Toward a Better Understanding of the Thermal and Cardiovascular Strain Experienced by Older Adults During Extreme Heat Events

Robert Meade, MSc.

Thesis submitted to the University of Ottawa in partial fulfillment of the requirements for the degree of Doctor of Philosophy

Human and Environmental Physiology Research Unit, School of Human Kinetics,
Faculty of Health Sciences, University of Ottawa, Ottawa, Ontario, Canada, K1N 6N5

THESIS ABSTRACT

This thesis evaluated physiological responses of young and older adults during extreme heat events and the extent to which commonly recommended heat-health guidelines (indoor temperature limits) and heat mitigation strategies (cooling centres) are effective at limiting hyperthermia and cardiovascular burden. A multidisciplinary narrative review and three experimental studies were conducted. In the review, the mechanisms by which aging impairs the regulation of body temperature and hemodynamic stability, and how they may contribute to the increased risk of heat-related mortality and morbidity in older adults, were summarized. A lack of ecologically minded study designs in previous research evaluating the physiological responses supporting homeostasis and health during heat stress (i.e., body temperature regulation and cardiovascular stability) was also identified. The three experiments were therefore designed as day-long (8-9 hour) extreme heat simulations to 1) evaluate age-related alterations in thermoregulatory and cardiovascular function during peak heat conditions; 2) assess how these responses translate to indoor environments; and 3) quantify the effectiveness of cooling centers, a widely recommended heat mitigation strategy, for limiting hyperthermia and cardiovascular burden. In the first study, healthy older adults (age: 64-78 years; n=19) stored 87 kJ [95% confidence limits: 33, 141] more heat than their younger (age: 19-31 years; n=20) counterparts (328 [71] kJ vs. 241 [SD: 87]; $P<0.001$) during the first three hours of a 9-hour exposure to extreme heat (40°C and 15% relative humidity). This resulted in a 0.4°C [0.2, 0.6] greater increase in body core temperature in the older adults that was maintained throughout exposure (1.0 [0.3] vs 0.6 [0.3]°C; $P<0.001$). These findings were extended in the second study, wherein it was demonstrated that healthy older adults (age: 66-78 years, n=8) exhibit progressive elevations in body temperatures (P<0.001) and attenuations in cardiovascular autonomic function (P<0.001) during 8 hours of rest in conditions representative of those experienced indoors during extreme heat events. These ranged from an actively cooled environment (22°C), through indoor temperature thresholds recommended by Toronto Public Health (26°C) and the World Health Organization (31°C), to poorly insulated and ventilated homes and/or dwellings without access to air conditioning (36°C; 45% relative humidity in all conditions). In the third study, it was shown that short-term exposure to a cool environment midway through (hours 5-6) a day-long (9 hour) simulated heat event reduced core temperature in a group of healthy older adults (age: 67-78 years; n=8) by 0.8°C [0.6, 1.0] compared to an age-matched group not removed from the heat (from study 1). Despite this, core temperature rose rapidly upon return to the heat and was statistically equivalent in both groups by the end of exposure (37.8 [0.3] vs 37.9 [0.3]°C; P=0.011). The findings of this thesis indicate that even healthy older adults experience sustained elevations in body temperature and cardiovascular burden during extreme heat events and that commonly recommended heat-health guidelines (indoor temperature limits) and mitigation strategies (cooling centres) may not provide adequate protection. Collectively, this work represents a considerable advance in our understanding of the physiological burden experienced by older adults during hot weather and extreme heat events.

ACKNOWLEDGEMENTS

Although mine is the only name to appear on the title page of this document, this work would not have been possible were it not for the guidance and support of a great many individuals. I would like to take a moment to sincerely thank those who have contributed to the completion of this thesis.

First and foremost, I am indebted to the volunteers who participated in the studies of the thesis. Without their invaluable contribution, none of this would have been possible.

