiol* 2021;106:244–57. doi:10.1113/EP088480
- 120 Murray KO, Brant JO, Iwaniec JD, *et al.* Exertional heat stroke leads to concurrent long-term epigenetic memory, immunosuppression and altered heat shock response in female mice. *J Physiol* 2021;599:119–41. doi:10.1113/jp280518
- 121 Murray KO, Clanton TL, Horowitz M. Epigenetic responses to heat: From adaptation to maladaptation. *Experimental Physiology*;n/a.
- 122 Berbudi A, Rahmadika N, Tjahjadi AI, *et al.* Type 2 diabetes and its impact on the immune system. *Curr Diabetes Rev* 2020;16:442–9. doi:10.2174/1573399815666191024085838
- 123 Casqueiro J, Casqueiro J, Alves C. Infections in patients with diabetes mellitus: a review of pathogenesis. *Indian J Endocrinol Metab* 2012;16 Suppl 1:S27–36. doi:10.4103/2230-8210.94253
- 124 Chahal S, Vohra K, Syngle A. Association of sudomotor function with peripheral artery disease in type 2 diabetes. *Neuro Sci* 2017;38:151–6. doi:10.1007/s10072-016-2742-3
- 125 Chan NN, Vallance P, Colhoun HM. Endothelium-Dependent and -independent vascular dysfunction in type 1 diabetes: role of conventional risk factors, sex, and glycemic control. *Arterioscler Thromb Vasc Biol* 2003;23:1048–54. doi:10.1161/01.ATV.0000072968.00157.6B
- 126 Rodríguez-Mañas L, López-Dóriga P, Petidier R, *et al.* Effect of glycaemic control on the vascular nitric oxide system in patients with type 1 diabetes. *J Hypertens* 2003;21:1137–43. doi:10.1097/00004872-200306000-00013
- 127 DeGroot DW, O'Connor FG, Roberts WO. Exertional heat stroke: an evidence based approach to clinical assessment and management. *Exp Physiol*;22. doi:10.1113/EP090488
- 128 Laitano O, Murray KO, Leon LR. Overlapping mechanisms of exertional heat stroke and malignant hyperthermia: evidence vs. conjecture. *Sports Med* 2020;50:1581–92. doi:10.1007/s40279-020-01318-4
- 129 Bouchama A, Cafege A, Devol EB, *et al.* Ineffectiveness of dantrolene sodium in the treatment of heatstroke. *Crit Care Med* 1991;19:176–80. doi:10.1097/00003246-199102000-00011
- 130 Channa AB, Seraj MA, Sadique AA, *et al.* Is dantrolene effective in heat stroke patients? *Crit Care Med* 1990;18:290–2. doi:10.1097/00003246-199003000-00009
- 131 Travers G, Kippelen P, Trangmar SJ, *et al.* Physiological function during exercise and environmental stress in Humans-An integrative view of body systems and homeostasis. *Cells* 2022;11:383. doi:10.3390/cells11030383