Environment International 144 (2020) 105909

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Review article

Physiological factors characterizing heat-vulnerable older adults: A narrative review

Robert D. Meade[a], Ashley P. Akerman[a], Sean R. Notley[a], Ryan McGinn[b], Paul Poirier[c], Pierre Gosselin[d], Glen P. Kenny[a,e,*]

[a] Human and Environmental Physiology Research Unit, School of Human Kinetics, University of Ottawa, Ottawa, Ontario, Canada
[b] Department of Anesthesiology and Pain Medicine, The Ottawa Hospital, University of Ottawa, Ottawa, ON, Canada
[c] Institut Universitaire de Cardiologie et de Pneumologie de Québec, Université Laval, Québec, Québec, Canada
[d] Institut National de Santé Publique du Québec and Université Laval, Québec, Québec, Canada
[e] Clinical Epidemiology Program, Ottawa Hospital Research Institute, Ottawa, Ontario, Canada

ARTICLE INFO

Handling Editor: Zorana Jovanovic Andersen

Keywords:
Aging
Heatwaves
Heat stress
Chronic disease
Climate change
Thermoregulation
Cardiovascular

ABSTRACT

More frequent and intense periods of extreme heat (heatwaves) represent the most direct challenge to human health posed by climate change. Older adults are particularly vulnerable, especially those with common age-associated chronic health conditions (e.g., cardiovascular disease, hypertension, obesity, type 2 diabetes, chronic kidney disease). In parallel, the global population is aging and age-associated disease rates are on the rise. Impairments in the physiological responses tasked with maintaining homeostasis during heat exposure have long been thought to contribute to increased risk of health disorders in older adults during heatwaves. As such, a comprehensive overview of the provisional links between age-related physiological dysfunction and elevated risk of heat-related injury in older adults would be of great value to healthcare officials and policy makers concerned with protecting heat-vulnerable sectors of the population from the adverse health impacts of heatwaves. In this narrative review, we therefore summarize our current understanding of the physiological mechanisms by which aging impairs the regulation of body temperature, hemodynamic stability and hydration status. We then examine how these impairments may contribute to acute pathophysiological events common during heatwaves (e.g., heatstroke, major adverse cardiovascular events, acute kidney injury) and discuss how age-associated chronic health conditions may exacerbate those impairments. Finally, we briefly consider the importance of physiological research in the development of climate-health programs aimed at protecting heat-vulnerable individuals.

1. Introduction

The most direct threat to human health posed by climate change is heat stress stemming from global increases in the frequency, intensity, and duration of extreme heat events (heatwaves) (Haines and Ebi, 2019; Watts et al., 2019). Heatwaves are accompanied by elevated morbidity and mortality in vulnerable sectors of the population due to multiple acute pathophysiological conditions (e.g., heatstroke, adverse cardiovascular events, kidney injury) (Semenza et al., 1999, 1996; Huang et al., 2012; Vaidyanathan et al., 2019). Older adults are among the most at risk, especially those with age-associated chronic conditions linked with heat-vulnerability (e.g., cardiovascular disease, type 2 diabetes, obesity) (Bouchama et al., 2007; Kenny et al., 2010; Semenza et al., 1999; Vandentorren et al., 2006). The global population is aging and the prevalence of age-associated disease is on the rise (Suzman et al., 2015). Coupled with more frequent and intense heatwaves, this means that a growing number of vulnerable older adults are at increasing risk of heat-related illness and injury. To this end, the World Health Organization has projected that annual heat-related deaths in individuals aged ≥65 years will increase by as much as 250,000 by mid-century, unless rapid progress toward climate adaptation is made (World Health Organization, 2014).

Improving climate resiliency and reducing heat-related burden necessitates the development of appropriate public health programs (e.g., heat warnings, heat-health action plans) and training of healthcare providers to better recognize, manage, and communicate the health impacts of extreme heat (Haines and Ebi, 2019; Mayrhuber et al., 2018). A critical step in realizing these goals is the identification and

* Corresponding author at: University of Ottawa, School of Human Kinetics, 125 University, Room 367, Montpetit Hall, Ottawa, Ontario K1N 6N5, Canada.
E-mail address: gkenny@uottawa.ca (G.P. Kenny).

https://doi.org/10.1016/j.envint.2020.105909
Received 16 April 2020; Received in revised form 24 May 2020; Accepted 17 June 2020
Available online 09 September 2020

characterization of factors associated with heat-vulnerability (Frumkin et al., 2015). It is widely appreciated that impaired physiological responses to heat exposure contribute to reduced thermotolerance in older adults, especially those with common age-associated chronic conditions (Flynn et al., 2005; Haines and Ebi, 2019; Kenney et al., 2014; Kenny et al., 2010). It is also likely not a coincidence that the organ systems tasked with maintaining homeostasis during heat stress often exhibit the greatest strain or injury (Flynn et al., 2005; Kenney et al., 2014). A more complete understanding of the physiological basis of heat vulnerability would therefore aid healthcare officials and policy makers concerned with protecting vulnerable sectors of the population from the adverse health impacts of extreme heat.

Here, we provide a comprehensive overview of the mechanisms by which aging impairs the acute physiological response to heat stress, highlighting dysregulation in the physiological systems responsible for maintaining body temperature and haemodynamic stability. We then examine how these impairments may contribute to acute heat-related injury and impact pre-existing chronic health conditions. Finally, we briefly consider the emerging role of physiological research in addressing climate-related health challenges.

2. Aging and the integrated physiological response to heat exposure

Heat-vulnerability is influenced by advanced age more than any other non-modifiable risk factor (Haines and Ebi, 2019; Mayrhuber et al., 2018; Watts et al., 2019). For instance, during the European heatwave of 2003 (~70,000 heat-attributable deaths), mortality in France increased by 40–100% in older adults (≥65 years), with relatively modest elevations in middle-aged adults (35–64 years; ~20–30%) and little change in the young (< 35 years) (Fouillet et al., 2006; Robine et al., 2008). As previously reviewed, in brief, by Kenny et al. (2010) and Kenney et al. (2014), impaired regulation of body temperature and haemodynamic stability (maintenance of arterial blood pressure and end-organ perfusion) are thought to contribute to the development of heat-vulnerability with aging. In this section we discuss the physiological mechanisms supporting homeostasis during heat exposure (Fig. 1) and how they are impacted by aging independent of the development of overt chronic health conditions (hereafter referred to as healthy aging) (Fig. 2). Older adults are considered as individuals over the age of 65 years (Suzman et al., 2015), with middle-age encompassing those aged 35–64 years. It should be noted, however, that the physiological alterations associated with aging and, by extension, heat vulnerability are progressive and complex and strongly related to genetic and lifestyle factors.

2.1. Body temperature regulation

To maintain a stable internal environment conducive to health, humans strive to regulate body temperature within a narrow range (~36.5–37.0°C). This requires a fine balance between endogenous heat produced as a by-product of metabolism and the dry (convection, radiation, conduction) and evaporative heat exchanges between the individual and surrounding environment. Those heat exchanges occur according to thermal- and water-pressure gradients between the skin and the environment, which can be modified by behavioral and autonomic thermoeffector responses. The most powerful thermoeffectors are of behavioral origin (Flouris and Schlader, 2015). Moving to a cooler location and use of air-conditioning, for example, have been linked to lower morbidity and mortality during heatwaves (Bouchama et al., 2007; Kenny et al., 2010; Mayrhuber et al., 2018; Semenza et al., 1999). However, some older adults may be unable to modify their behavior due to impaired functional and cognitive capacity and/or ability to sense their own thermal state (Guergova and Dufour, 2011; Matthies et al., 2008). In other cases, elderly adults are unwilling or unable to employ simple measures such as opening windows due to costs, ambient noise and pollution, or fear of crime (Klinenberg, 2015). These individuals must rely more heavily on the autonomic regulation of body temperature, which will be the primary focus of this review.

Upon exposure to a hot environment, dry heat gain will initially exceed the rate of heat loss, causing an increase in body heat storage that is further augmented by any elevations in heat production from physical activity (Kenny and Jay, 2013). The resultant rise in body temperature is sensed by thermoreceptors located primarily in the central nervous system and skin (Hensel, 1974). Feedback from these receptors is integrated in the preoptic anterior hypothalamus (Boulant, 1981), which triggers thermoeffector mechanisms to restore a balance between heat gain and loss to prevent continued rises in body temperature (Kenny and Jay, 2013). Sympathetically-driven cutaneous vasodilation and eccrine sweating comprise the primary autonomic thermoreffector responses to heat stress. Cutaneous vasodilation facilitates blood flow and convective heat delivery to the skin. The resultant increase in skin temperature augments dry heat loss in temperate environments by widening the skin-environment thermal gradient and buffers dry heat gain in hotter conditions (Kenny and Jay, 2013). Simultaneously, blood-borne heat is released through the evaporation of sweat secreted by the 2–3 million eccrine sweat glands distributed across the skin surface (Taylor and Machado-Moreira, 2013). Sweat evaporation provides the greatest capacity for heat dissipation and is the primary avenue of heat loss during exposure to hot, dry environments (Kenny and Jay, 2013). This is because evaporative heat loss occurs independent of environmental temperature along the skin-environment water-vapour gradient. However, this also means that increased ambient humidity reduces evaporative heat loss (Chen et al., 2019).

In instances where heat loss is sufficient to offset heat gain (compensable conditions), the rate of body heat storage will return to zero and core temperature will stabilize, albeit, at an elevated level (Fig. 3). By contrast, hotter and more humid conditions can cause the rate of evaporative heat loss required to attain heat balance to exceed the maximal heat loss permitted by the environment (Kenny and Jay, 2013). In such conditions, termed uncompensable, continued exposure will cause a progressive rise in body temperature that can compromise health if left unchecked.

2.2. Thermoregulation in older adults

Recent years have seen marked advances in our understanding of age-related impairments in thermoregulatory function (Kenney, 2017; Meade et al., 2019c). Early investigations in this domain led to the belief that aging is associated with increased skin blood flow during heat stress (Hellon and Lind, 1956, 1958). However, following seminal work by Kenney (1988), who demonstrated blunted elevations in forearm blood flow with increasing body temperature in middle-aged-to-older (55–68 years-old) compared to young men (19–30 years-old) during exercise, studies have consistently demonstrated impaired vascular responses to heat stress in middle-aged and older adults (Kenney, 2017). This impairment is primarily owed to attenuated nitric-oxide (NO)-dependent vasodilation secondary to reductions in NO bioavailbility resulting from elevated reactive oxygen species (ROS) and arginase activity (Holowatz et al., 2006; Meade et al., 2019a). Also contributing to compromised skin blood flow in heat-stressed older adults is blunted autonomic control of the cutaneous circulation (Greaney et al., 2016) and reduced cardiac reserve (Kenney et al., 2014).

Aging is also associated with reductions in sweat production. While the number of sweat glands responsive to thermal stimuli is unaffected by aging (Inoue et al., 1991), the output from each gland for a given change in body temperature or in response to pharmacological stimuli is attenuated (Inoue et al., 1999b; Kenney and Fowler, 1988). A reduced contribution of NO (Meade et al., 2019a) and altered sweat gland potassium channel function (McGarr et al., 2019) have been shown to

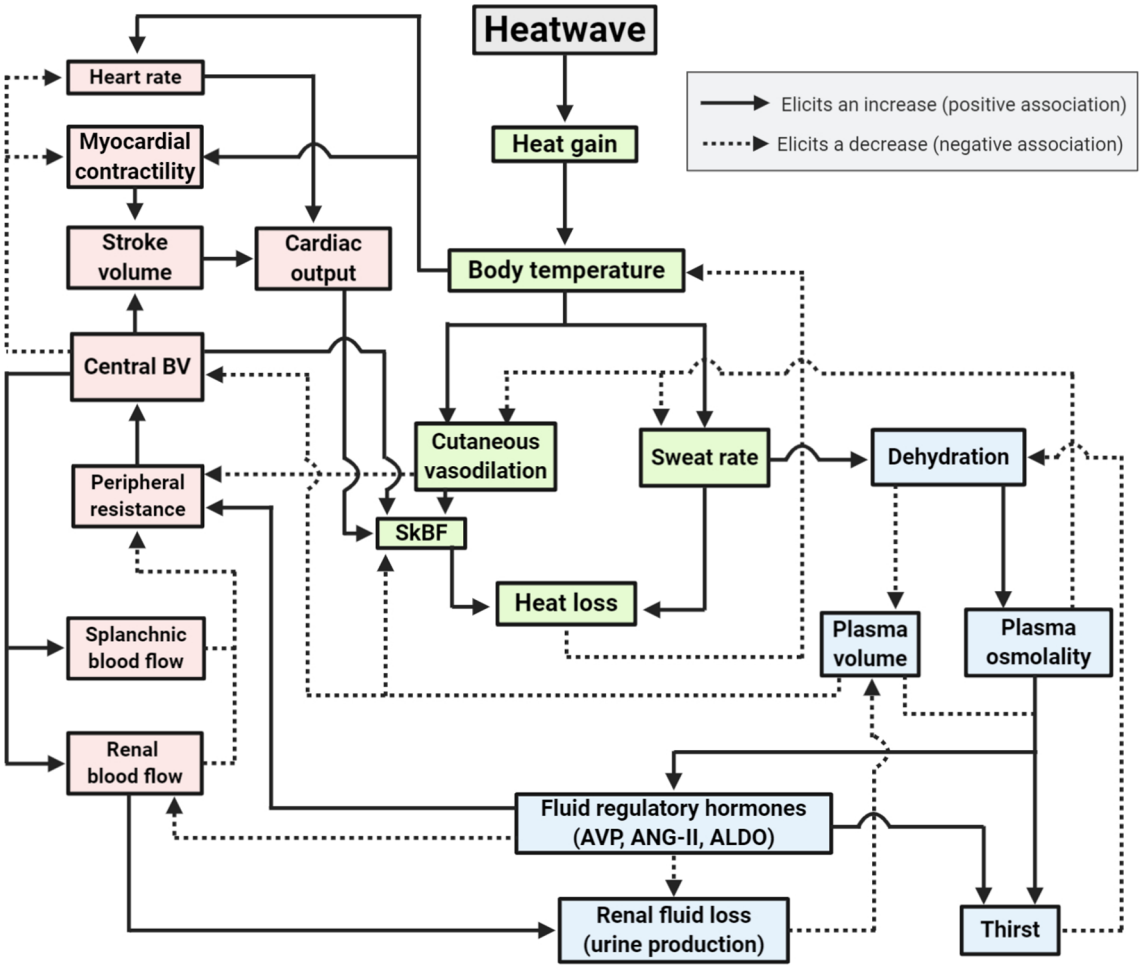

Fig. 1. A schematic summary of the integrated physiological responses tasked with maintaining homeostasis during extreme heat exposure. The green, red and blue boxes denote the thermoregulatory, cardiovascular and fluid regulatory systems, respectively. These broad classifications reflect the discussion of these systems in the main text. Positive associations (e.g., increase in one factor elicits an increase in the of the downstream factor) are denoted by the solid arrows. Negative associations (e.g., increase in one factor elicits a decrease in the downstream factor) are denoted by the dashed arrows. Abbreviations: BV, blood volume; SkBF, skin blood flow; AVP, arginine vasopressin; ANG-II, angiotensin II; ALDO, aldosterone). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

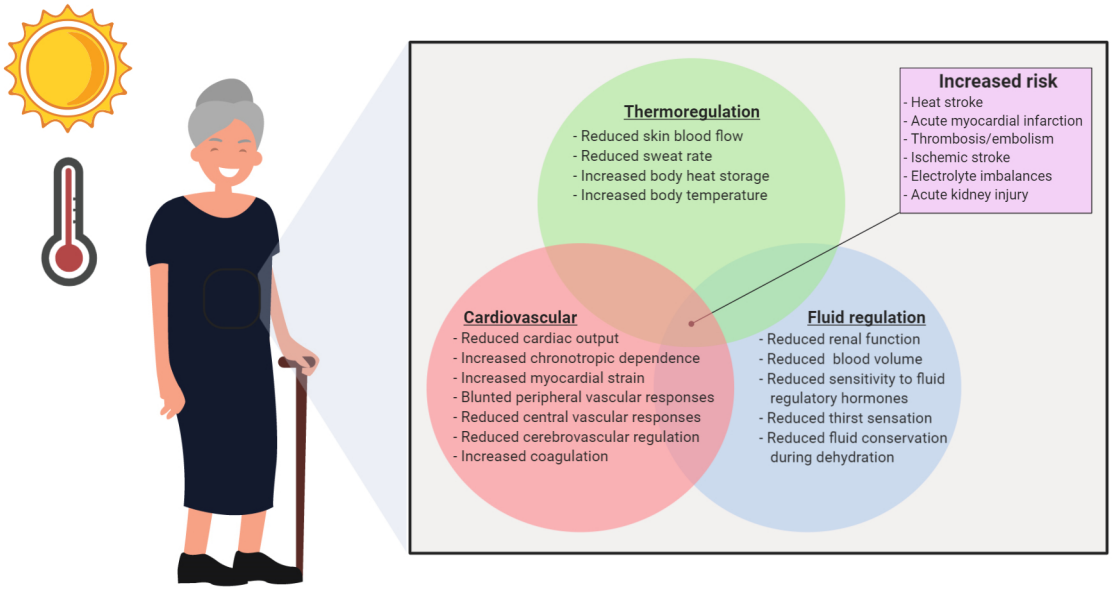

Fig. 2. A Venn diagram summarizing the age-related impairments in the integrated physiological responses to heat stress thought to contribute to the increased risk of acute adverse health events in older relative to young adults during heatwaves (see main text for details).