Thank you, Dr. Glen Kenny, for providing me the opportunity to undertake this work in your laboratory. Your support and tutelage over the past 7 years (MSc and PhD, yikes) has allowed me to develop into the scientist I am today. I am extremely fortunate to have been able to train under and learn from such a committed and knowledgeable individual.

Dr. Pascal Imbeault and Dr. Michael De Lisio, your guidance and feedback throughout the completion of this thesis has been immensely helpful. Thank you.

I would also like to extend my thanks to the members of the Human and Environmental Physiological Research Unit. In particular, I owe a huge debt of gratitude to Dr. Sean Notley and Dr. Ashley Akerman for their guidance throughout the execution of the thesis studies. I would also like to thank Dr. Gregory McGarr, Dr. Jeremy McCormick, Dr. Ryan McGinn, Dr. Pierre Gosselin, Dr. Paul Poirier, Kelli King, Jeremy Nehme, Emileigh Binet, Brodie Richards, and Emma McCourt, who all played important roles in this work.

To my parents, Kevin and Cathy, thank you for your unconditional support throughout this and all of my endeavours. You have always encouraged me to follow my heart, and I credit much of what I have accomplished to you because of that. I love you.

Thank you Bunard, Dee, and Charlie. While I feel your presence in my life has helped me maintain my sanity, I wonder whether your mention here is an indication that I am drifting ever farther from it.

Finally, to the love of my life, Emily, a million times thank you. Your borderline pathological level-headedness has been more help to me than you will ever know. I consider myself extremely fortunate to have had you in my corner through this chapter of my life.

TABLE OF CONTENTS

LIST OF FIGURES

Literature review

Thesis Article 1

Thesis Article 2

Thesis Article 3

Thesis Article 4

Thesis Discussion

LIST OF TABLES

Thesis Article 1

Thesis Article 2

Thesis Article 3

Thesis Article 4

CHAPTER 1 – INTRODUCTION

1.1 Introduction

Rising global temperatures and the accompanying increases in the incidence and severity of extreme heat events (heatwaves) represent a major challenge to human health[1,2]. Among the most affected by the adverse health impacts of extreme heat are older adults[1-3] (most often defined as individuals aged ≥60-65 years[4,5]), especially the infirm and those living with age-associated chronic health conditions linked with heat-vulnerability[6-9]. Coupled with an aging global population[4,5], more frequent and intense periods of extreme heat[10,11] mean that a growing number of heat-vulnerable older adults are increasingly exposed to extreme heat events[12]. To this end, the World Health Organization has projected an additional 250,000 yearly heat-related deaths in individuals aged ≥65 by mid-century unless progress toward climate adaptation is made[12].

Based on classic studies describing age-related impairments in the acute physiological responses to rapid and extreme whole-body heating, it has long been suggested that impaired regulation of body temperature and cardiovascular stability (i.e., arterial pressure and tissue perfusion) contribute to reduced heat tolerance in older adults[13-16]. Despite the important contributions those studies made to elucidating the effect of healthy aging on the physiological response to heat, they were generally of low ecological validity; that is, the employed conditions were likely not representative of those commonly experienced during extreme heat events. Ultimately, a move toward ecologically minded study designs is required, especially considering the growing role of physiological research in quantifying the effects of climate change on health[17] and the effectiveness of heat mitigation strategies[18].

During heat stress, increased deep-body (i.e., core) and peripheral (i.e., skin, muscle) temperatures elicit sympathetically mediated elevations in skin blood flow and sweat secretion to facilitate heat loss and maintain core body temperature within physiological limits[19-24]. Many classic studies have shown attenuated cutaneous vasodilatory and sudomotor responses to exercise and passively induced heat stress in older adults compared to young controls[25-27]. Recent work has furthered those findings by demonstrating that age-related impairments in cutaneous vasodilation and sweating translate to reductions in the maximal rate of heat dissipation in individuals as young as 40 years of age[28-35]. However, many of those studies utilized exercise models[28-36] wherein heat stress is induced through increases in endogenous (metabolic) heat production, which can quickly surpass environmental heat gain, even in extreme ambient temperatures[37]. Further, most individuals[38], and older adults in particular[39], exhibit low levels of habitual physical activity. As such, exercise-heat stress likely overestimates the heat stress experienced during extreme heat events, especially in older individuals.

Some studies have assessed thermoregulatory function in older adults resting in hot environments. In a notable example, Kenny et al.[40] demonstrated that older adults (aged ~62 years) stored ~70% more heat than their younger counterparts (aged ~23 years) during 3-hours of exposure to extreme heat conditions (44°C, 30% relative humidity). More importantly, the older group did not achieve a state of heat balance (i.e., rate of heat gain balanced by heat loss; thermal equilibrium). Based on those findings, the authors postulated that continual increases in heat storage and therefore body temperature would have occurred, reaching potentially dangerous levels, if exposure duration was extended[40]. These findings are supported by Stapleton et al.[41], who observed that older adults were not able to achieve heat balance during 2 hours of exposure to hot-dry (36.5°C, 20% relative humidity) or hot-humid (36.5°C, 60% relative humidity) conditions.

It is important to note that in those and other similar studies, exposure duration was often limited to ≤180 min (see Table 1 of Section 3.1 Thesis Article 1). This highlights a critical problem in past designs since extreme heat events, by definition, last over extended periods[42], with the incidence of adverse health events often peaking late in the day[43]. Furthermore, most studies describing age-related alterations in resting thermoregulatory function have exposed older adults to oppressive conditions not representative of those typically experienced during extreme heat events (in temperate continental climates). In addition to the work by Kenny et al. (44°C; 30% relative humidity; heat index: 52°C), examples include studies by Miescher and Fortney (45°C, 25% relative humidity; heat index: 51°C)[44] and Drinkwater et al. (40°C, 40% relative humidity; heat index: 48°C)[45]. By comparison, conditions during the recent 2018 North American extreme heat event (≥74 deaths in Quebec, Canada over ~9 days) were relatively cooler, reaching a peak of ~34°C and 58% relative humidity (heat index: 41°C)[46]. Similarly, conditions in France during the 2003 European heat event (~70,000 deaths across Europe over ~3 months[47]) were ~38°C and 25% relative humidity (heat index: 38°C)[48]. In the aforementioned physiological studies, extreme heat stress was likely employed to ensure detection of an influence of age on thermoregulatory function. However, further research is still required to evaluate the magnitude of the effects of aging on whole-body heat dissipation and body temperature regulation under more realistic exposures.

Although catastrophic failure of body temperature regulation (e.g., heat exhaustion and heat stroke) results in significant mortality and morbidity during extreme heat events, most heat-related adverse health events are of cardiovascular origin[14,49]. Heat stress places considerable burden on the cardiovascular system. To facilitate the transfer of blood-borne heat from the central to peripheral circulation where it can be dissipated to the environment, dilation of the cutaneous vasculature increases skin blood flow from ~0.3 L/min at rest to as high as ~7-8 L/min in young adults during extreme heat stress[50]. Compensating for the consequent fall in peripheral vascular resistance are integrative physiological responses aimed at maintaining blood pressure, driven by elevations in sympathetic activity proportionate to the magnitude of heat stress[51]. Specifically, cardiac output increases by up to 6 L/min, primarily through elevations in heart rate[52,53]. Stroke volume is maintained (or slightly elevated), despite falling central venous pressure and cardiac preload, via increased myocardial contractility[54-58]. Concurrent vasoconstriction of the splanchnic and renal vascular beds facilitates re-distribution of blood to central and cutaneous regions[50,59-61].