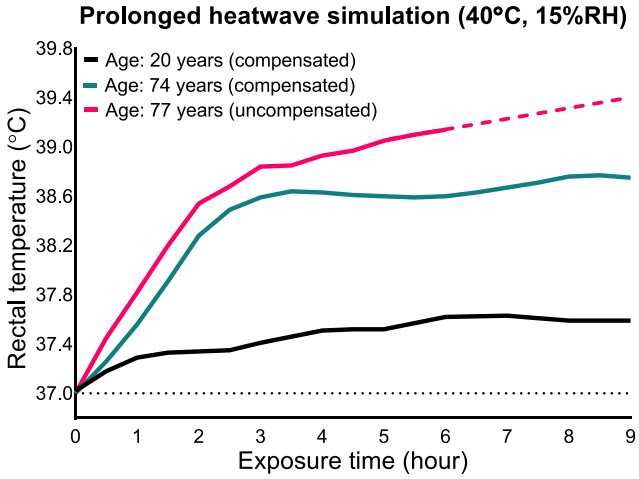

Fig. 3. Unpublished data from our laboratory showing rectal temperature in one young and two older women over a 9-h heatwave simulation (40°C, ~15% relative humidity; heat index: 38°C). These conditions were chosen to simulate the heat index experienced during recent heatwaves in North America in 2018 (Ottawa, Ontario; 34°C and 58%; heat index: 41°C) and Europe in 2003 (Paris, France; 38°C and 25%; heat index: 38°C). In the young (20 years; black line) and older (74 years; green line) women, thermal equilibrium is achieved by the end of exposure; albeit, at an elevated temperature in the older participant likely due to altered onset and thermosensitivity but a similar plateau to the young woman, as shown in panel A. In the 77-year-old woman (pink line), conditions have overwhelmed the body's capacity to dissipate heat (and achieve heat balance) and body temperature continues to rise. This participant was removed from the heat after 6 h due to feelings of light headedness and nausea. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

contribute. The net effect is a reduction in whole-body sweat rate, limiting the potential for evaporative heat loss (Meade et al., 2019c).

As a result of these alterations, activation of cutaneous vasodilation and sweating with increasing body temperature is blunted with aging (Kenney and Munce, 2003; Shibasaki et al., 2013). Consequently, studies have generally reported greater elevations in body heat storage and core temperature in older compared to younger adults during environmental heat exposure (Table 1). For example, Kenny et al. (2017) observed ~80% greater heat storage (equivalent to a ~0.5°C greater elevation in mean body temperature) in middle-aged-to-older (55–73 years-old) compared to young adults (18–28 years-old) during 3-hours of resting heat exposure. More importantly, the latter group did not achieve heat balance. Based on this, the authors postulated that continual increases in heat storage and body temperature would have occurred, reaching potentially dangerous levels if exposure duration was extended (Kenny et al., 2017). That said, it is important to note, that most studies that have evaluated the effect of age on physiological responses to environmental heat exposure have employed extreme ambient conditions (Table 1) that likely do not represent those experienced during heatwaves. Whether older adults experience progressive increases in heat storage and body temperature during heatwaves remains to be evaluated; though, this hypothesis is supported by preliminary data from our laboratory (Fig. 3).

2.3. Haemodynamic regulation

During heat stress, profound cardiovascular adjustments act to support body temperature regulation and maintain haemodynamics. In young adults, cutaneous vasodilation can elevate skin perfusion from ~0.3 L/min at rest to ~6–7 L/min during extreme heat stress (Minson et al., 1998). To compensate for the resultant fall in peripheral resistance, cardiac output increases by up to 7 L/min, primarily through elevations in heart rate (Rowell et al., 1969). Stroke volume is maintained (or slightly elevated), despite falling central venous pressure and cardiac preload, via increased myocardial contractility (Bundgaard-Nielsen et al., 2010). Concurrent vasoconstriction of the splanchnic and renal vascular beds facilitates re-distribution of blood to central and cutaneous regions (Chapman et al., 2019; Minson et al., 1998). These alterations are coordinated by sympathetic activation in proportion to the magnitude of heat stress (Gagnon et al., 2015; Rowell, 1990) and, in young adults, are typically sufficient to maintain cutaneous perfusion and arterial pressure (Crandall and Wilson, 2015).

2.4. Aging and haemodynamic regulation during heat stress

Compared to their younger counterparts, older individuals exhibit smaller increases in cardiac output during heat stress, limiting elevations in skin blood flow (Minson et al., 1998). There are several putative contributing mechanisms: endothelial dysfunction, central artery stiffening, reductions in cardiac reserve, and blunted autonomic function. Regarding the former, aging is associated with diffuse endothelial vascular dysfunction. This is due, primarily, to systemic reductions in NO bioavailability that impair vasodilation of the cutaneous microvasculature (Kenney, 2017) and the upstream peripheral arteries (Celermajer et al., 1994). Reduced endothelium-dependent vasodilation along with other structural (e.g., vessel fibrosis) and functional (e.g., altered autocrine and paracrine signaling) changes contribute to increasing stiffness of the central and conduit vessels (Chirinos et al., 2019; Zieman et al., 2005). Central arteries stiffen with aging (Mitchell et al., 2004) and the associated loss of vessel elasticity results in a widening of the arterial pulse pressure and increasing variability in the rate of forward flow (Hashimoto and Ito, 2010). This mechanism is likely involved in the reduced ability of the systemic circulation to respond to heat exposure, given that indices of arterial stiffness in older adults are not altered by acute heat stress (Schlader et al., 2019b), though future research is required to confirm this hypothesis.

Age-related central cardiac dysfunction also contributes to the inadequate cardiovascular responses to heat exposure. Elevations in cardiac output during heat stress are blunted in older adults (Minson et al., 1998), likely due to attenuated beta-adrenergic responsiveness and altered cardiac mechanics (Spina et al., 1998), which limit maximal cardiac output (Fleg et al., 1995). Further, stroke volume is reduced for a given left ventricular filling pressure in non-heat stressed (Arbab-Zadeh et al., 2004) and heat stressed conditions (Minson et al., 1998). While the stroke volume response to whole-body heating does not appear altered by aging, older adults exhibit lesser elevations in heart rate, contributing to the attenuated increases in cardiac output (Gagnon et al., 2016). Age-related reductions in maximal heart rate also mean that older adults rely more heavily on a limited heart rate reserve to facilitate cardiac adjustments during hyperthermia (Kenney et al., 2014).

Finally, aging is associated with impaired autonomic regulation of blood pressure (e.g., baroreflex sensitivity) (Monahan, 2007), which may further compromise the systemic cardiovascular response and maintenance of blood pressure during heat stress (Engelland et al., 2020; Schlader et al., 2016). Relatedly, older adults exhibit lesser reductions in renal and splanchnic blood flow during whole-body heating due to impaired sympathetic vasoconstrictor responses in these vascular beds (Minson et al., 1998). As such, they are less able to redistribute blood from the peripheral to central vascular beds to support elevated circulatory demands. It should be noted, however, that as with previous work detailing the effect of age on thermoregulatory responses, the hemodynamic adjustments to heat stress in young and older adults have been delineated primarily during conditions with low ecological validity (e.g., encapsulated, water-perfused suit). Consequently, further work is required to assess the extent to which the above highlighted age-related differences translate to conditions more representative of heatwaves (discussed in Section 4).

Table 1
Summary of studies assessing differences in thermoregulatory function between young (18–34 years-old) and middle-aged (35–59 years-old) or older (≥65 years-old) adults during resting exposure to hot environments.

Study	Participants		Environmental conditions[c]	Exposure duration	Primary findings[d]
	n[a]	Age (years)[b]			
Drinkwater et al. (1982)	10 women 10 women	38 (2) 58 (2)	40°C, 40% RH Heat index: 48°C	120 min	No differences in evaporative heat loss (determined via sweat losses) were observed between groups. Rectal temperature increased by ~0.1–0.2°C during exposure but was not different between age groups.
Dufour and Candas (2007)	15 men 15 men 15 men	24 (12) 45 (12) 68 (14)	40°C, 43% RH Heat index: 50°C	90 min	Older adults and middle-aged had lower local sweat rates (forehead, chest, thigh, calf) compared to younger adults. Sublingual temperature was ~0.4°C greater in the older and middle-aged men compared to the young group.
Hellon and Lind (1956)	12 men 12 men	18–23 44–57	38°C, 58% RH Heat index: 54°C	65 min	Whole-body sweat rate was not different between age-groups. Rectal temperature increased by ~0.2–0.3°C during exposure but was not different between age groups.
Hellon and Lind (1958)	6 men 6 men	17–26 41–57	38°C, 58% RH Heat index: 54°C	150 min	Forearm blood flow was higher in the older adults compared to their younger counterparts (~50%). Rectal temperature increases by ~0.2°C but was not different between groups.
	6 men 6 men	17–26 41–57	38°C, 58% RH Heat index: 54°C	65 min	Forearm blood flow was higher in the older adults compared to their younger counterparts (~50%). Rectal temperature increases by ~0.1°C but was not different between groups.
Kenny et al. (2017)	30 adults 30 adults	23 (3) 62 (6)	44°C, 30% RH Heat index: 52°C	180 min	Compared to younger adults, older adults stored 80% more heat (~175 kJ), equivalent to a ~0.5°C difference in mean body temperature. Rectal temperature was ~0.2°C greater in the older adults.
Miescher and Fortney (1989)	6 men 5 men	26 (2) 64 (2)	45°C, 25% RH Heat index: 51°C	240 min	Increase in rectal temperature was ~0.6°C greater in the older compared to younger men.
Sagawa et al. (1988)	10 men 6 men	27 (7) 66 (4)	40°C, 40% RH Heat index: 48°C	135 min	No differences in sweat loss or local sweat rate (chest, head, forearm, abdomen, thigh). Esophageal temperature at end exposure was ~0.2°C greater in the older vs young adults.
Shoenfeld et al. (1978)	29 adults 14 adults 17 adults	24 (3) 42 (1) 63 (4)	80–90°C, 3–4% RH Heat index: 56–65°C	10 min	Rectal temperature increased by ~0.3–0.5°C during exposure but was not different between age groups.
Stapleton et al. (2013)	12 adults 12 adults 12 adults 12 adults	21 (3) 65 (5) 21 (3) 65 (5)	36.5°C, 20% RH Heat index: 35°C 36.5°C, 60% RH Heat index: 50°C	120 min 120 min	Compared to younger adults, older adults stored 36% more heat (~75 kJ). Rectal temperature was ~0.3°C greater in the older adults. Compared to younger adults, older adults stored 26% more heat (~125 kJ). Rectal temperature was ~0.4°C greater in the older men.

Notes:
[a] Sex of study groups designated as men, women, or adults (both men and women).
[b] Age groups designated as they appear as published. Age is presented as a range or mean (SD).
[c] Environmental conditions indicate air temperature relative humidity (RH).
[d] Data represent the change (Δ) in rectal temperature from baseline/resting to end-exposure (imputed when not provided).

2.5. Body fluid regulation

Precise regulation of body fluid balance is crucial to the maintenance of intravascular volume to support hemodynamic stability and heat loss. As heat exposure progresses, marked dehydration can develop due to sustained elevations in sweat rate which can reach ~0.3 L/h during resting heat exposure (Kenny et al., 2017; Morris et al., 2019) and ≥2 L/h during physical activity in a hot environment (Sawka et al., 2007). Since sodium and other electrolytes are reabsorbed during the production of sweat from the plasma-derived precursor fluid (Sato, 1977), heat-induced dehydration elicits a state of hemoconcentration (Harrison, 1985), reduced circulating volume (hypovolemia), and elevated serum osmolality (hyperosmotic/hypernatremic) (Cheuvront and Kenefick, 2014). These alterations attenuate cutaneous vasodilation and sweating responses for a given body temperature (Sawka et al., 1985; Senay, 1968), which in turn widens the core-to-skin temperature gradient, lowering the required skin blood flow and sweating to maintain heat balance. This response likely facilitates haemodynamic stability while also preventing further fluid loss in low heat-stress conditions. At higher levels of heat stress, however, dehydration attenuates the heat loss that is achievable (Meade et al., 2019b), potentially lowering the environmental threshold for uncompensibility. At the same time, cardiovascular strain is exacerbated by dehydration as the absolute hypovolemia (due to fluid loss) compounds the heat-induced relative hypovolemia resulting from reduced peripheral resistance (Sawka et al., 2015).

Dehydration triggers regulatory adjustments to restore a state of euhydration. Alterations in plasma osmolality are relayed to the hypothalamus from central osmoreceptors in the internal carotid artery (Bourque, 2008). Increases in osmolality of as little as 1–2% promote water acquisition (thirst) and renal water conservation via direct neural signaling and the secretion of arginine vasopressin, which acts on the kidney to reduce free water clearance (Andreoli et al., 2010; Tamma et al., 2015). Hormonal control of fluid balance is supported by the activation of the renin-angiotensin-aldosterone system (RAAS) secondary to renal hypoperfusion. RAAS activation elicits elevations in circulating angiotensin-II, which has myriad effects on the cardiorenal axis (e.g., reduces renal blood flow, augments thirst and vasopressin release), and the subsequent release of aldosterone by the adrenal cortex to promote renal sodium retention (Andreoli et al., 2010). Hemodynamic alterations sensed via low pressure baroreceptors located in the systemic veins and walls of the heart also influence vasopressin secretion (Andreoli et al., 2010) and thirst (Stachenfeld et al., 1997). Highly sensitive physiological control of extracellular volume and osmolality result in daily fluid intake that closely matches fluid loss under non-heat stressed conditions. During heat stress, however, most individuals undergo a net fluid loss (voluntary dehydration), even with unrestricted access to fluids (Greenleaf and Sargent, 1965).

2.6. Aging and body fluid during heat stress

Aging may compromise body fluid regulation during heatwaves via multiple mechanisms. Compared to the young, older adults have a diminished thirst response to dehydration (Phillips et al., 1984; Takamata et al., 1999), which may be explained by blunted sensitivity to elevations in plasma osmolality (Phillips et al., 1991) and reduced involvement of the baroreflex (Stachenfeld et al., 1997). Diminished thirst is compounded by impaired renal water conservation (Dontas et al., 1972; Mack et al., 1994) resulting from blunted renal sensitivity to vasopressin (Tamma et al., 2015) and dysregulation of the RAAS (Takamata et al., 1999; Yoon and Choi, 2014). Further, while dehydration has been consistently shown to attenuate whole-body sweat rate during heat stress in young adults (Sawka et al., 1985; Senay, 1968), this effect appears blunted by aging (Meade et al., 2019b). As such, older adults exhibit an impaired ability to mitigate further sweat-induced fluid losses during dehydration; though, the significance of this alteration to fluid balance is likely minor.

Altered body fluid regulation renders older adults at increased susceptibility for dehydration. This is particularly relevant given their lower total body water (Schoeller, 1989) and intravascular volume (Davy and Seals, 1994); a given absolute fluid loss represents a larger reduction in the volume of these compartments compared younger adults. Despite this, the daily fluid intake of older adults is generally within normal ranges in non-heat stressed conditions (Lowik et al., 1989). Thus, community living older individuals are not typically hypohydrated, despite often overstated reports to the contrary (see Kenney and Chiu (2001)). That said, it should be noted that older adults undergo greater voluntary dehydration during heat-exposure compared to their younger counterparts (Takamata et al., 1999) and oral rehydration is delayed following heat stress and/or water deprivation (Phillips et al., 1984). Thus, even healthy older adults are at increased risk of dehydration during prolonged and repeated heat exposure, as occurs during a heatwave.

3. Acute and chronic dysfunction during heatwaves

To summarize the preceding section, healthy aging causes myriad physiological alterations that limit the homeostatic response to heat exposure. Unsurprisingly, heatwaves are associated with stark elevations in hospital admissions (Bobb et al., 2014) and deaths (Semenza et al., 1996) due to catastrophic failure of body temperature regulation (heatstroke). In many cases, however, acute injury during heatwaves results from pathophysiological conditions typically considered to be non-heat-related (e.g., adverse cardiovascular events, acute kidney injury). This is not to say that altered body temperature regulation does not contribute. Even in compensable conditions, heat balance will be achieved at higher body temperatures in older adults during heat exposure (Fig. 3). Since heatwaves last days to weeks, low-to-moderate levels of hyperthermia, cardiovascular strain, and dehydration may be sustained over protracted periods (e.g., during peak daytime hours over multiple days). To fully appreciate the etiology of heat-related injury, we must therefore consider the physiological effects of prolonged and/or repeated elevations of body temperature, as these will ultimately determine compensatory alterations, strain, and injury in vulnerable bodily systems.

For logistical and ethical reasons, research on the quantitative links between age-related maladaptation and elevated risk of adverse health outcomes is scarce. We can, however, draw provisional links between known physiological alterations accompanying aging and disease and the development of acute injury and dysfunction in the context of heat exposure. An overview is provided in Fig. 4, along with supplemental information on conditions not covered in the main text. Throughout this discussion it is important to consider that although each is presented separately, there is considerable overlap between the etiology and pathophysiology of aging and the discussed conditions. Further, they rarely develop in isolation; over half of adults in the United States aged ≥65 years, for example, are living with two or more chronic conditions (Centers for Disease Control Prevention, 2015). Along these same lines, it would be remiss to ignore the effects of common medications on the mechanisms discussed (Table 2). All this to say that there is likely no single common pathway of heat-related injury; rather, it is the nexus of physiological impairment(s) and pathophysiological states that determines the risk for an individual exposed to extreme heat (Rothman, 1976; Sturmberg et al., 2019).

3.1. Heat illness

Heat illness is a blanket term used to describe multiple pathophysiological conditions related directly to elevated body temperature. These exist on a continuum describing the extent of dysregulation, ranging from heat edema, heat-cramps and heat rash, to heat exhaustion and heat stroke (Székely et al., 2015). Many of these conditions are associated primarily with discomfort and contribute minimally to heat-related mortality. In this section, we will focus on the deadliest heat-illness: heat stroke.

3.1.1. Heat stroke (extreme hyperthermia)

Heat stroke is a medical emergency in which elevated ambient (classic or non-exertional form) and/or metabolic (exertional form) heat stress overwhelms the physiological capacity for heat dissipation leading to extreme hyperthermia (typically core temperature of ≥40°C) and a rapid cascade of systemic dysfunction. During heatwaves, older adults are at particular risk of classic heat stroke (Epstein and Yanovich, 2019; Leon and Bouchama, 2015). Mortality rates in those affected can reach > 50% (Epstein and Yanovich, 2019; Jones et al., 1982) and survivors often experience long-term functional limitations and an elevated risk of future morbidity and mortality (Argaud et al., 2007; Wang et al., 2019). The etiology of heat stroke is complex and the associated pathophysiological mechanisms have been detailed extensively (Epstein and Yanovich, 2019; Leon and Bouchama, 2015). Briefly, heat-induced cytotoxicity in sensitive tissues (e.g., brain, vasculature, gastrointestinal tract) leads to the development of systemic inflammatory response syndrome (SIRS) and disseminated intravascular coagulopathy (DIC) causing central nervous system dysfunction, multi-organ damage and, if left untreated, death.

There are several mechanisms by which aging may influence the development of heat stroke. For one, age-related impairments in cutaneous vasodilation and sweating mean that older adults experience greater levels of hyperthermia compared to young adults during heat exposure (Table 2) and body temperature regulation may be overwhelmed at lower levels of heat stress (Fig. 3). Coupled with inadequate cardiovascular responses to support elevated circulatory demand, especially during superimposed dehydration, older adults are at greater risk of extreme elevations in core temperature and cardiovascular collapse, setting the stage for the development of SIRS, DIC, and ensuing organ damage (Leon and Bouchama, 2015).

Older adults are also likely predisposed to SIRS, a key event in heatstroke pathogenesis, which occurs due to dysregulation of the inflammatory response (Leon and Bouchama, 2015). The severity of SIRS can be magnified by accompanying endotoxemia that develops due to increased gastrointestinal permeability (Moseley et al., 1994) secondary to oxidative and ischemic damage to the mesenteric epithelium (Hall et al., 2001). Aging is characterized by chronic low-grade inflammation stemming from increased basal levels of pro-inflammatory mediators (e.g., TNF-α, IL-6) and ROS (e.g., superoxide, H_2O_2) along with reductions in their anti-inflammatory and antioxidant counterparts (Liguori et al., 2018; Michaud et al., 2013). Consequently, older

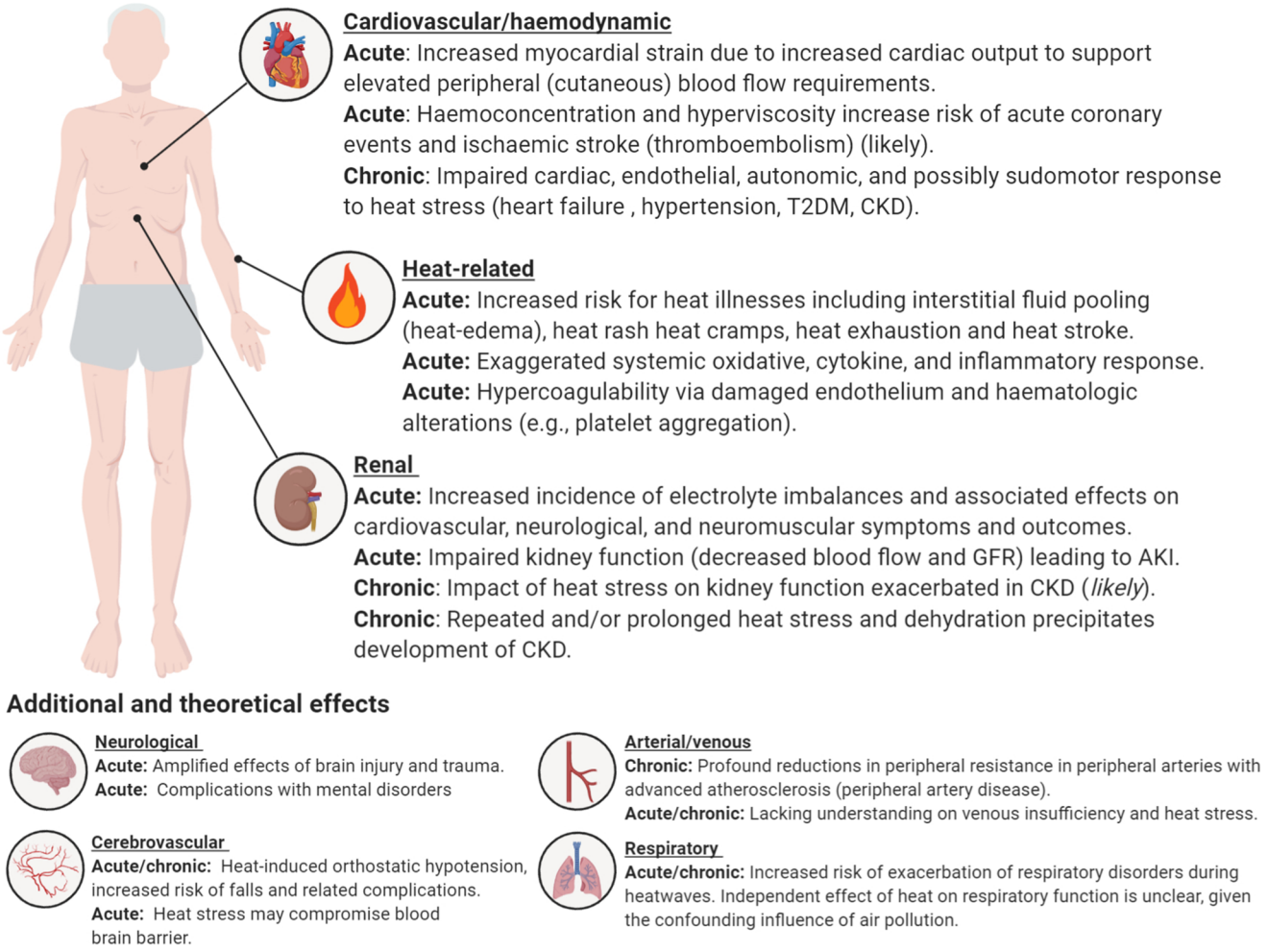

Fig. 4. Overview of the pathways by which heat stress may influence the development of acute injury and impact chronic physiological dysfunction in multiple physiological systems in older adults during heat exposure (see main text for details). AKI, acute kidney injury; CKD, chronic kidney disease; GFR, glomerular filtration rate; T2DM, type 2 diabetes mellitus. Also provided is supplemental information regarding the effect of heat exposures on conditions not covered in the main text: neurological (Hermstad and Adams, 2010; Lohmus, 2018), cerebrovascular (Bain et al., 2015; Lavados et al., 2018; Schlader et al., 2016), arterial/venous (Thomas et al., 2017) and respiratory (De Sario et al., 2013). These conditions have been shown to be worse during heat exposure and/or heatwaves, but mechanistic links are relatively undefined.

adults exhibit a reduced ability to buffer inflammatory/oxidative insults, and likely experience greater inflammatory and oxidative tissue damage during heat stress; a hypothesis supported by work in humans (Wright et al., 2014) and animals (Del Vesco et al., 2017; Ilievska et al., 2016).

Heat stroke can also lead to DIC, in which diffuse microvascular emboli develop (Leon and Bouchama, 2015), due to damage to the vascular endothelium (Bouchama et al., 1996). Also involved is cross-talk with the above-discussed inflammatory pathways, as highlighted in a case-control analysis linking elevations in pro-inflammatory cytokines, endothelial dysfunction and coagulation in heatstroke victims during the 2003 European heatwave (Huisse et al., 2008). Elevated body temperatures and reduced central blood volume during heat stress elicit a state of hypercoagulability (Meyer et al., 2013). In older adults, this is compounded by endothelial dysfunction, vascular remodeling (e.g., atherosclerosis) (Previtali et al., 2011), and hematological changes (e.g., increased platelet aggregation) (Le Blanc and Lordkipanidze, 2019) that promote thrombosis and the development of acquired coagulopathies (Wilkerson and Sane, 2002) and, by extension, DIC. Thus, not only are older adults at elevated risk of extreme hyperthermia during heatwaves, they are likely pre-disposed to SIRS and DIC due to exacerbated activation of inflammatory, oxidative stress, and coagulation pathways.

3.2. Major adverse cardiovascular events and cardiovascular disease

As much as 90% of heatwave-associated mortality is attributable to major adverse cardiovascular events (MACE; e.g., myocardial infarction, ischemic stroke) (Huang et al., 2012; Lavados et al., 2018; Semenza et al., 1996). Importantly, the risk of MACE in extreme ambient temperatures is not only elevated in those with pre-existing cardiovascular diseases (CVD) but also in individuals without overt CVD (Bhaskaran et al., 2012; Kenney et al., 2014). Many of these events occur unexpectedly, before individuals are hospitalized. This manifests as marked elevations in out-of-hospital deaths due to cardiac arrest or circulatory disease (Kang et al., 2016; Linares and Diaz, 2008), yet little-to-no change, or even decreases, in cardiovascular-related hospitalizations (Bobb et al., 2014; Linares and Diaz, 2008; Vaidyanathan et al., 2019).

The physiological basis for increased risk of cardiovascular events

Table 2
Potential effects of common medications on physiological responses during heat exposure.

Classifications	Used to treat	Potential effects during heat exposure
ACE inhibitors and ARBs e.g., *ramipril, perindopril, losartan, candesartan*	- Hypertension - Heart failure - Chronic kidney disease - Diabetic nephropathy	- Increased risk for AKI, electrolyte imbalances - Dehydration, hypovolemia - Hypotension - Blunted sensation of thirst - Impaired renal autoregulation
Anti-adrenergics and beta-blockers e.g., *prazosin, metoprolol*	- Hypertension - Arrhythmias	- Increased risk for heatstroke - Impaired sweating - Blunted chronotropic reserve - Hypotension
Antiarrhythmics e.g., *amiodarone, digoxin, quinidine*	- Arrhythmias	- Can cause diarrhea, increased risk for dehydration - May inhibit sweating (disopyramide) - Kinetic profile and toxicity influenced by dehydration and reduced renal clearance (digoxin)
Calcium channel blockers e.g., *amlodipine, diltiazem*	- Hypertension - Arrhythmias	- Increased risk for heatstroke - Can cause diarrhea, increasing risk for dehydration, hypovolemia - Hypotension (amlodipine) - Blunted chronotropic reserve (diltiazem and verapamil)
Diuretics e.g., *hydrochlorothiazide, furosemide, Spironolactone*	- Hypertension - Heart failure - Kidney failure - Edema - Liver failure	- Increased risk for heatstroke, AKI, electrolyte imbalances (hyperkalemia with spironolactone) - Dehydration, hypovolemia - Blunted increase in cardiac output - Hypotension
NSAIDs e.g., *ibuprofen, naproxen*	- Arthritis, bursitis, tendonitis - Analgesia	- Increased risk for AKI - Nephrotoxic – may compound the risk for AKI during heat stress and dehydration - Impair renal autoregulation
Anticholinergics e.g., *antimuscarinics, antinicotinics*	- Dizziness (vertigo, motion-sickness) - GI disorders - Respiratory disorders (COPD)	- Increased risk for heatstroke (hyperthermia) - Impaired sweating - Blunted increase in cardiac output - Hypotension
Antidepressants e.g., *SSRIs, tricyclics*	- Depressive disorders - Anxiety disorders	- Increased risk for heatstroke (tricyclic, SSRI) - Increased risk for hyponatremia (SSRIs) - May impair sweat rate (many) - Limit increase in cardiac output (tricyclic) - Hypotension (tricyclic)
Antipsychotics e.g., *haloperidol, loxapine thioridazine*	- Dementia - Schizophrenia - Bipolar disorder	- Impaired sweating - May induce hyperthermia (neuroleptic malignant syndrome)
Other medications e.g., *metformin, insulin dapagliflozin, anti-coagulants*	- Diabetes - Coagulation disorders - Others (many)	- Kinetic profile and toxicity influenced by dehydration and reduced renal clearance - Potential for masked symptoms of hypoglycemia (sweating, tachycardia, fatigue)

Notes: ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; AKI, acute kidney injury; COPD, chronic obstructive pulmonary disease; GI, gastro intestinal; NSAIDs, non-steroidal anti-inflammatory drugs; SSRIs, selective serotonin reuptake inhibitors. Information compiled from Blachère and Perreault (2012); Blachère et al. (2011); Westaway et al. (2015).

during heatwaves has been discussed in depth by Kenney et al. (2014). In general, increased incidence of MACE in older adults is thought to stem from reduced myocardial perfusion (Crandall et al., 2008) and augmented myocardial strain (Davido et al., 2006; Hausfater et al., 2010). Concurrently, impaired regulation of body temperature and fluid status are associated with hyperviscosity and hypercoagulability, increasing the risk for acute coronary events (Keatinge et al., 1986; Roberts et al., 2008) and ischemic stroke (Lavados et al., 2018). Relatedly, hyperthermia may elevate the risk of atherosclerotic plaque rupture by exacerbating on-going inflammation or perhaps through more direct mechanisms (Stefanadis et al., 2017; Verheye et al., 2002). It should be cautioned, however, that much of the support for these mechanisms is based on clinical and experimental (animal) observations in heatstroke victims (Davido et al., 2006; Hausfater et al., 2010; Roberts et al., 2008). Future work is therefore required to confirm the mechanisms through which protracted heat stress influences the etiology of MACE.

3.2.1. Cardiovascular diseases

More people die of CVD every year than of any other cause (World Health Organization, 2019). Perhaps unsurprisingly, pre-existing CVD has been reported to increase mortality risk during a heatwave by as much as 6-fold (Bouchama et al., 2007; Kenny et al., 2010). The umbrella term CVD encapsulates acquired and congenital disorders related to the heart and blood vessels. The mechanistic foundation of each disease progression is beyond the scope of this review, but deteriorations in cardiac (Fouad et al., 1984; Redfield et al., 2003), vascular (Feihl et al., 2009; Mattace-Raso et al., 2006) and autonomic function (Palatini and Julius, 2009), and inflammatory status (Diaz et al., 2019; Shah and Lecis, 2019) are evident across the spectrum of CVD. Chronic

deterioration in those regulatory systems likely acts to compound the acute dysfunction addressed above, further increasing mortality risk when exposed to extreme heat events. The physiological impact of isolated common disease states and co-morbidities on responses to heat stress, where data are available, are addressed below and in Fig. 4.

Most heat stress-related research has focused on congestive heart failure. While there are relatively fewer hospital admissions due to heart failure during summer months and heatwaves, those that are admitted have a worse prognosis (Bobb et al., 2014; Gotsman et al., 2010). As discussed, however, reduced hospitalizations for heart failure may reflect increased of out-of-hospital incidents (Linares and Diaz, 2008). Chronic heart failure results in widespread changes in the structure (Wroblewski et al., 1995) and function of the peripheral vasculature (Green et al., 2006; Kubo et al., 1991) along with over-activation of the RAAS (Diaz et al., 2019). Consequently, cutaneous vasodilation is attenuated during passive heating (Cui et al., 2005; Green et al., 2006). Further, heart failure - by definition - is associated with reductions in cardiac function that limit the appropriate haemodynamic adjustments to heat stress (Cui and Sinoway, 2014), likely increasing the risk of cardiovascular decompensation (Wilker et al., 2012) and kidney injury (discussed below), especially in those undergoing treatment with diuretics (Table 2) (Cruz et al., 2015).

3.2.2. Hypertension

Chronically elevated blood pressure is the leading risk factor for premature mortality globally (Mills et al., 2020). Hypertension was common among those who died during the Chicago 1995 heatwave (Klinenberg, 2015) and was associated with a ~24% greater risk of hospitalization (Semenza et al., 1999), though this is not a universal finding (Kenny et al., 2010). Even at rest, the coordination between cardiac and cutaneous vascular activity is reduced progressively with aging and exacerbated with hypertension, even when managed with medication (Ticcinelli et al., 2017). Those with untreated hypertension exhibit endothelial dysfunction and attenuated cutaneous vasodilation during localized skin heating (Carberry et al., 1992; Smith et al., 2011). Similar responses have been observed during whole-body passive heating, and have been partially attributed to elevated oxidative stress and upregulated arginase activity (Holowatz and Kenney, 2007a, 2007b).

Consistent with these findings, non-medicated, middle-aged men with hypertension display blunted cardiovascular responses (cardiac output, forearm blood flow) relative to their normotensive counterparts during moderate (exercise) heat stress (Kenney and Kamon, 1984; Kenney et al., 1984). Despite this, increases in body temperature did not differ between groups. These studies therefore support the notion that hypertension does not have a direct effect on thermoregulation, but it is associated with impaired cardiovascular responses to heat exposure. While the development of hypertension is thought to stem, in large part, from alterations in renal sodium and fluid handling (Johnson et al., 2015), its implications for fluid balance during prolonged heat stress are as of yet unknown. Elucidating the impact of hypertension on physiological responses to heat stress is complicated by its involvement in a variety of other chronic conditions (e.g., type 2 diabetes mellitus, chronic kidney disease) and that many common medications used in its treatment may also have important effects on thermoregulation and haemodynamic function (Table 2).