In the young, the cardiovascular responses to heat stress are generally sufficient to maintain arterial blood pressure[62,63]. By contrast, older individuals exhibit attenuated increases in cardiac output and cutaneous blood flow relative to their younger counterparts[50,64]. This insufficiency stems from age-associated changes to the structure and function of the peripheral and central vasculature as well as the heart[65-67]. Also contributing is blunted sympathetic responsiveness[68-70], which, as described above, is primarily responsible for coordinating the cardiovascular (and thermoregulatory) responses to maintain blood pressure (and body temperature) during heat stress[27,51]. Heat-induced circulatory strain (e.g., elevated myocardial work) imposed on a compromised cardiovascular system is therefore thought to precipitate the deleterious cardiovascular outcomes seen in older individuals during extreme heat events[14].

As with past studies detailing the thermoregulatory responses, the effect of age on the cardiovascular adjustments to heat stress have typically not been evaluated under ecologically relevant conditions. Most studies in this domain have used whole-body convective heating induced by perfusion of hot water through an encapsulated, tube-lined garment worn by the participant. While this technique allows for precise control over the absolute and temporal profiles of the resultant rise in body core temperature[62,63], heat transfer is restricted due to the encapsulated design. Consequently, body temperatures are not allowed to naturally equilibrate with the environment (i.e., heat balance cannot be achieved) and extreme hyperthermia can quickly develop[53]. Further, because heat transfer is rapid through water (25 times greater thermal conductivity compared to dry air)[71], skin temperatures can reach ≥40°C[50]. Highly elevated skin temperatures can exacerbate elevations in cutaneous vascular conductance by 1) activation of sympathetic cutaneous vasodilator activity, increasing skin blood flow[63]; and, 2) directly augmenting cutaneous venous capacitance and volume[72]. Furthermore, since passive heating studies are often conducted with participants in the supine position, end-diastolic volume is maintained[59] supporting the marked elevations in cardiac output[53].

Even in very hot environments, skin temperature rarely exceeds ~36.5°C. Thus, cardiovascular strain is likely elevated for a given body core temperature during encapsulated passive heating compared to ambient heat exposure. In the older adults studied by Kenny et al.[40], forearm blood flow was elevated by ~3% whereas cardiac output remained at stable levels similar to baseline values at the end of the 3-hour ambient heat exposure period (44°C; 30% relative humidity)[40]. These responses are considerably lower than the ~10% and ~35% increases in forearm blood flow and cardiac output, respectively, observed in passively heated older adults by Minson et al.[50] As mentioned, the discrepancies between models likely relate to the lower body core (37.8 vs 38.5°C) and mean skin (36.2 vs 40.0°C) temperatures in the ambient heat exposure design employed by Kenny et al.[40,50] Despite this, the large cardiovascular strain observed in passive heating is often cited as evidence for the extreme cardiovascular toll experienced during extreme heat events[14,73]. Whether thermal and cardiovascular strain comparable to encapsulated heat stress would eventually develop during long-duration exposure to ambient heat stress is currently unknown.

Multiple epidemiological reports have detailed the relations between outdoor temperature and mortality and morbidity in heat vulnerable populations[74-77]. Concurrently, laboratory-based physiology studies have evaluated the effect of age on resting physiological responses to supra-heatwave levels of heat stress. However, most people, especially older adults, spend ≥70% of their time in the home[78,79], where temperatures can range anywhere from ≤22°C, if the home is actively cooled, to ≥35°C in the case of insulated and poorly ventilated domiciles[80]. To protect individuals against heat stress in the home, a recent report published by Toronto Public Health recommended that the maximum indoor temperature for multi-unit residential buildings should be set at 26°C[81,82]. The World Health Organization has also provided recommendations for maximal indoor temperatures, though their threshold is set considerably higher at 32°C[83]. Importantly, much of the evidence used to support these guidelines is indirect, based primarily on thermal comfort and relations between mortality and outdoor temperatures[81,82]. Moreover, both guidelines offer a ‘one-size-fits-all’ solution, such that neither explicitly considers the thermoregulatory and cardiovascular insufficiencies that may reduce the range of tolerable indoor conditions for vulnerable populations (e.g., older adults). Despite these limitations, the thermal and cardiovascular strain experienced in indoor environments, where older adults spend most of their time, has not been evaluated.