3.3. Metabolic disorders

3.3.1. Obesity

Obesity is a global epidemic characterized by the accumulation of abdominal adiposity (Barzilai et al., 2012) and excess fat deposition in muscle (Slawik and Vidal-Puig, 2006) due to complex interactions between genetics, environmental, and lifestyle factors (Jura and Kozak, 2016; Neeland et al., 2018). Obesity is highly prevalent in older individuals and has been suggested to hasten the aging process and the development of other age-associated chronic conditions (Ahima, 2009; Jura and Kozak, 2016). Overweight and obese adults are also at greater risk for heat-related illness or injury (Koppe et al., 2004). Indeed, obese older adults were twice as likely to die during the 2003 European heatwave compared to their non-obese counterparts (Vandentorren et al., 2006), findings consistent with observations of heatstroke occurring at a rate 3.5 times higher in obese or overweight individuals compared to those of normal weight (Henschel, 1967).

The increased risk of heat-related injury in obesity may stem, at least in part, from morphological and functional alterations affecting heat loss. With increases in body size, surface area increases at a proportionally slower rate than body mass. Despite a greater capacity to store heat due to their larger mass, this means that obese individuals also have a lower surface area per unit body mass from which to lose heat compared to their non-obese counterparts (Bar-Or et al., 1969; Speakman, 2018). Further, due to its lower thermal conductivity, increasing subcutaneous fat may impair core-to-skin heat transfer (Bhowmik et al., 2015). These alterations mean that obesity is associated with a morphological configuration that is disadvantageous to body temperature regulation during heat exposure. It has also been suggested that high adiposity may directly impair heat loss independent of morphology (Dervis et al., 2016); though, this effect is likely minor (Notley et al., 2019a).

Obese individuals are likely at greater risk of cardiovascular events during heatwaves owing to structural and functional alterations to the cardiovascular system (Lee et al., 2014; Skrapari et al., 2007) and predisposition for CVD (Vasan, 2003). Likewise, obesity has been linked to altered water homeostasis and dehydration (Rosinger et al., 2016), plasma hyperosmolality (Stookey et al., 2007) and kidney dysfunction (Stevens et al., 2010), which may elevate the risk of electrolyte imbalances and renal disorders. Despite these theoretical links, however, to date there exists little research on the impacts of obesity on body temperature and haemodynamic regulation in older adults exposed to natural or simulated heatwaves.

3.3.2. Type 2 diabetes

Type 2 diabetes mellitus (T2DM) is associated with acquired insulin resistance, hyperinsulinemia and dysglycemia, vascular inflammation, stiffening, and atherosclerosis (Climie et al., 2019; Kenny et al., 2016). T2DM predominantly affects older adults, though its global prevalence is on the rise in all age-groups alongside growing rates of obesity and associated lifestyle factors (World Health Organization, 2016). Heat exposure does not appear to alter the risk of T2DM-related complications. For instance, neither Bobb et al. (2014) nor Semenza et al. (1999) observed increased hospital admissions for diabetes-related causes (e.g., hyper- or hypoglycemia), whereas Vaidyanathan et al. (2019) reported small elevations (~5%) at high ambient temperatures in some, but not all, regions of the continental United States. That said, individuals with diabetes have a greater risk of dying or being hospitalized during exposure to temperature extremes (Kenny et al., 2010; Semenza et al., 1999), which may stem from T2DM-associated alterations in thermoregulatory and cardiovascular function that increase the risk of heat-related disorders over that associated with aging *per se* (Kenny et al., 2016).

Individuals with T2DM exhibit impaired increases in cutaneous vasodilation in response to pharmacological stimulation (Beer et al., 2008; Williams et al., 1996), local skin heating, and whole-body passive heat stress (Sokolnicki et al., 2009; Wick et al., 2006). These alterations likely stem from endothelial dysfunction as well as endothelium-independent changes in control of skin blood flow secondary to structural

alterations of the vasculature, hyperglycemia and/or atherosclerosis (Kenny et al., 2016). Reductions in sweat rate are also characteristic of the disease (Petrofsky et al., 2005b; Rand et al., 2008), which typically manifest as lower body anhidrosis (inability to sweat normally) with compensatory upper body hyperhidrosis (abnormally excessive sweating) early in the disease, progressing to whole-body impairments over the long-term (Kenny et al., 2016). While duration of diabetes, long-term glycemic control, and presence of neuropathy are thought to determine the progression of these alterations (Fealey et al., 1989; Luo et al., 2012), even individuals with well-controlled T2DM exhibit a compromised ability to dissipate heat and regulate body temperature during moderate-to-high (exercise) heat stress (Kenny et al., 2013; Notley et al., 2019b). Conversely, a recent study demonstrated similar thermal and cardiovascular responses between middle-aged-to-older adults with and without T2DM during environmental heat exposure, though the participants with T2DM were physically active with well-controlled blood glucose (Poirier et al., 2020). Whether less active individuals with poor glycemic control or related comorbidities (e.g., neurophathy) display similar responses, is currently unknown.

Much of the general diabetes-related health burden stems from macrovascular and microvascular complications (Atkinson et al., 2014). In fact, cardiovascular events comprise the most common cause of death in individuals with T2DM (Tancredi et al., 2015). Compared with healthy aging, T2DM is associated with altered cardiovascular and autonomic function (Petrofsky et al., 2010; Rand et al., 2008), which can manifest as impaired blood pressure regulation (Low et al., 1975). These cardiovascular alterations are closely related to the extent of insulin resistance (Pikkujämsä et al., 1998) and glycemic control (Petrofsky et al., 2005a). T2DM is also associated with altered body water handling. Acute increases in blood glucose induce osmotic diuresis, which may lead to hypovolemia (Kenny et al., 2016) and those with T2DM are at increased risk of developing electrolyte disorders (Liamis et al., 2014). Along these lines, prolonged hyperglycemia causes kidney dysfunction and is a leading cause of chronic renal failure (Molitch et al., 2004; Satirapoj, 2013). These conditions also disrupt fluid regulation, further increasing the risk of dehydration and associated deleterious health impacts (see below).

3.4. Fluid and electrolyte balance and kidney function

Emerging evidence clearly highlights the negative consequences of heat exposure and dehydration on kidney health (de Lorenzo and Liano, 2017). This risk is likely greater in older adults due to structural and functional senescence in the kidney leading to impaired water and electrolyte handling (Flynn et al., 2005; Ó Flatharta et al., 2019). Disorders of body water balance (e.g., electrolyte disorders) and kidney dysfunction during heatwaves are well documented (Bobb et al., 2014; Conti et al., 2007; Lim et al., 2018; McTavish et al., 2018; Semenza, 1999; Semenza et al., 1999; Vaidyanathan et al., 2019). Protracted and/or repeated heat stress may also increase this risk of developing chronic kidney disease (CKD) (de Lorenzo and Liano, 2017). This increasingly common disease can, in turn, have a multitude of deleterious health consequences during heat exposure. Compared to the conditions highlighted in the preceding sections, the physiological links between heat and electrolyte balance and kidney function are relatively well defined, likely due, in large part, to the growing epidemic of heat-related CKD in Mesoamerican agricultural workers (Lunyera et al., 2016; Schlader et al., 2019a).

3.4.1. Fluid and electrolyte imbalance

The incidence of electrolyte imbalances in older adults increases during heatwaves (Bobb et al., 2014; Vaidyanathan et al., 2019). Severe changes in body concentrations of sodium and potassium (among other electrolytes) disrupt cellular electrochemical gradients, which can have extreme effects in 'excitable' tissues (e.g., brain, heart, muscles) leading to a host of neurological (e.g., weakness, confusion) cardiovascular (e.g., peaked T waves, ST depression) and neuromuscular (e.g., tremors, cramps) signs and symptoms (Weiner and Epstein, 1970). The etiology and clinical manifestations of electrolyte disorders are thereby numerous and complex, and are, for those reasons, largely beyond the scope of the current review (see Weiner and Epstein (1970)). Here we focus primarily on hyper- and hyponatremia, the most common electrolyte imbalances seen in older adults and during heat exposure. Hyperkalemia will be addressed briefly in the section on CKD; though, the risk of developing this dangerous electrolyte disorder is also elevated in older adults without overt CKD (Flynn et al., 2005; Perazella, 1996).

Heat stress precipitates the development of hypernatremia (elevated circulating sodium concentration). During the production of sweat, dissolved electrolytes (chiefly sodium) are reabsorbed from the plasma-derived precursor fluid (Sato, 1977). Progressive sweating-induced fluid losses thereby elicit a state of hypernatremic (hyperosmotic) hypovolemia; that is, sodium loss accompanied by a relatively greater loss of water from the body. This can lead to reductions in thermoregulatory and cardiovascular function which, if severe enough, can contribute to the development of heatstroke, MACE and kidney injury. Aging does not appear to influence sweat sodium reabsorption (Inoue et al., 1999a) but is associated with a reduced ability to concentrate urine (Dontas et al., 1972). Older adults are thereby pre-disposed to hypernatremia if fluid losses are not properly replenished by water acquisition, which, as previously discussed, is blunted with aging.

The risk for hyponatremia (reduced circulating sodium concentration) during heat stress is also elevated by aging. For instance, Giordano and colleagues (Giordano et al., 2018, 2017) observed that the prevalence of mild and severe hyponatremia during emergency room visits in older adults was elevated in the summer (~12.5 and 4.2%, respectively) compared to the preceding winter (~9.4 and 0.3%), whereas no seasonal variations were detected in younger controls (~3.7% and 0.3%). While mild hyponatremia is common and not typically damaging (Moore et al., 2003), severe hyponatremia causes significant morbidity (Arieff, 1986). In fact, individuals hospitalized with serum sodium < 127 mEq/L have a ~2-fold greater risk of in-hospital mortality compared to those with normal sodium (Wald et al., 2010). As discussed, prolonged sweating elicits a *relative* hypernatremia as proportional water loss is greater than that of sodium; however, absolute extracellular sodium still decreases (Cheuvront and Kenefick, 2014). Thus, when older adults do drink, the consumption of hypotonic fluid (e.g., water) can lead to dilutional hyponatremia and perturbations in physiological function. There are a number of other age-associated contributing factors. For one, dietary sodium decreases in the summer (Leshem, 2017) and is generally lower in older adults due to reduced caloric intake (Hendi and Leshem, 2014). Additionally, senescent kidneys are less able to excrete excess free water (Dontas et al., 1972). As such, age-related risks for hyponatremia (Giordano et al., 2016; Lindner et al., 2014) are likely compounded by heat stress, particularly in individuals with comorbidities (e.g., T2DM, heart, renal failure) and/or taking medications that affect fluid balance (e.g., certain diuretics; Table 2).

3.4.2. Acute kidney injury

In addition to electrolyte imbalances, extreme heat is associated with elevations in morbidity and mortality due to kidney disorders (Conti et al., 2007; Flynn et al., 2005). This includes an increased incidence of acute kidney injury (AKI), particularly in older adults (Lim et al., 2018; McTavish et al., 2018). AKI involves the onset of kidney damage or failure over the course of hours to days, indicated primarily by a reduction in glomerular filtration rate (GFR; < 60 ml/min/

1.73 m^2) and azotemia (increased circulating urea and creatinine) (Basile et al., 2012; Kellum et al., 2012). Broadly speaking, AKI can be divided into three major classifications describing its etiology (pre-renal, intrinsic, post-renal) (Thadhani et al., 1996). Reduced kidney function and a predisposition for dehydration place older adults at increased susceptibility for the pre-renal form, especially those with underlying conditions (e.g., T2DM, hypertension, CKD) or taking medications affecting kidney function (Table 2) (Pascual et al., 1995). In pre-renal AKI, reduced GFR occurs due to up-stream haemodynamic alterations (e.g., reduced systemic or renal blood flow). In most cases, this condition is easily reversed by addressing the underlying cause (Thadhani et al., 1996). However, marked and/or prolonged renal hypoperfusion can progress to intrinsic AKI, which is associated with tubular ischemia and injury (Basile et al., 2012) and can lead to potentially life-threatening conditions (e.g., hyperkalemia) (Doyle and Forni, 2016).

Heat-stress and dehydration superimposed upon age-related alterations in renal autoregulation may explain the increased incidence of AKI in older adults during heatwaves. During heat stress, reductions in renal blood flow occur due to sympathetically-mediated vasoconstriction (Chapman et al., 2019). Heat-induced renal vasoconstriction and reductions in renal blood flow are attenuated with aging (Minson et al., 1998). However, it is important to note that basal renal blood flow decreases by ~10% per decade after the 4th decade (from ~1200 ml/min) (Hollenberg et al., 1974). As a result, absolute renal blood flow is lower in older adults compared to their younger counterparts under both normal and heat-stressed conditions (Minson et al., 1998).

Renal hypoperfusion during heat stress is amplified by concurrent dehydration (Smith et al., 1952) via increases in sympathetic nervous system activity (Stocker et al., 2005) as well as elevated circulating vasopressin and angiotensin II (Bie, 1980; Di Nicolantonio and Mendelsohn, 1986). Although the systemic actions of these hormones are reduced in older adults (Tamma et al., 2015; Weinstein and Anderson, 2010; Yoon and Choi, 2014), vasoactive sensitivity of the renal medulla to angiotensin II and other vasoconstrictors (e.g., adenosine) appears preserved or even increased (Chen et al., 2001; Tank et al., 1994) due to age-related oxidative stress (Ouzeau et al., 2016; Zou et al., 2001). Oxidative stress may also reduce renal production of NO and prostaglandins, which would normally act to oppose the actions of renal vasoconstrictors (Baylis, 2009; Weinstein and Anderson, 2010). Thus, reductions in renal perfusion during dehydration are likely exacerbated in older adults, especially in those taking medication that further impair renal autoregulation (Table 2).

Renal hypoperfusion causes ischemic damage to the vascular endothelium and tubular epithelium in a complex process involving ATP depletion and increased generation of pro-inflammatory mediators and ROS (Basile et al., 2012; Nath and Norby, 2000). As ischemia progresses, microvascular injury contributes to sustained tissue hypoxia, inflammation and oxidative stress, extending the tubular insult (Basile et al., 2012; Nath and Norby, 2000; Thadhani et al., 1996). During heatwaves, tubular injury may be compounded by hyperosmolality-induced upregulation of the polyol-fructokinase pathway, which initiates the release of inflammatory mediators and ROS during the metabolism of fructose in the proximal tubule (Cirillo et al., 2009). This pathway is thought to be a major contributor to the on-going epidemic of heat-nephropathy and CKD in agricultural workers (de Lorenzo and Liano, 2017) and has also been implicated in the age- and disease-related decline in kidney function (Lanaspa et al., 2014; Roncal-Jimenez et al., 2016). Recent work in rodents also indicates that moderate but repeated elevations in body temperature (~1°C) may hasten kidney injury by increasing inflammation and oxidative stress (Sato et al., 2019).

In summary, multiple lines of evidence indicate that physiological alterations occurring during healthy aging may increase the risk of AKI during heatwaves by facilitating the initial ischemic event and/or by amplifying and extending the ensuing inflammatory cascade. Due to structural and functional senescence in the kidney (Thadhani et al., 1996), older adults are also less able to resolve tubular injury and recover from AKI (Schmitt et al., 2008).

3.4.3. Chronic kidney disease (CKD)

The prevalence of overt kidney disease is rapidly increasing in older adults (Stevens et al., 2010), progressing from asymptomatic reductions in renal function (chronically reduced GFR and azotemia) to end-stage kidney failure (Levey and Coresh, 2012). Diabetes, hypertension (Stevens et al., 2010), inflammation and oxidative stress (Vlassara et al., 2009) as well as previous incidents of AKI (Ishani et al., 2009) augment the risk of developing CKD. Currently, CKD is a leading cause of death globally and its burden is on the rise (Stevens et al., 2011). In fact, CKD now affects 24–36% of individuals aged ≥64 years (Zhang and Rothenbacher, 2008) and as many as 50% of individuals over the age of 70 years in the United States (Stevens et al., 2011).

Information pertaining to thermoregulatory function in older adults with CKD is scarce. One expects that, due to diminished ability to regulate bodily fluid and electrolytes (Abuelo, 2007), individuals with CKD would experience more rapid declines in cardiovascular and perhaps thermoregulatory function during heat exposure. As such, CKD presumably hastens and/or amplifies the development of heat stress-associated MACE (Flynn et al., 2005), electrolyte imbalances (Mahaldar, 2012) and AKI (Levey and Coresh, 2012). Chronically injured kidneys exhibit a blunted ability to concentrate urine increasing the risk for hypernatremia whereas complications with the disease (e.g., non-osmotic release of vasopressin) can precipitate hyponatremia (Mahaldar, 2012). Similarly, impaired potassium excretion (Musso et al., 2006) and regulation of acid-base balance (Frassetto and Sebastian, 1996) can contribute to the development of hyperkalemia, which can lead to fatal arrhythmias. Finally, upregulation of coagulation pathways increases the risk of thrombotic complications (Flynn et al., 2005; Huang et al., 2017). While this is typically associated with patients with end stage renal failure (Darlington et al., 2011; Vaziri et al., 1994), elevated levels of procoagulant factors (e.g., fibrinogen, d-dimer) have been observed in individuals with moderate CKD (Huang et al., 2017). Both mechanisms are thought to have contributed to increased mortality in older adults during recent heatwaves (Flynn et al., 2005).

4. Next steps: Integrating physiological research with public health

An organism's ability to maintain internal consistency in the face of external (environmental) perturbations is central to health (Fig. 5). In the context of the preceding discussion, it is evident that our understanding of the mechanistic links between heat exposure and health is still in its infancy. Given the scope of the problem, elucidating those links will require an integrated research approach, combining techniques and expertise from multiple disciplines including (but not limited to) public health, medicine and physiology (Capon et al., 2019). Physiological research is inherently integrated (Billman, 2020), spanning the divide between assessing homeostatic regulation in isolated cells and organs to evaluating the physiological effects of a multitude of environmental factors on health and performance (Joyner, 2011). These tenets lend themselves to translational and integrated research approaches aimed at addressing pressing public health concerns (Seals, 2013).

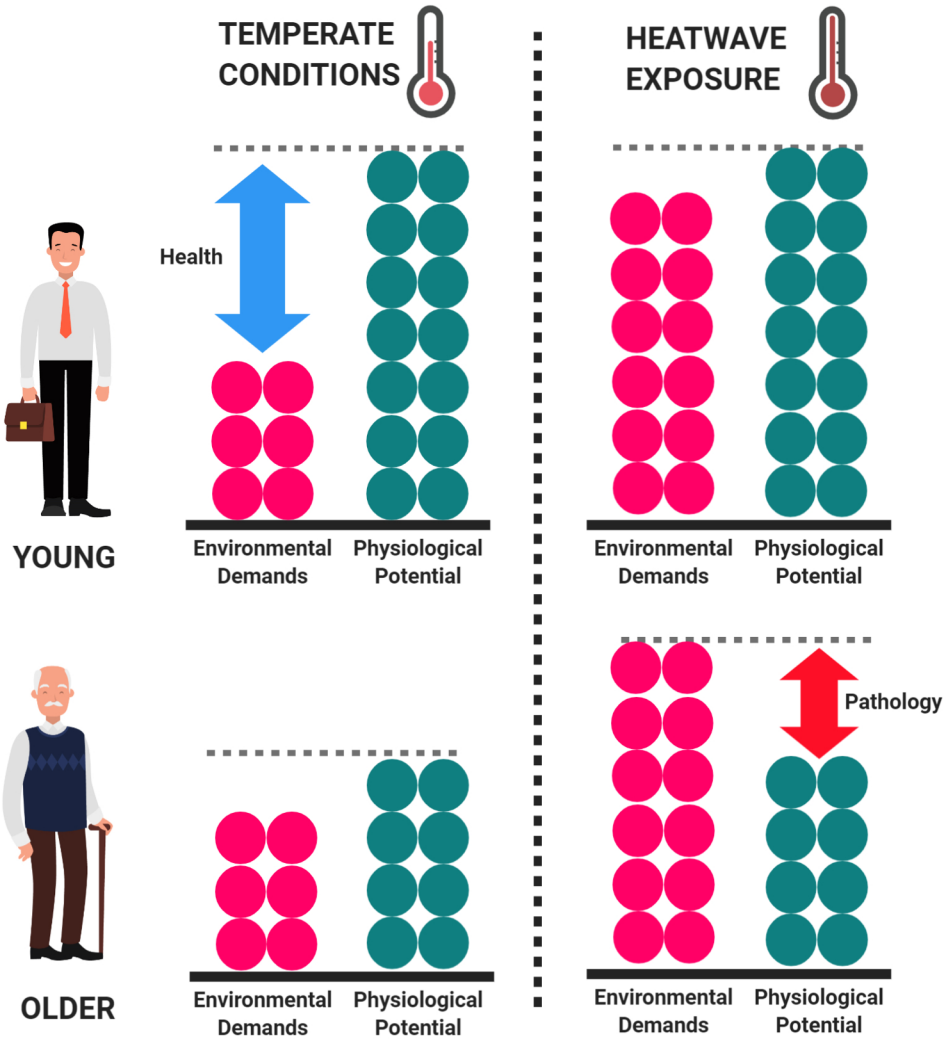

Fig. 5. Bircher's model of health (Bircher, 2005) applied to heatwaves. In this example health is seen as a *balance* between physiological potential (complex and adaptive interactions between physiological systems) and environmental demands (determined by the number and magnitude of environmental stressors). In temperate conditions, internal physiological function (health, blue arrow) is maintained in both young and older adults since biological potential exceeds environmental demands. During exposure to heatwave conditions, integrated physiological responses in young adults (reflected in their elevated physiological potential) are sufficient to meet increased environmental demands and health is maintained. In older adults, age- and/or disease-related reductions in potential impede the blunted physiological response to elevated environmental demand, resulting in acute pathology (red arrow). Note that, for the purpose of this discussion, this view has been simplified to include only demands imposed by the environment and inherited biological (physiological) potential. Ones' potential to respond to life demands is also influenced by acquired potential related to education, psychological and spiritual development, socioeconomic status, social capital and physical ability (e.g., aerobic fitness). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

As a crucial first step, a move toward ecological study design is warranted to improve our ability to utilize the results from physiological research to help generate and refine public health guidance during heatwaves. For example, much of our understanding of the thermoregulatory and cardiovascular responses to resting heat stress comes from studies employing whole-body passive heating. In this model, convective heating of the subject is typically induced through perfusion of hot water through an encapsulated, tube-lined garment (Rowell, 1974), allowing for precise control over the absolute and temporal profiles of the resultant rise in body core temperature. The integrated physiological responses are then evaluated. However, because heat transfer is restricted due to the encapsulated design, body temperatures are not allowed to naturally equilibrate with the environment (i.e., heat balance cannot be achieved) and extreme hyperthermia can quickly develop (Rowell et al., 1969). Further, because of the rapid transfer of heat through water (25 times greater thermal conductivity vs dry air) (Parsons, 2014) and restricted sweat evaporation due to the encapsulated design, skin temperatures can reach upwards of ~40°C (Minson et al., 1998). Highly elevated skin temperatures can exacerbate elevations in cutaneous vascular conductance by 1) activation of sympathetic cutaneous vasodilator activity, increasing skin blood flow (Crandall and Wilson, 2015) and 2) directly augmenting cutaneous venous capacitance (Rowell et al., 1971). Furthermore, since whole-body passive heating studies are often conducted with participants in the supine position, end-diastolic volume is maintained (Crandall et al., 2008) supporting the marked elevations in cardiac output (Rowell et al., 1969)

By contrast, studies that have employed resting environmental heat exposure have generally shown attenuated elevations in body temperature and cardiovascular adjustments compared to suit-heating models in both young and older adults (see Fig. 6 for example). In that work, however, exposure duration has been relatively short (≤4 h) (Table 1) whereas heatwaves, by definition, occur over extended periods (e.g., days to weeks). Further, most of those studies have employed conditions unrepresentative of heatwaves. For instance, the heat index (an effective temperature index that considers the effects of air temperature and ambient humidity) of the environmental heat-exposure studies highlighted in Table 1 generally ranged from 48 to 65°C (median: 51°C), with the exception of the study by Stapleton et al. (2013) (heat index: 35°C). By comparison, peak day-time outdoor conditions in several large heatwaves from 1995 to 2012 were less severe ~36–51°C (median: 43°C) (Jay et al., 2015). Furthermore, most people, especially older adults, spend ≥70% (average of ~17 h/day) of their time in the home (Spalt et al., 2016), where summer temperatures in continental climates can range anywhere from ≤ 22°C, if the home is actively cooled, to ≥35°C in the case of insulated and poorly ventilated domiciles (White-Newsome et al., 2012). In order for evidence-based public health policies to capitalize on physiological research, a critical first step is the development and refinement of study designs to better assess physiological responses of healthy and vulnerable populations during exposures with durations and intensities more representative of those experienced during heatwaves.

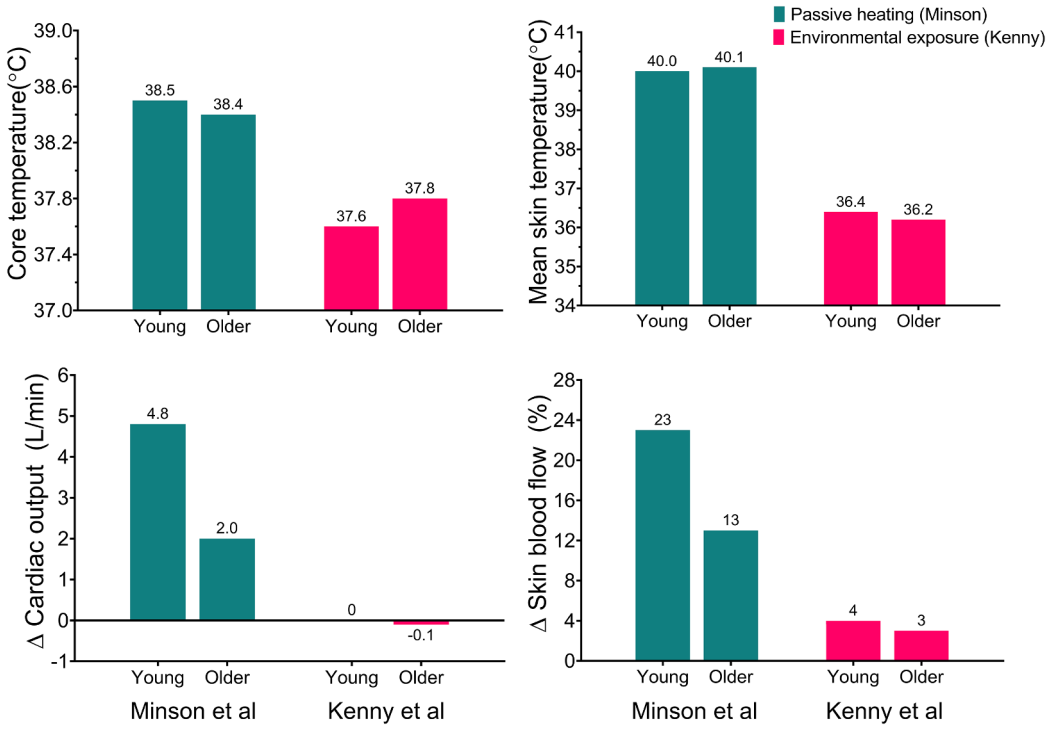

Fig. 6. Differences in thermal and cardiovascular responses during whole-body passive heating and environmental exposure. Data presented are changes in core and mean skin temperatures, cardiac output and forearm blood flow forearm blood flows in studies by Kenny et al. (2017) and Minson et al. (1998). In the study by Kenny et al, semi-recumbent participants (n = 30 young adults [23/7 men/women], aged ~23 years; n = 30 older adults [24/6 men/women], aged ~62 years) were exposed to a hot environment (44°C, 35% relative humidity) for 3 h. By contrast, Minson et al. heated supine participants (n = 7 young men, aged ~23 years; n = 7 older men, aged ~70 years) by perfusing 50°C water through a tube-lined perfusion garment covering the entire body surface until core (esophageal) temperature reached 39.5°C, or until the participant could not control their ventilation or expressed they were unable to continue. Body core temperature was estimated from rectal temperature in the study by Kenny et al. and esophageal temperature in the study by Minson et al. In both studies, cardiac output was approximated non-invasively via inert gas rebreathing. The increase in skin blood flow was indexed via the forearm blood flow response measured using venous occlusion plethysmography.

5. Summary

In this review, we summarized current knowledge on the mechanisms by which aging limits the acute physiological response to heat stress and discussed how dysregulation in the implicated physiological systems – those responsible for body temperature, cardiovascular, and fluid regulation – may contribute to increased risk of adverse health events during heatwaves. We also considered the role of age-associated chronic disease and other comorbidities in modifying that risk. Our understanding of the mechanistic links between heatwaves and health are, in many cases, still insufficient. In our view, a move toward ecological study design is required to better integrate physiological research in public health programs and climate-health models and improve our ability to protect vulnerable sectors of the population.

Funding

This work was supported by Health Canada (all funds held by Glen P. Kenny). R.D. Meade is supported by an Ontario Graduate Scholarship. A.P. Akerman and S.R. Notley are supported by Postdoctoral Fellowships from the Human and Environmental Physiology Research Unit.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

Abuelo, J.G., 2007. Normotensive ischemic acute renal failure. N. Engl. J. Med. 357, 797–805.
Ahima, R.S., 2009. Connecting obesity, aging and diabetes. Nat. Med. 15, 996–997.
Andreoli, T.E., Reeves, W.B., Bichet, D.G., 2010. Endocrine control of water balance. In: Terjung, R. (Ed.), Comprehensive Physiology. John Wiley, Hoboken. https://doi.org/10.1002/cphy.cp070314.
Arbab-Zadeh, A., Dijk, E., Prasad, A., Fu, Q., Torres, P., Zhang, R., Thomas, J.D., Palmer, D., Levine, B.D., 2004. Effect of aging and physical activity on left ventricular compliance. Circulation 110, 1799–1805.
Argaud, L., Ferry, T., Le, Q.H., Marfisi, A., Ciorba, D., Achache, P., Ducluzeau, R., Robert, D., 2007. Short- and long-term outcomes of heatstroke following the 2003 heat wave in Lyon, France. Arch. Intern. Med. 167, 2177–2183.
Arieff, A.I., 1986. Hyponatremia, convulsions, respiratory arrest, and permanent brain damage after elective surgery in healthy women. N. Engl. J. Med. 314, 1529–1535.
Atkinson, M.A., Eisenbarth, G.S., Michels, A.W., 2014. Type 1 diabetes. Lancet 383, 69–82.
Bain, A.R., Nybo, L., Ainslie, P.N., 2015. Cerebral vascular control and metabolism in heat stress. Compr. Physiol. 5, 1345–1380.
Bar-Or, O., Lundegren, H.M., Buskirk, E.R., 1969. Heat tolerance of exercising obese and lean women. J. Appl. Physiol. 26, 403–409.
Barzilai, N., Huffman, D.M., Muzumdar, R.H., Bartke, A., 2012. The critical role of metabolic pathways in aging. Diabetes 61, 1315–1322.
Basile, D.P., Anderson, M.D., Sutton, T.A., 2012. Pathophysiology of acute kidney injury. Compr. Physiol. 2, 1303–1353.
Baylis, C., 2009. Sexual dimorphism in the aging kidney: differences in the nitric oxide system. Nat. Rev. Nephrol. 5, 384–396.
Beer, S., Feihl, F., Ruiz, J., Juhan-Vague, I., Aillaud, M.F., Wetzel, S.G., Liaudet, L., Gaillard, R.C., Waeber, B., 2008. Comparison of skin microvascular reactivity with hemostatic markers of endothelial dysfunction and damage in type 2 diabetes. Vasc. Health Risk Manag. 4, 1449–1458.
Bhaskaran, K., Armstrong, B., Hajat, S., Haines, A., Wilkinson, P., Smeeth, L., 2012. Heat and risk of myocardial infarction: hourly level case-crossover analysis of MINAP database. BMJ 345, e8050.
Bhowmik, A., Repaka, R., Mishra, S.C., 2015. Thermal analysis of the increasing subcutaneous fat thickness within the human skin—a numerical study. Numer. Heat Transfer, Part A: Appl. 67, 313–329.