With the rising incidence and severity of extreme heat events, there have been increasing calls for adaptive strategies to protect at-risk individuals from extreme heat. The most effective of these is the use of air-conditioning to cool the domicile[6-9]. However, because home-cooling can be cost-prohibitive and not accessible to all individuals[84], health agencies including the World Health Organization and Health Canada recommend that a minimum of 1-3 hours per day be spent in an air-conditioned area during extreme heat events in order to cool the body[85,86]. This can include visiting air-conditioned shopping malls, apartment lobbies or cooling centres. The latter refers to designated locations set up as a temporary reprieve from extreme heat events, often providing basic health services such as on-site medical care[84,87]. Despite widespread deployment of these centres during extreme heat events, multiple studies have identified social and behavioral barriers that may limit their effectiveness[88-90]. What has been less often considered is whether temporary ambient cooling leads to lasting reductions in physiological strain as suggested by health agencies[85,86] .

The regulation of body temperature is under negative feedback control, such that heat stress induces elevations in core and skin temperatures that in turn elicit proportional activation of cutaneous vasodilation and sweating to facilitate heat loss and cool the body[24]. Steady state core temperatures (thermal equilibrium) in a given environment will therefore depend on the relation between the active physiological control of the heat loss responses as well as the passive heat exchange between the body and the environment. Temporary exposure to a cooled environment (e.g., visiting a cooling centre) will cause a reduction in body temperature and a subsequent deactivation of cutaneous vasodilation and sweating. As a consequence, one would expect that heat would be rapidly gained upon return to a hot environment until thermal equilibrium is re-established; though, this hypothesis has not been directly evaluated. Ultimately, this knowledge gap and those raised above highlight the need for a move toward ecologically minded study design to improve our understanding of the challenges to thermoregulatory and cardiovascular function experienced in older adults during extreme heat events.

1.2 Rationale and statement of the problem

The effect of aging on thermoregulatory and cardiovascular function during short-duration and extreme heat stress has been long studied. In recent years, those findings have been used to describe the physiological-basis for the increased risk experienced by older adults during extreme heat events[13-16]. However, thermoregulatory and cardiovascular responses to short-duration, extreme and often encapsulated heat exposure are likely inconsistent with those seen during ambient exposure to high heat conditions, though this has never been formally evaluated. This seriously limits the applicability of those study findings to prolonged heat-stress during extreme heat events. A series of comprehensive studies directed at advancing our understanding of thermal and cardiovascular responses, particularly in older adults, during day-long (8-9 hour) exposures to environments representative of those experienced outdoors and indoors during extreme heat events is therefore required. Such work would represent an important advancement in our ability to characterize the human physiological responses during extreme heat events as well as the effectiveness of heat policy and mitigation strategies.

1.3 Objectives

The objectives of this thesis were as follows:

1) Review the mechanisms by which aging (and chronic disease) impair the regulation of body temperature and hemodynamic stability during heat stress and how this may contribute to the increased heat-related mortality and morbidity seen in older adults during extreme heat events (**Article 1**).
2) Assess the effect of age on whole-body heat exchange and the development of thermal and cardiovascular strain during a day-long exposure to simulated peak heat event conditions (**Article 2**).
3) Evaluate the effect of a range of environments experienced indoors during extreme heat events on body temperature and autonomic cardiovascular function in older adults (**Article 3**).
4) Determine whether short-duration (~2 hour) exposure to an air-conditioned environment following heat exposure results in lasting reductions in thermal and cardiovascular strain upon return to the heat (**Article 4**).