Bie, P., 1980. Osmoreceptors, vasopressin, and control of renal water excretion. Physiol. Rev. 60, 961–1048.
Billman, G.E., 2020. Homeostasis: the underappreciated and far too often ignored central organizing principle of physiology. Front. Physiol. 11, 200.
Bircher, J., 2005. Towards a dynamic definition of health and disease. Med. Health Care Philos. 8, 335–341.
Blachère, J.-C., Perreault, S., 2012. Médicaments des systèmes cardiovasculaire et rénal et canicules: rapport et recommandations edˆeds: Direction de la santé environnementale et de la toxicologie. Institut ….
Blachère, J.-C., Perreault, S., Bélanger, D., Gosselin, P., Côté, R., Kergoat, M., 2011. Médicaments du système nerveux central et canicules: rapport et recommandations edˆeds: Direction de la santé environnementale et de la toxicologie. Institut ….
Bobb, J.F., Obermeyer, Z., Wang, Y., Dominici, F., 2014. Cause-specific risk of hospital admission related to extreme heat in older adults. JAMA 312, 2659–2667.
Bouchama, A., Dehbi, M., Mohamed, G., Matthies, F., Shoukri, M., Menne, B., 2007. Prognostic factors in heat wave related deaths: a meta-analysis. Arch. Intern. Med. 167, 2170–2176.
Bouchama, A., Hammami, M.M., Haq, A., Jackson, J., Al-Sedairy, S., 1996. Evidence for endothelial cell activation/injury in heatstroke. Crit. Care Med. 24, 1173–1178.
Boulant, J.A., 1981. Hypothalamic mechanisms in thermoregulation. Federation Proc.
Bourque, C.W., 2008. Central mechanisms of osmosensation and systemic osmoregulation. Nat. Rev. Neurosci. 9, 519–531.
Bundgaard-Nielsen, M., Wilson, T.E., Seifert, T., Secher, N.H., Crandall, C.G., 2010. Effect of volume loading on the Frank-Starling relation during reductions in central blood volume in heat-stressed humans. J. Physiol. 588, 3333–3339.
Capon, A., Jay, O., Ebi, K., Lo, S., 2019. Heat and health: a forthcoming Lancet Series. Lancet 394, 551–552.
Carberry, P.A., Shepherd, A.M., Johnson, J.M., 1992. Resting and maximal forearm skin blood flows are reduced in hypertension. Hypertension 20, 349–355.
Celermajer, D.S., Sorensen, K.E., Spiegelhalter, D.J., Georgakopoulos, D., Robinson, J., Deanfield, J.E., 1994. Aging is associated with endothelial dysfunction in healthy men years before the age-related decline in women. J. Am. Coll. Cardiol. 24, 471–476.
Centers for Disease Control Prevention, 2015. Percent of US adults 55 and over with chronic conditions.
Chapman, C.L., Benati, J.M., Johnson, B.D., Vargas, N.T., Lema, P.C., Schlader, Z.J., 2019. Renal and segmental artery hemodynamics during whole body passive heating and cooling recovery. J. Appl. Physiol. (1985) 127, 974–983.
Chen, X., Li, N., Liu, J., Zhang, Z., Liu, Y., 2019. Global heat wave hazard considering humidity effects during the 21st century. Int. J. Environ. Res. Public Health 16.
Chen, Y.F., Li, P.L., Zou, A.P., 2001. Oxidative stress enhances the production and actions of adenosine in the kidney. Am. J. Physiol. Regul. Integr. Comp. Physiol. 281, R1808–R1816.
Cheuvront, S.N., Kenefick, R.W., 2014. Dehydration: physiology, assessment, and performance effects. Compr. Physiol. 4, 257–285.
Chirinos, J.A., Segers, P., Hughes, T., Townsend, R., 2019. Large-artery stiffness in health and disease: JACC state-of-the-art review. J. Am. Coll. Cardiol. 74, 1237–1263.
Cirillo, P., Gersch, M.S., Mu, W., Scherer, P.M., Kim, K.M., Gesualdo, L., Henderson, G.N., Johnson, R.J., Sautin, Y.Y., 2009. Ketohexokinase-dependent metabolism of fructose induces proinflammatory mediators in proximal tubular cells. J. Am. Soc. Nephrol. 20, 545–553.
Climie, R.E., van Sloten, T.T., Bruno, R.-M., Taddei, S., Empana, J.-P., Stehouwer, C.D., Sharman, J.E., Boutouyrie, P., Laurent, S., 2019. Macrovasculature and microvasculature at the crossroads between type 2 diabetes mellitus and hypertension. Hypertension 73, 1138–1149.
Conti, S., Masocco, M., Meli, P., Minelli, G., Palummeri, E., Solimini, R., Toccaceli, V., Vichi, M., 2007. General and specific mortality among the elderly during the 2003 heat wave in Genoa (Italy). Environ. Res. 103, 267–274.
Crandall, C.G., Wilson, T.E., 2015. Human cardiovascular responses to passive heat stress. Compr. Physiol. 5, 17–43.
Crandall, C.G., Wilson, T.E., Marving, J., Vogelsang, T.W., Kjaer, A., Hesse, B., Secher, N.H., 2008. Effects of passive heating on central blood volume and ventricular dimensions in humans. J. Physiol. 586, 293–301.
Cruz, D.N., Giuliani, A., Ronco, C., 2015. Acute kidney injury in heart failure. In: Turner N.N., Lameire N., Goldsmith D.J., Winearls C.G., Hummelfarb J., Remuizzi G., Bennet W.G., de Broe M.E., Chapman J.R., A. C., Jha V., Sheeri N., Unwin R., Woolf A.D. (Eds.), Oxford Textbook of Clinical Nephrology, fourth ed. Oxford University Press.
Cui, J., Arbab-Zadeh, A., Prasad, A., Durand, S., Levine, B.D., Crandall, C.G., 2005. Effects of heat stress on thermoregulatory responses in congestive heart failure patients. Circulation 112, 2286–2292.
Cui, J., Sinoway, L.I., 2014. Cardiovascular responses to heat stress in chronic heart failure. Curr. Heart Fail Rep. 11, 139–145.
Darlington, A., Ferreiro, J.L., Ueno, M., Suzuki, Y., Desai, B., Capranzano, P., Capodanno, D., Tello-Montoliu, A., Bass, T.A., Nahman, N.S., Angiolillo, D.J., 2011. Haemostatic profiles assessed by thromboelastography in patients with end-stage renal disease. Thromb. Haemost. 106, 67–74.
Davido, A., Patzak, A., Dart, T., Sadier, M., Méraud, P., Masmoudi, R., Sembach, N., Cao, T., 2006. Risk factors for heat related death during the August 2003 heat wave in Paris, France, in patients evaluated at the emergency department of the Hôpital Européen Georges Pompidou. Emerg. Med. J. 23, 515–518.
Davy, K.P., Seals, D.R., 1994. Total blood volume in healthy young and older men. J. Appl. Physiol. (1994) 76, 2059–2062.
de Lorenzo, A., Liano, F., 2017. High temperatures and nephrology: the climate change problem. Nefrologia 37, 492–500.
De Sario, M., Katsouyanni, K., Michelozzi, P., 2013. Climate change, extreme weather events, air pollution and respiratory health in Europe. Eur. Respir. J. 42, 826–843.
Del Vesco, A.P., Khatlab, A.S., Goes, E.S.R., Utsunomiya, K.S., Vieira, J.S., Oliveira Neto, A.R., Gasparino, E., 2017. Age-related oxidative stress and antioxidant capacity in heat-stressed broilers. Animal 11, 1783–1790.
Dervis, S., Coombs, G.B., Chaseling, G.K., Filingeri, D., Smoljanic, J., Jay, O., 2016. A comparison of thermoregulatory responses to exercise between mass-matched groups with large differences in body fat. J. Appl. Physiol. (1985) 120, 615–623.
Di Nicolantonio, R., Mendelsohn, F., 1986. Plasma renin and angiotensin in dehydrated and rehydrated rats. Am. J. Physiol.-Regulatory, Integrative Comp. Physiol. 250, R898–R901.
Diaz, H.S., Toledo, C., Andrade, D.C., Marcus, N.J., Del Rio, R., 2019. Neuroinflammation in heart failure: new insights for an old disease. J. Physiol.
Dontas, A.S., Marketos, S.G., Papanayiotou, P., 1972. Mechanisms of renal tubular defects in old age. Postgrad. Med. J. 48, 295–303.
Doyle, J.F., Forni, L.G., 2016. Acute kidney injury: short-term and long-term effects. Crit. Care 20, 188.
Drinkwater, B.L., Bedi, J.F., Loucks, A.B., Roche, S., Horvath, S.M., 1982. Sweating sensitivity and capacity of women in relation to age. J. Appl. Physiol. Respir. Environ. Exerc. Physiol. 53, 671–676.
Dufour, A., Candas, V., 2007. Ageing and thermal responses during passive heat exposure: sweating and sensory aspects. Eur. J. Appl. Physiol. 100, 19–26.
Engelland, R.E., Hemingway, H.W., Tomasco, O.G., Olivencia-Yurvati, A.H., Romero, S.A., 2020. Neural control of blood pressure is altered following isolated leg heating in aged humans. Am. J. Physiol. Heart Circ. Physiol.
Epstein, Y., Yanovich, R., 2019. Heatstroke. N. Engl. J. Med. 380, 2449–2459.
Fealey, R.D., Low, P.A., Thomas, J.E., 1989. Thermoregulatory sweating abnormalities in diabetes mellitus. Mayo Clin. Proc. 64, 617–628.
Feihl, F., Liaudet, L., Waeber, B., 2009. The macrocirculation and microcirculation of hypertension. Curr. Hypertens. Rep. 11, 182–189.
Fleg, J.L., O'Connor, F., Gerstenblith, G., Becker, L.C., Clulow, J., Schulman, S.P., Lakatta, E.G., 1985. Impact of age on the cardiovascular response to dynamic upright exercise in healthy men and women. J. Appl. Physiol. 1995 (78), 890–900.
Flouris, A., Schlader, Z., 2015. Human behavioral thermoregulation during exercise in the heat. Scand. J. Med. Sci. Sports 25, 52–64.
Flynn, A., McGreevy, C., Mulkerrin, E., 2005. Why do older patients die in a heatwave? QJM 98, 227–229.
Fouad, F.M., Slominski, J.M., Tarazi, R.C., 1984. Left ventricular diastolic function in hypertension: relation to left ventricular mass and systolic function. J. Am. Coll. Cardiol. 3, 1500–1506.
Fouillet, A., Rey, G., Laurent, F., Pavillon, G., Bellec, S., Guihenneuc-Jouyaux, C., Clavel, J., Jougla, E., Hemon, D., 2006. Excess mortality related to the August 2003 heat wave in France. Int. Arch. Occup. Environ. Health 80, 16–24.
Frassetto, L., Sebastian, A., 1996. Age and systemic acid-base equilibrium: analysis of published data. J. Gerontol. A Biol. Sci. Med. Sci. 51, B91–B99.
Frumkin, H., Hess, J., Luber, G., 2015. Public health policies and actions. In: Levy, B.S., Patz, J.A. (Eds.), Climate Change and Public Health. Oxford University Press, New York.
Gagnon, D., Romero, S.A., Ngo, H., Sarma, S., Cornwell 3rd, W.K., Poh, P.Y., Stoller, D., Levine, B.D., Crandall, C.G., 2016. Healthy aging does not compromise the augmentation of cardiac function during heat stress. J Appl Physiol (1985) 121, 885–892.
Gagnon, D., Schlader, Z.J., Crandall, C.G., 2015. Sympathetic activity during passive heat stress in healthy aged humans. J. Physiol. 593, 2225–2235.
Giordano, M., Ciarambino, T., Adinolf, L., 2018. Severe hyponatremia in the elderly: the seasonalvariability in the emergency department. Italian J. Emerg. Med. 1, 1–14.
Giordano, M., Ciarambino, T., Castellino, P., Malatino, L., Cataliotti, A., Rinaldi, L., Paolisso, G., Adinolfi, L.E., 2017. Seasonal variations of hyponatremia in the emergency department: age-related changes. Am. J. Emerg. Med. 35, 749–752.
Giordano, M., Ciarambino, T., Castellino, P., Malatino, L., Di Somma, S., Biolo, G., Paolisso, G., Adinolfi, L.E., 2016. Diseases associated with electrolyte imbalance in the ED: age-related differences. Ame. J. Emergency Med. 34, 1923–1926.
Gotsman, I., Zwas, D., Admon, D., Lotan, C., Keren, A., 2010. Seasonal variation in hospital admission in patients with heart failure and its effect on prognosis. Cardiology 117, 268–274.
Greaney, J.L., Kenney, W.L., Alexander, L.M., 2016. Sympathetic regulation during thermal stress in human aging and disease. Auton. Neurosci. 196, 81–90.
Green, D.J., Maiorana, A.J., Siong, J.H., Burke, V., Erickson, M., Minson, C.T., Bilsborough, W., O'Driscoll, G., 2006. Impaired skin blood flow response to environmental heating in chronic heart failure. Eur. Heart J. 27, 338–343.
Greenleaf, J.E., Sargent, F., 1965. Voluntary dehydration in man. J. Appl. Physiol. 20, 719–724.
Guergova, S., Dufour, A., 2011. Thermal sensitivity in the elderly: a review. Ageing Res. Rev. 10, 80–92.
Haines, A., Ebi, K., 2019. The imperative for climate action to protect health. N. Engl. J. Med. 380, 263–273.
Hall, D.M., Buettner, G.R., Oberley, L.W., Xu, L., Matthes, R.D., Gisolfi, C.V., 2001. Mechanisms of circulatory and intestinal barrier dysfunction during whole body hyperthermia. Am. J. Physiol.-Heart Circulatory Physiol. 280, H509–H521.
Harrison, M.H., 1985. Effects on thermal stress and exercise on blood volume in humans. Physiol. Rev. 65, 149–209.
Hashimoto, J., Ito, S., 2010. Pulse pressure amplification, arterial stiffness, and peripheral wave reflection determine pulsatile flow waveform of the femoral artery. Hypertension 56, 926–933.
Hausfater, P., Doumenc, B., Chopin, S., Le Manach, Y., Santin, A., Dautheville, S., Patzak, A., Hericord, P., Mégarbane, B., Andronikof, M., 2010. Elevation of cardiac troponin I during non-exertional heat-related illnesses in the context of a heatwave. Crit. Care 14, R99.

Hellon, R.F., Lind, A.R., 1956. Observations on the activity of sweat glands with special reference to the influence of ageing. J. Physiol. 133, 132–144.
Hellon, R.F., Lind, A.R., 1958. The influence of age on peripheral vasodilatation in a hot environment. J. Physiol. 141, 262–272.
Hendi, K., Leshem, M., 2014. Salt appetite in the elderly. Br. J. Nutr. 112, 1621–1627.
Henschel, A., 1967. Obesity as an occupational hazard. Can. J. Public Health 58, 491–493.
Hensel, H., 1974. Thermoreceptors. Annu. Rev. Physiol. 36, 233–249.
Hermstad, E., Adams, B., 2010. Traumatic brain injury complicated by environmental hyperthermia. J Emerg Trauma Shock 3, 66–69.
Hollenberg, N.K., Adams, D.F., Solomon, H.S., Rashid, A., Abrams, H.L., Merrill, J.P., 1974. Senescence and the renal vasculature in normal man. Circ. Res. 34, 309–316.
Holowatz, L.A., Kenney, W.L., 2007a. Local ascorbate administration augments NO- and non-NO-dependent reflex cutaneous vasodilation in hypertensive humans. Am. J. Physiol. Heart Circ. Physiol. 293, H1090–H1096.
Holowatz, L.A., Kenney, W.L., 2007b. Up-regulation of arginase activity contributes to attenuated reflex cutaneous vasodilatation in hypertensive humans. J. Physiol. 581, 863–872.
Holowatz, L.A., Thompson, C.S., Kenney, W.L., 2006. L-Arginine supplementation or arginase inhibition augments reflex cutaneous vasodilatation in aged human skin. J. Physiol. 574, 573–581.
Huang, C., Barnett, A.G., Wang, X., Tong, S., 2012. Effects of extreme temperatures on years of life lost for cardiovascular deaths: a time series study in Brisbane, Australia. Circ. Cardiovasc. Qual. Outcomes 5, 609–614.
Huang, M.J., Wei, R.B., Wang, Y., Su, T.Y., Di, P., Li, Q.P., Yang, X., Li, P., Chen, X.M., 2017. Blood coagulation system in patients with chronic kidney disease: a prospective observational study. BMJ Open 7, e014294.
Huisse, M.-G., Pease, S., Hurtado-Nedelec, M., Arnaud, B., Malaquin, C., Wolff, M., Gougerot-Pocidalo, M.-A., Kermarrec, N., Bezeaud, A., Guillin, M.-C., 2008. Leukocyte activation: the link between inflammation and coagulation during heatstroke. A study of patients during the 2003 heat wave in Paris. Critical Care Med. 36, 2288–2295.
Ilievska, J., Cicimov, V., Antova, E., Gjorgoski, I., Hadzy-Petrushev, N., Mladenov, M., 2016. Heat-induced oxidative stress and inflammation in rats in relation to age. Res. Phys. Education, Sport Health 5.
Inoue, Y., Havenith, G., Kenney, W.L., Loomis, J.L., Buskirk, E.R., 1999a. Exercise- and methylcholine-induced sweating responses in older and younger men: effect of heat acclimation and aerobic fitness. Int. J. Biometeorol. 42, 210–216.
Inoue, Y., Nakao, M., Araki, T., Murakami, H., 1991. Regional differences in the sweating responses of older and younger men. J. Appl. Physiol. (1985) 71, 2453–2459.
Inoue, Y., Shibasaki, M., Ueda, H., Ishizashi, H., 1999b. Mechanisms underlying the age-related decrement in the human sweating response. Eur. J. Appl. Physiol. 79, 121–126.
Ishani, A., Xue, J.L., Himmelfarb, J., Eggers, P.W., Kimmel, P.L., Molitoris, B.A., Collins, A.J., 2009. Acute kidney injury increases risk of ESRD among elderly. J. Am. Soc. Nephrol. 20, 223–228.
Jay, O., Cramer, M.N., Ravanelli, N.M., Hodder, S.G., 2015. Should electric fans be used during a heat wave? Appl Ergon 46 (Pt A), 137–143.
Johnson, R.J., Lanaspa, M.A., Gabriela Sanchez-Lozada, L., Rodriguez-Iturbe, B., 2015. The discovery of hypertension: evolving views on the role of the kidneys, and current hot topics. Am. J. Physiol. Renal. Physiol. 308, F167–F178.
Jones, T.S., Liang, A.P., Kilbourne, E.M., Griffin, M.R., Patriarca, P.A., Wassilak, S.G.F., Mullan, R.J., Herrick, R.F., Donnell, H.D., Choi, K., 1982. Morbidity and mortality associated with the July 1980 heat wave in St Louis and Kansas City, Mo. Jama 247, 3327–3331.
Joyner, M.J., 2011. Physiology: alone at the bottom, alone at the top. J. Physiol. 589, 1005.
Jura, M., Kozak, L.P., 2016. Obesity and related consequences to ageing. Age (Dordr) 38, 23.
Kang, S.H., Oh, I.Y., Heo, J., Lee, H., Kim, J., Lim, W.H., Cho, Y., Choi, E.K., Yi, S.M., Sang Do, S., Kim, H., Youn, T.J., Chae, I.H., Oh, S., 2016. Heat, heat waves, and out-of-hospital cardiac arrest. Int. J. Cardiol. 221, 232–237.
Keatinge, W.R., Coleshaw, S.R., Easton, J.C., Cotter, F., Mattock, M.B., Chelliah, R., 1986. Increased platelet and red cell counts, blood viscosity, and plasma cholesterol levels during heat stress, and mortality from coronary and cerebral thrombosis. Am. J. Med. 81, 795–800.
Kellum, J.A., Lameire, N., Aspelin, P., Barsoum, R.S., Burdmann, E.A., Goldstein, S.L., Herzog, C.A., Joannidis, M., Kribben, A., Levey, A.S., 2012. Kidney disease: improving global outcomes (KDIGO) acute kidney injury work group. KDIGO clinical practice guideline for acute kidney injury. Kidney Int. Suppl. 2, 1–138.
Kenney, W.L., 1988. Control of heat-induced cutaneous vasodilatation in relation to age. Eur. J. Appl. Physiol. Occup. Physiol. 57, 120–125.
Kenney, W.L., 2017. Edward F. Adolph Distinguished Lecture: Skin-deep insights into vascular aging. J. Appl. Physiol. (1985) 123, 1024–1038.
Kenney, W.L., Chiu, P., 2001. Influence of age on thirst and fluid intake. Med. Sci. Sports Exerc. 33, 1524–1532.
Kenney, W.L., Craighead, D.H., Alexander, L.M., 2014. Heat waves, aging, and human cardiovascular health. Med. Sci. Sports Exerc. 46, 1891–1899.
Kenney, W.L., Fowler, S.R., 1988. Methylcholine-activated eccrine sweat gland density and output as a function of age. J. Appl. Physiol. 65, 1082–1086.
Kenney, W.L., Kamon, E., 1984. Comparative physiological responses of normotensive and essentially hypertensive men to exercise in the heat. Eur. J. Appl. Physiol. Occup. Physiol. 52, 196–201.
Kenney, W.L., Kamon, E., Buskirk, E., 1984. Effect of mild essential hypertension on control of forearm blood flow during exercise in the heat. J. Appl. Physiol. 56, 930–935.
Kenney, W.L., Munce, T.A., 2003. Invited review: aging and human temperature regulation. J. Appl. Physiol. (1985) 95, 2598–2603.
Kenny, G.P., Jay, O., 2013. Thermometry, calorimetry, and mean body temperature during heat stress. Compr. Physiol. 3, 1689–1719.
Kenny, G.P., Poirier, M.P., Metsios, G.S., Boulay, P., Dervis, S., Friesen, B.J., Malcolm, J., Sigal, R.J., Seely, A.J., Flouris, A.D., 2017. Hyperthermia and cardiovascular strain during an extreme heat exposure in young versus older adults. Temperature (Austin) 4, 79–88.
Kenny, G.P., Sigal, R.J., McGinn, R., 2016. Body temperature regulation in diabetes. Temperature (Austin) 3, 119–145.
Kenny, G.P., Stapleton, J.M., Yardley, J.E., Boulay, P., Sigal, R.J., 2013. Older adults with type 2 diabetes store more heat during exercise. Med. Sci. Sports Exerc. 45, 1906–1914.
Kenny, G.P., Yardley, J., Brown, C., Sigal, R.J., Jay, O., 2010. Heat stress in older individuals and patients with common chronic diseases. CMAJ 182, 1053–1060.
Klinenberg, E., 2015. Heat wave: A social autopsy of disaster in Chicago ed˜eds. University of Chicago Press.
Koppe, C., Sari Kovats, R., Menne, B., Jendritzky, G., Wetterdienst, D., Organization, W.H., 2004. Heat-Waves: Risks and Responses. WHO Regional Office for Europe, Copenhagen.
Kubo, S.H., Rector, T.S., Bank, A.J., Williams, R.E., Heifetz, S.M., 1991. Endothelium-dependent vasodilation is attenuated in patients with heart failure. Circulation 84, 1589–1596.
Lanaspa, M.A., Ishimoto, T., Cicerchi, C., Tamura, Y., Roncal-Jimenez, C.A., Chen, W., Tanabe, K., Andres-Hernando, A., Orlicky, D.J., Finol, E., Inaba, S., Li, N., Rivard, C.J., Kosugi, T., Sanchez-Lozada, L.G., Petrash, J.M., Sautin, Y.Y., Ejaz, A.A., Kitagawa, W., Garcia, G.E., Bonthron, D.T., Asipu, A., Diggle, C.P., Rodriguez-Iturbe, B., Nakagawa, T., Johnson, R.J., 2014. Endogenous fructose production and fructokinase activation mediate renal injury in diabetic nephropathy. J. Am. Soc. Nephrol. 25, 2526–2538.
Lavados, P.M., Olavarría, V.V., Hoffmeister, L., 2018. Ambient temperature and stroke risk: evidence supporting a short-term effect at a population level from acute environmental exposures. Stroke 49, 255–261.
Le Blanc, J., Lordkipanidze, M., 2019. Platelet function in aging. Front. Cardiovasc. Med. 6, 109.
Lee, J.F., Harrison, M.L., Christmas, K.M., Kim, K., Hurr, C., Brothers, R.M., 2014. Elevated resting heart rate and reduced orthostatic tolerance in obese humans. Clin. Auton. Res. 24, 39–46.
Leon, L.R., Bouchama, A., 2015. Heat stroke. Compr. Physiol. 5, 611–647.
Leshem, M., 2017. Salt appetite is not increased in summer heat. Appetite 108, 28–31.
Levey, A.S., Coresh, J., 2012. Chronic kidney disease. Lancet 379, 165–180.
Liamis, G., Liberopoulos, E., Barkas, F., Elisaf, M., 2014. Diabetes mellitus and electrolyte disorders. World J. Clin. Cases 2, 488–496.
Liguori, I., Russo, G., Curcio, F., Bulli, G., Aran, L., Della-Morte, D., Gargiulo, G., Testa, G., Cacciatore, F., Bonaduce, D., Abete, P., 2018. Oxidative stress, aging, and diseases. Clin. Interv. Aging 13, 757–772.
Lim, Y.-H., So, R., Lee, C., Hong, Y.-C., Park, M., Kim, L., Yoon, H.-J., 2018. Ambient temperature and hospital admissions for acute kidney injury: a time-series analysis. Sci. Total Environ. 616, 1134–1138.
Linares, C., Diaz, J., 2008. Impact of high temperatures on hospital admissions: comparative analysis with previous studies about mortality (Madrid). Eur. J. Public Health 18, 317–322.
Lindner, G., Pfortmüller, C.A., Leichtle, A.B., Fiedler, G.M., Exadaktylos, A.K., 2014. Age-related variety in electrolyte levels and prevalence of dysnatremias and dyskalemias in patients presenting to the emergency department. Gerontology 60, 420–423.
Lohmus, M., 2018. Possible biological mechanisms linking mental health and heat-a contemplative review. Int. J. Environ. Res. Public Health 15.
Low, P.A., Walsh, J.C., Huang, C.Y., McLeod, J.G., 1975. The sympathetic nervous system in diabetic neuropathy. A clinical and pathological study. Brain 98, 341–356.
Lowik, M.R., Westenbrink, S., Hulshof, K.F., Kistemaker, C., Hermus, R.J., 1989. Nutrition and aging: dietary intake of “apparently healthy” elderly (Dutch Nutrition Surveillance System). J. Am. Coll. Nutr. 8, 347–356.
Lunyera, J., Mohottige, D., Von Isenburg, M., Jeuland, M., Patel, U.D., Stanifer, J.W., 2016. CKD of uncertain etiology: a systematic review. Clin. J. Am. Soc. Nephrol. 11, 379–385.
Luo, K.R., Chao, C.C., Hsieh, P.C., Lue, J.H., Hsieh, S.T., 2012. Effect of glycemic control on sudomotor denervation in type 2 diabetes. Diabetes Care 35, 612–616.
Mack, G.W., Weseman, C.A., Langhans, G.W., Scherzer, H., Gillen, C.M., Nadel, E.R., 1994. Body fluid balance in dehydrated healthy older men: thirst and renal osmoregulation. J. Appl. Physiol. (1985) 76, 1615–1623.
Mahaldar, A.R., 2012. Acid base and fluid electrolyte disturbances in chronic kidney disease. Clin. Queries: Nephrol. 1, 295–299.
Mattace-Raso, F.U., van der Cammen, T.J., Hofman, A., van Popele, N.M., Bos, M.L., Schalekamp, M.A., Asmar, R., Reneman, R.S., Hoeks, A.P., Breteler, M.M., Witteman, J.C., 2006. Arterial stiffness and risk of coronary heart disease and stroke: the Rotterdam Study. Circulation 113, 657–663.
Matthies, F., Bickler, G., Marín, N.C., Hales, S., 2008. Heat-Health Action Plans: Guidance. World Health Organization.
Mayrhuber, E.A., Duckers, M.L.A., Wallner, P., Arnberger, A., Allex, B., Wiesbock, L., Wanka, A., Kolland, F., Eder, R., Hutter, H.P., Kutalek, R., 2018. Vulnerability to heatwaves and implications for public health interventions - a scoping review. Environ. Res. 166, 42–54.
McGarr, G.W., Fujii, N., Muia, C.M., Nishiyasu, T., Kenny, G.P., 2019. Separate and combined effects of KCa and KATP channel blockade with NOS inhibition on cutaneous vasodilation and sweating in older men during heat stress. Am. J. Physiol. Regul. Integr. Comp. Physiol. 317, R113–R120.

McTavish, R.K., Richard, L., McArthur, E., Shariff, S.Z., Acedillo, R., Parikh, C.R., Wald, R., Wilk, P., Garg, A.X., 2018. Association between high environmental heat and risk of acute kidney injury among older adults in a northern climate: a matched case-control study. Am. J. Kidney Dis. 71, 200–208.
Meade, R.D., Fujii, N., McGarr, G.W., Alexander, L.M., Boulay, P., Sigal, R.J., Kenny, G.P., 2019a,. Local arginase inhibition does not modulate cutaneous vasodilation or sweating in young and older men during exercise. J. Appl. Physiol. (1985) 126, 1129–1137.
Meade, R.D., Notley, S.R., D'Souza, A.W., Dervis, S., Boulay, P., Sigal, R.J., Kenny, G.P., 2019b. Interactive effects of age and hydration state on human thermoregulatory function during exercise in hot-dry conditions. Acta Physiol. (Oxf) 226, e13226.
Meade, R.D., Notley, S.R., Kenny, G.P., 2019c. Aging and human heat dissipation during exercise-heat stress: an update and future directions. Curr. Opin. Physiol.
Meyer, M.A., Ostrowski, S.R., Overgaard, A., Ganio, M.S., Secher, N.H., Crandall, C.G., Johansson, P.I., 2013. Hypercoagulability in response to elevated body temperature and central hypovolemia. J. Surg. Res. 185, e93–e100.
Michaud, M., Balardy, L., Moulis, G., Gaudin, C., Peyrot, C., Vellas, B., Cesari, M., Nourhashemi, F., 2013. Proinflammatory cytokines, aging, and age-related diseases. J. Am. Med. Dir. Assoc. 14, 877–882.
Miescher, E., Fortney, S.M., 1989. Responses to dehydration and rehydration during heat exposure in young and older men. Am. J. Physiol. 257, R1050–R1056.
Mills, K.T., Stefanescu, A., He, J., 2020. The global epidemiology of hypertension. Nat. Rev. Nephrol. 16, 223–237.
Minson, C.T., Wladkowski, S.L., Cardell, A.F., Pawelczyk, J.A., Kenney, W.L., 1998. Age alters the cardiovascular response to direct passive heating. J. Appl. Physiol. (1985) 84, 1323–1332.
Mitchell, G.F., Parise, H., Benjamin, E.J., Larson, M.G., Keyes, M.J., Vita, J.A., Vasan, R.S., Levy, D., 2004. Changes in arterial stiffness and wave reflection with advancing age in healthy men and women: the Framingham Heart Study. Hypertension 43, 1239–1245.
Molitch, M.E., DeFronzo, R.A., Franz, M.J., Keane, W.F., 2004. Nephropathy in diabetes. Diabetes care 27, S79.
Monahan, K.D., 2007. Effect of aging on baroreflex function in humans. Am. J. Physiol. Regul. Integr. Comp. Physiol. 293, R3–R12.
Moore, K., Thompson, C., Trainer, P., 2003. Disorders of water balance. Clin. Med. (Lond) 3, 28–33.
Morris, N.B., English, T., Hospers, L., Capon, A., Jay, O., 2019. The effects of electric fan use under differing resting heat index conditions: a clinical trial. Ann. Intern. Med.
Moseley, P.L., Gapen, C., Wallen, E.S., Walter, M.E., Peterson, M.W., 1994. Thermal stress induces epithelial permeability. Am. J. Physiol. 267, C425–C434.
Musso, C., Liakopoulos, V., De Miguel, R., Imperiali, N., Algranati, L., 2006. Transtubular potassium concentration gradient: comparison between healthy old people and chronic renal failure patients. Int. Urol. Nephrol. 38, 387–390.
Nath, K.A., Norby, S.M., 2000. Reactive oxygen species and acute renal failure. Am. J. Med. 109, 665–678.
Neeland, I.J., Poirier, P., Despres, J.P., 2018. Cardiovascular and metabolic heterogeneity of obesity: clinical challenges and implications for management. Circulation 137, 1391–1406.
Notley, S.R., Lamarche, D.T., Meade, R.D., Flouris, A.D., Kenny, G.P., 2019a. Revisiting the influence of individual factors on heat exchange during exercise in dry heat using direct calorimetry. Exp. Physiol. 104, 1038–1050.
Notley, S.R., Poirier, M.P., Sigal, R.J., D'Souza, A., Flouris, A.D., Fujii, N., Kenny, G.P., 2019b. Exercise heat stress in patients with and without type 2 diabetes. JAMA 322, 1409–1411.
Ó Flatharta, T., Flynn, A., Mulkerrin, E.C., 2019. Heat-related chronic kidney disease mortality in the young and old: differing mechanisms, potentially similar solutions? BMJ Evid. Based Med. 24, 45–47.
Ouzeau, G., Soubeyroux, J.-M., Schneider, M., Vautard, R., Planton, S., 2016. Heat waves analysis over France in present and future climate: application of a new method on the EURO-CORDEX ensemble. Clim. Serv. 4, 1–12.
Palatini, P., Julius, S., 2009. The role of cardiac autonomic function in hypertension and cardiovascular disease. Curr. Hypertens. Rep. 11, 199–205.
Parsons, K., 2014. Human Thermal Environments: The Effects Of Hot, Moderate, and Cold Environments on Human Health, Comfort, and Performance. CRC Press.
Pascual, J., Liaño, F., Ortuno, J., 1995. The elderly patient with acute renal failure. J. Am. Soc. Nephrol. 6, 144–153.
Perazella, M., 1996. Hyperkalemia in the elderly: a group at high risk. Conn. Med. 60, 195–198.
Petrofsky, J., Lee, S., Macnider, M., Navarro, E., 2005a. Autonomic, endothelial function and the analysis of gait in patients with type 1 and type 2 diabetes. Acta Diabetol. 42, 7–15.
Petrofsky, J.S., Focil, N., Prowse, M., Kim, Y., Berk, L., Bains, G., Lee, S., 2010. Autonomic stress and balance—the impact of age and diabetes. Diabetes Technol. Ther. 12, 475–481.
Petrofsky, J.S., Lee, S., Patterson, C., Cole, M., Stewart, B., 2005b. Sweat production during global heating and during isometric exercise in people with diabetes. Med. Sci. Monit. 11, CR515-521.
Phillips, P.A., Bretherton, M., Johnston, C.I., Gray, L., 1991. Reduced osmotic thirst in healthy elderly men. Am. J. Physiol. 261, R166–R171.
Phillips, P.A., Rolls, B.J., Ledingham, J.G., Forsling, M.L., Morton, J.J., Crowe, M.J., Wollner, L., 1984. Reduced thirst after water deprivation in healthy elderly men. N. Engl. J. Med. 311, 753–759.
Pikkujämsä, S.M., Huikuri, H.V., Airaksinen, K.J., Rantala, A.O., Kauma, H., Lilja, M., Savolainen, M.J., Kesäniemi, Y.A., 1998. Heart rate variability and baroreflex sensitivity in hypertensive subjects with and without metabolic features of insulin resistance syndrome. Am. J. Hypertens. 11, 523–531.
Poirier, M.P., Notley, S.R., Boulay, P., Sigal, R.J., Friesen, B.J., Malcolm, J., Flouris, A.D., Kenny, G.P., 2020. Type 2 diabetes does not exacerbate body heat storage in older adults during brief, extreme passive heat exposure. Temperature. https://doi.org/10.1080/23328940.2020.1736760.
Previtali, E., Bucciarelli, P., Passamonti, S.M., Martinelli, I., 2011. Risk factors for venous and arterial thrombosis. Blood Transfus 9, 120–138.
Rand, S., Petrofsky, J.S., Zimmerman, G., 2008. Diabetes: sweat response and heart rate variability during electrical stimulation in controls and people with diabetes. J. Appl. Reliab. 8, 48.
Redfield, M.M., Jacobsen, S.J., Burnett Jr., J.C., Mahoney, D.W., Bailey, K.R., Rodeheffer, R.J., 2003. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. JAMA 289, 194–202.
Roberts, G.T., Ghebeh, H., Chishti, M.A., Al-Mohanna, F., El-Sayed, R., Al-Mohanna, F., Bouchama, A., 2008. Microvascular injury, thrombosis, inflammation, and apoptosis in the pathogenesis of heatstroke: a study in baboon model. Arterioscler. Thromb. Vasc. Biol. 28, 1130–1136.
Robine, J.M., Cheung, S.L., Le Roy, S., Van Oyen, H., Griffiths, C., Michel, J.P., Herrmann, F.R., 2008. Death toll exceeded 70,000 in Europe during the summer of 2003. C.R. Biol. 331, 171–178.
Roncal-Jimenez, C.A., Ishimoto, T., Lanaspa, M.A., Milagres, T., Hernando, A.A., Jensen, T., Miyazaki, M., Doke, T., Hayasaki, T., Nakagawa, T., 2016. Aging-associated renal disease in mice is fructokinase dependent. Am. J. Physiol.-Renal Physiol. 311, F722–F730.
Rosinger, A.Y., Lawman, H.G., Akinbami, L.J., Ogden, C.L., 2016. The role of obesity in the relation between total water intake and urine osmolality in US adults, 2009–2012. Am. J. Clin. Nutr. 104, 1554–1561.
Rothman, K.J., 1976. Causes. Am. J. Epidemiol. 104, 587–592.
Rowell, L.B., 1974. Human cardiovascular adjustments to exercise and thermal stress. Physiol. Rev. 54, 75–159.
Rowell, L.B., 1990. Hyperthermia: a hyperadrenergic state. Hypertension 15, 505–507.
Rowell, L.B., Brengelmann, G.L., Detry, J.M., Wyss, C., 1971. Venomotor responses to local and remote thermal stimuli to skin in exercising man. J. Appl. Physiol. 30, 72–77.
Rowell, L.B., Brengelmann, G.L., Murray, J.A., 1969. Cardiovascular responses to sustained high skin temperature in resting man. J. Appl. Physiol. 27, 673–680.
Sagawa, S., Shiraki, K., Yousef, M.K., Miki, K., 1988. Sweating and cardiovascular responses of aged men to heat exposure. J. Gerontol. 43, M1–M8.
Satirapoj, B., 2013. Nephropathy in Diabetes. Diabetes. Springer.
Sato, K., 1977. The physiology, pharmacology, and biochemistry of the eccrine sweat gland. Reviews of Physiology, Biochemistry and Pharmacology, vol. 79. Springer.
Sato, Y., Roncal-Jimenez, C.A., Andres-Hernando, A., Jensen, T., Tolan, D.R., Sanchez-Lozada, L.G., Newman, L.S., Butler-Dawson, J., Sorensen, C., Glaser, J., Miyazaki, M., Diaz, H.F., Ishimoto, T., Kosugi, T., Maruyama, S., Garcia, G.E., Lanaspa, M.A., Johnson, R.J., 2019. Increase of core temperature affected the progression of kidney injury by repeated heat stress exposure. Am. J. Physiol. Renal Physiol. 317, F1111–F1121.
Sawka, M.N., Burke, L.M., Eichner, E.R., Maughan, R.J., Montain, S.J., Stachenfeld, N.S., 2007. American College of Sports Medicine position stand. Exercise and fluid replacement. Med. Sci. Sports Exerc. 39, 377–390.
Sawka, M.N., Cheuvront, S.N., Kenefick, R.W., 2015. Hypohydration and human performance: impact of environment and physiological mechanisms. Sports Med. 45 (Suppl 1), S51–S60.
Sawka, M.N., Young, A.J., Francesconi, R.P., Muza, S.R., Pandolf, K.B., 1985. Thermoregulatory and blood responses during exercise at graded hypohydration levels. J. Appl. Physiol. (1985) 59, 1394–1401.
Schlader, Z.J., Hostler, D., Parker, M.D., Pryor, R.R., Lohr, J.W., Johnson, B.D., Chapman, C.L., 2019a. The potential for renal injury elicited by physical work in the heat. Nutrients 11 (9), 2087.
Schlader, Z.J., Okada, Y., Best, S.A., Fu, Q., Crandall, C.G., 2019b. Arterial stiffness during whole-body passive heat stress in healthy older adults. Physiol. Rep. 7, e14094.
Schlader, Z.J., Wilson, T.E., Crandall, C.G., 2016. Mechanisms of orthostatic intolerance during heat stress. Auton. Neurosci. 196, 37–46.
Schmitt, R., Coca, S., Kanbay, M., Tinetti, M.E., Cantley, L.G., Parikh, C.R., 2008. Recovery of kidney function after acute kidney injury in the elderly: a systematic review and meta-analysis. Am. J. Kidney Dis. 52, 262–271.
Schoeller, D.A., 1989. Changes in total body water with age. Am. J. Clin. Nutr. 50, 1176–1181.
Seals, D.R., 2013. Translational physiology: from molecules to public health. J. Physiol. 591, 3457–3469.
Semenza, J.C., 1999. Acute renal failure during heat waves. Am. J. Prev. Med. 17, 97.
Semenza, J.C., McCullough, J.E., Flanders, W.D., McGeehin, M.A., Lumpkin, J.R., 1999. Excess hospital admissions during the July 1995 heat wave in Chicago. Am. J. Prev. Med. 16, 269–277.
Semenza, J.C., Rubin, C.H., Falter, K.H., Selanikio, J.D., Flanders, W.D., Howe, H.L., Wilhelm, J.L., 1996. Heat-related deaths during the July 1995 heat wave in Chicago. N. Engl. J. Med. 335, 84–90.
Senay Jr., L.C., 1968. Relationship of evaporative rates to serum [Na+], [K+], and osmolarity in acute heat stress. J. Appl. Physiol. 25, 149–152.
Shah, P.K., Lecis, D., 2019. Inflammation in atherosclerotic cardiovascular disease. F1000Res 8.
Shibasaki, M., Okazaki, K., Inoue, Y., 2013. Aging and thermoregulation. J. Phys. Fitness Sports Med. 2, 37–47.
Shoenfeld, Y., Udassin, R., Shapiro, Y., Ohri, A., Sohar, E., 1978. Age and sex difference in response to short exposure to extreme dry heat. J. Appl. Physiol. Respir. Environ. Exerc. Physiol. 44, 1–4.
Skrapari, I., Tentolouris, N., Perrea, D., Bakoyiannis, C., Papazafiropoulou, A.,