The first objective (**Article 1**) was achieved through a comprehensive narrative review conducted as a collaborative effort with physicians working in clinical and public health contexts. Here, we summarized our current understanding of age- and chronic disease-related impairments in thermoregulatory, cardiovascular, and fluid regulatory responses to heat stress, and how these may contribute to the increased risk of heat-related injury that occurs with aging. We also briefly considered the importance of physiological study in the broader context of climate-health research.

The second objective (**Article 2**) was accomplished by comparing whole-body heat loss and storage (measured via combined direct and indirect calorimetry) and the accompanying changes in body temperature (i.e., rectal and mean skin temperature) and haemodynamic responses (e.g., cardiac output, heart rate, rate pressure product, etc.) between young and older adults during a 9-hour resting exposure to 40°C and 15% relative humidity conditions. This project thereby allowed for the determination of i) whether extreme heat event conditions exceed the physiological capacity for heat dissipation in older adults and ii) how thermal and cardiovascular strain develop during long-duration heat exposure.

The third objective (**Article 3**) was addressed by evaluating thermal and cardiovascular responses in a group of older adults resting for 8-hours in a range of conditions representative of those experienced indoors during extreme heat events – from an actively-cooled environment (22°C), through recommended indoor temperature thresholds set by Toronto Public Health (26°C)[81,82] and the World Health Organization (31°C)[83], to insulated and poorly ventilated domiciles and/or dwellings without air-conditioning (36°C)[80]. To assess how the strain experienced in these conditions affects cardiovascular regulation in turn, this study also included clinically validated tests of cardiovascular function selected to mimic autonomic challenges experienced during activities of daily living (e.g., quickly standing from a lying position). Combining resting measurements of physiological strain with autonomic functional tests allowed for the assessment of i) whether the age-related impairments observed in Study 1 persist in relatively cooler ambient temperatures (e.g., indoor environments), and ii) how the associated hyperthermia may in turn impact cardiovascular function and stability. The latter objective is of particular importance given that most adverse health effects during extreme heat events are of cardiovascular origin[14,49].

The fourth objective (**Article 4**) was accomplished by comparing physiological responses in the older adults from Study 1 to a separate age-matched group removed from the heat to spend ~2 hours in a cooled environment (22-23°C) approximately mid-way through the day-long simulated heat event (hours 5-6). Comparing the heat storage and changes in body temperature and cardiovascular responses before and after short-term ambient cooling to the non-cooled group of older adults from Study 1 allowed for determination of whether short-term cooling (such as experienced in a cooling centre) leads to prolonged reductions in thermal and cardiovascular strain or if the cooling-induced physiological alterations (if any) occur only transiently.

1.4 Hypotheses

General hypothesis of the thesis

It was hypothesized that, when compared to their younger counterparts (age: 19-31 years), older adults (age: 64-78 years) would exhibit progressive elevations in indices of thermal and cardiovascular strain due to an inability to achieve a state of heat balance during a day-long exposure to simulated heat event conditions. The elevated physiological strain in the older adults would be reflected in blunted autonomic cardiovascular regulation in proportion to the level of heat stress. Finally, a brief exposure to a cool environment at near the mid-point of a day-long exposure to heat would reverse increases in body temperature and cardiovascular responses, although only transiently, as strain would quickly return to pre-cooling levels upon re-exposure to a hot environment.

Specific hypotheses of the thesis

Study 1 (Article 2): Older individuals would exhibit reduced whole-body heat loss compared to young adults during a 9-hour exposure to simulated heat event conditions (40°C, 15% relative humidity) such that heat balance (i.e., rate of heat loss balancing the rate of heat gain; thermal equilibrium) would not be attained in the older adults. As a result, a greater thermal (i.e., rectal temperature) and cardiovascular (i.e., heart rate, rate pressure product, cardiac output, etc.) burden would be observed in the older adults and these between-group differences would worsen as exposure progressed.