Katsilambros, N., 2007. Baroreflex sensitivity in obesity: relationship with cardiac autonomic nervous system activity. Obesity (Silver Spring) 15, 1685–1693.
Slawik, M., Vidal-Puig, A.J., 2006. Lipotoxicity, overnutrition and energy metabolism in aging. Ageing Res. Rev. 5, 144–164.
Smith, C.J., Santhanam, L., Bruning, R.S., Stanhewicz, A., Berkowitz, D.E., Holowatz, L.A., 2011. Upregulation of inducible nitric oxide synthase contributes to attenuated cutaneous vasodilation in essential hypertensive humans. Hypertension 58, 935–942.
Smith, J.H., Robinson, S., Pearcy, M., 1952. Renal responses to exercise, heat and dehydration. J. Appl. Physiol. 4, 659–665.
Sokolnicki, L.A., Strom, N.A., Roberts, S.K., Kingsley-Berg, S.A., Basu, A., Charkoudian, N., 2009. Skin blood flow and nitric oxide during body heating in type 2 diabetes mellitus. J. Appl. Physiol. (1985) 106, 566–570.
Spalt, E.W., Curl, C.L., Allen, R.W., Cohen, M., Adar, S.D., Stukovsky, K.H., Avol, E., Castro-Diehl, C., Nunn, C., Mancera-Cuevas, K., Kaufman, J.D., 2016. Time-location patterns of a diverse population of older adults: the Multi-Ethnic Study of Atherosclerosis and Air Pollution (MESA Air). J. Expo Sci. Environ. Epidemiol. 26, 436.
Speakman, J.R., 2018. Obesity and Thermoregulation. Handbook of Clinical Neurology. Elsevier.
Spina, R.J., Turner, M.J., Ehsani, A.A., 1998. Beta-adrenergic-mediated improvement in left ventricular function by exercise training in older men. Am. J. Physiol. 274, H397–H404.
Stachenfeld, N.S., DiPietro, L., Nadel, E.R., Mack, G.W., 1997. Mechanism of attenuated thirst in aging: role of central volume receptors. Am. J. Physiol. 272, R148–R157.
Stapleton, J.M., Larose, J., Simpson, C., Flouris, A.D., Sigal, R.J., Kenny, G.P., 2013. Do older adults experience greater thermal strain during heat waves? Appl. Physiol. Nutr. Metab. 39, 292–298.
Stefanadis, C., Antoniou, C.K., Tsiachris, D., Pietri, P., 2017. Coronary atherosclerotic vulnerable plaque: current perspectives. J. Am. Heart Assoc. 6.
Stevens, L.A., Li, S., Tamura, M.K., Chen, S.-C., Vassalotti, J.A., Norris, K.C., Whaley-Connell, A.T., Bakris, G.L., McCullough, P.A., 2011. Comparison of the CKD epidemiology collaboration (CKD-EPI) and modification of diet in renal disease (MDRD) study equations: risk factors for and complications of CKD and mortality in the kidney early evaluation program (KEEP). Am. J. Kidney Dis. 57, S9–S16.
Stevens, L.A., Viswanathan, G., Weiner, D.E., 2010. CKD and ESRD in the elderly: current prevalence, future projections, and clinical significance. Adv. Chronic Kidney Dis. 17, 293.
Stocker, S.D., Hunwick, K.J., Toney, G.M., 2005. Hypothalamic paraventricular nucleus differentially supports lumbar and renal sympathetic outflow in water-deprived rats. J. Physiol. 563, 249–263.
Stookey, J., Barclay, D., Arieff, A., Popkin, B., 2007. The altered fluid distribution in obesity may reflect plasma hypertonicity. Eur. J. Clin. Nutr. 61, 190.
Sturmberg, J.P., Picard, M., Aron, D.C., Bennett, J.M., Bircher, J., De Haven, M.J., Gijzel, S.M.W., Heng, H.H., Marcum, J.A., Martin, C.M., Miles, A., Peterson, C.L., Rohleder, N., Walker, C., Olde Rikkert, M.G.M., Melis, R.J.F., 2019. Health and disease-emergent states resulting from adaptive social and biological network interactions. Front. Med. (Lausanne) 6, 59.
Suzman, R., Beard, J.R., Boerma, T., Chatterji, S., 2015. Health in an ageing world–what do we know? Lancet 385, 484–486.
Székely, M., Carletto, L., Garami, A., 2015. The pathophysiology of heat exposure. Temperature: Multidisc. Biomed. J. 2, 452.
Takamata, A., Ito, T., Yaegashi, K., Takamiya, H., Maegawa, Y., Itoh, T., Greenleaf, J.E., Morimoto, T., 1999. Effect of an exercise-heat acclimation program on body fluid regulatory responses to dehydration in older men. Am. J. Physiol. 277, R1041–R1050.
Tamma, G., Goswami, N., Reichmuth, J., De Santo, N.G., Valenti, G., 2015. Aquaporins, vasopressin, and aging: current perspectives. Endocrinology 156, 777–788.
Tancredi, M., Rosengren, A., Svensson, A.-M., Kosiborod, M., Pivodic, A., Gudbjörnsdottir, S., Wedel, H., Clements, M., Dahlqvist, S., Lind, M., 2015. Excess mortality among persons with type 2 diabetes. N. Engl. J. Med. 373, 1720–1732.
Tank, J.E., Vora, J.P., Houghton, D.C., Anderson, S., 1994. Altered renal vascular responses in the aging rat kidney. Am. J. Physiol. 266, F942–F948.
Taylor, N.A., Machado-Moreira, C.A., 2013. Regional variations in transepidermal water loss, eccrine sweat gland density, sweat secretion rates and electrolyte composition in resting and exercising humans. Extrem. Physiol. Med. 2, 4.
Thadhani, R., Pascual, M., Bonventre, J.V., 1996. Acute renal failure. N. Engl. J. Med. 334, 1448–1460.
Thomas, K.N., van Rij, A.M., Lucas, S.J., Cotter, J.D., 2017. Lower-limb hot-water immersion acutely induces beneficial hemodynamic and cardiovascular responses in peripheral arterial disease and healthy, elderly controls. Am. J. Physiol. Regul. Integr. Comp. Physiol. 312, R281–R291.
Ticcinelli, V., Stankovski, T., Iatsenko, D., Bernjak, A., Bradbury, A.E., Gallagher, A.R., Clarkson, P.B.M., McClintock, P.V.E., Stefanovska, A., 2017. Coherence and coupling functions reveal microvascular impairment in treated hypertension. Front. Physiol. 8, 749.
Vaidyanathan, A., Saha, S., Vicedo-Cabrera, A.M., Gasparrini, A., Abdurehman, N., Jordan, R., Hawkins, M., Hess, J., Elixhauser, A., 2019. Assessment of extreme heat and hospitalizations to inform early warning systems. Proc. Natl. Acad. Sci. USA 116, 5420–5427.
Vandentorren, S., Bretin, P., Zeghnoun, A., Mandereau-Bruno, L., Croisier, A., Cochet, C., Riberon, J., Siberan, I., Declercq, B., Ledrans, M., 2006. August 2003 heat wave in France: risk factors for death of elderly people living at home. Eur. J. Public Health 16, 583–591.
Vasan, R.S., 2003. Cardiac function and obesity. Heart 89, 1127–1129.
Vaziri, N.D., Gonzales, E.C., Wang, J., Said, S., 1994. Blood coagulation, fibrinolytic, and inhibitory proteins in end-stage renal disease: effect of hemodialysis. Am. J. Kidney Dis. 23, 828–835.
Verheye, S., De Meyer, G.R., Van Langenhove, G., Knaapen, M.W., Kockx, M.M., 2002. In vivo temperature heterogeneity of atherosclerotic plaques is determined by plaque composition. Circulation 105, 1596–1601.
Vlassara, H., Torreggiani, M., Post, J.B., Zheng, F., Uribarri, J., Striker, G.E., 2009. Role of oxidants/inflammation in declining renal function in chronic kidney disease and normal aging. Kidney Int. Suppl. S3–S11.
Wald, R., Jaber, B.L., Price, L.L., Upadhyay, A., Madias, N.E., 2010. Impact of hospital-associated hyponatremia on selected outcomes. Arch. Intern. Med. 170, 294–302.
Wang, J.-C., Chien, W.-C., Chu, P., Chung, C.-H., Lin, C.-Y., Tsai, S.-H., 2019. The association between heat stroke and subsequent cardiovascular diseases. PLoS ONE 14, e0211386.
Watts, N., Amann, M., Arnell, N., Ayeb-Karlsson, S., Belesova, K., Boykoff, M., Byass, P., Cai, W., Campbell-Lendrum, D., Capstick, S., 2019. The 2019 report of The Lancet Countdown on health and climate change: ensuring that the health of a child born today is not defined by a changing climate. The Lancet 394, 1836–1878.
Weiner, M., Epstein, F., 1970. Signs and symptoms of electrolyte disorders. Yale J. Biol. Med. 43, 76.
Weinstein, J.R., Anderson, S., 2010. The aging kidney: physiological changes. Adv. Chronic Kidney Dis. 17, 302–307.
Westaway, K., Frank, O., Husband, A., McClure, A., Shute, R., Edwards, S., Curtis, J., Rowett, D., 2015. Medicines can affect thermoregulation and accentuate the risk of dehydration and heat-related illness during hot weather. J. Clin. Pharm. Ther. 40, 363–367.
White-Newsome, J.L., Sanchez, B.N., Jolliet, O., Zhang, Z., Parker, E.A., Dvonch, J.T., O'Neill, M.S., 2012. Climate change and health: indoor heat exposure in vulnerable populations. Environ. Res. 112, 20–27.
Wick, D.E., Roberts, S.K., Basu, A., Sandroni, P., Fealey, R.D., Sletten, D., Charkoudian, N., 2006. Delayed threshold for active cutaneous vasodilation in patients with Type 2 diabetes mellitus. J. Appl. Physiol. (1985) 100, 637–641.
Wilker, E.H., Yeh, G., Wellenius, G.A., Davis, R.B., Phillips, R.S., Mittleman, M.A., 2012. Ambient temperature and biomarkers of heart failure: a repeated measures analysis. Environ. Health Perspect. 120, 1083–1087.
Wilkerson, W.R., Sane, D.C., 2002. Aging and thrombosis. Seminars in thrombosis and hemostasis: Copyright© 2002 by Thieme Medical Publishers, Inc., 333 Seventh Avenue, New.
Williams, S.B., Cusco, J.A., Roddy, M.A., Johnstone, M.T., Creager, M.A., 1996. Impaired nitric oxide-mediated vasodilation in patients with non-insulin-dependent diabetes mellitus. J. Am. Coll. Cardiol. 27, 567–574.
World Health Organization, 2014. Quantitative risk assessment of the effects of climate change on selected causes of death, 2030s and 2050s.
World Health Organization, 2016. Global Report On Diabetes: Executive Summary. World Health Organization.
World Health Organization, 2019. Cardiovascular Diseases. World Health Organization.
Wright, H.E., McLellan, T.M., Larose, J., Hardcastle, S.G., Boulay, P., Kenny, G.P., 2014. Are circulating cytokine responses to exercise in the heat augmented in older men? Appl. Physiol. Nutr. Metab. 39, 117–123.
Wroblewski, H., Norgaard, T., Haunso, S., Kastrup, J., 1995. Microvascular distensibility in two different vascular beds in idiopathic dilated cardiomyopathy. Am. J. Physiol. 269, H1973–H1980.
Yoon, H.E., Choi, B.S., 2014. The renin-angiotensin system and aging in the kidney. Korean J. Intern. Med. 29, 291–295.
Zhang, Q.L., Rothenbacher, D., 2008. Prevalence of chronic kidney disease in population-based studies: systematic review. BMC Public Health 8, 117.
Zieman, S.J., Melenovsky, V., Kass, D.A., 2005. Mechanisms, pathophysiology, and therapy of arterial stiffness. Arterioscler. Thromb. Vasc. Biol. 25, 932–943.
Zou, A.P., Li, N., Cowley Jr., A.W., 2001. Production and actions of superoxide in the renal medulla. Hypertension 37, 547–553.