Study 2 (Article 3): Body temperatures and cardiovascular responses would not be appreciably modified in older adults resting in simulated indoor environments below the currently recommended thresholds set by Toronto Public Health (22°C and 26°C). However, thermal and cardiovascular strain would be elevated at higher indoor temperatures (31°C and 36°C) compared to the cooler conditions. The increased physiological strain in these conditions would be reflected in attenuated responses to validated cardiovascular autonomic functional tests.

Study 3 (Article 4): Over the final 3 hours of the 9-hour exposure (hours 7-9), body heat storage would be exacerbated in the older adults exposed to air-conditioning (hours 5-6) compared to the older adults from Study 1 not removed from the heat.

Consequently, comparable body temperatures and cardiovascular responses would be observed in each group at the end of the day-long exposure.

1.5. Relevance of the thesis

Current evidence indicates that global warming is already surpassing human adaptive capacity[91,92]. Older adults are among the most at risk of adverse health impacts during extreme heat events due, in large part, to impaired physiological responses to heat stress[13-16]. This thesis provides important and novel information regarding the thermoregulatory and cardiovascular burden experienced by older adults during exposure to simulated extreme heat event conditions. This knowledge has important implications for the development and improvement of ecologically minded studies for better assessing the health impacts of extreme heat as well as the creation and validation of evidence-based guidelines to better protect heat-vulnerable persons.

CHAPTER 2 – REVIEW OF THE LITERATURE

Much of the review of the literature was used in the development of Thesis Article 1 (Section 3.1)[93]. The text here has been condensed for the sake of brevity. In particular, the associations between climate change, heat exposure and health, along with the physiological responses to extreme heat are reviewed herein. In Thesis Article 1, the thermoregulatory and cardiovascular adjustments to heat stress are reiterated and expanded to discuss the influence of aging and common age-associated chronic health conditions on these processes, and how they may contribute to the development of acute injury during heat stress. In its final section, the review also introduces the need for prolonged, extreme heat simulation studies for better characterization of the physiological responses to extreme heat events, thus setting the stage for the ensuing thesis studies.

2.1 Climate change, heat exposure and health

Climate change and extreme heat

Global mean temperature has increased by ~1.2°C from pre-industrial levels[1]. Temperature fluctuations of this magnitude are easily met by the body's integrated thermoregulatory responses. However, rising surface temperatures coupled with increasing weather-variability give rise to more frequent and intense extreme heat events[11,94,95] that can overwhelm the ability to regulate internal temperature and cardiovascular stability[8,13,14,96]. These deadly metrological events were experienced by ~475 million more heat-vulnerable older adults in 2019 than at the turn of the century[1]. By 2050, the likelihood of so-called 'mega-heatwaves', like those that devastated Europe in 2003 and Russia in 2010 (~70,000[47] and ~54,000[97] heat-attributable deaths, respectively), is expected to increase by 5- to 100-fold[10,98] and, by 2100, as much as 50-75% of the global population will experience deadly heat on a yearly basis[99].

Elevations in morbidity and mortality during extreme heat events occur in proportion to the increase in ambient temperature above region-specific thresholds (typically based on local temperature percentiles)[74-77]. The extent of coming heat-related health impacts will therefore depend on the magnitude of future planetary warming (and accompanying increases in extreme heat event intensity and frequency) and individual/population capacity for adaptation[92,100]. Regarding the former, under a 'business as usual' emissions scenario, global mean temperature is expected to increase ~2.6-4.8°C over the remainder of the century[101]. Warming of this magnitude will make heat events as extreme as the 2003 European event common-place[102].

The projected health burden brought by such a rapid shift in planetary climate has prompted global concern and the United Nations' adoption of the Paris Agreement[103], which aims to prevent dangerous climate destabilisation by limiting warming to 1.5-2.0°C via aggressive energy reform and curtailing of global emissions[103-105]. Unfortunately, mitigation efforts have been sluggish, and the required decarbonisation and achievement of net-zero emissions is far from guaranteed[106]. Even if we, as a society, are able to meet these lofty goals, it is likely that a transient 1.0-1.5°C of warming (i.e., 2.0-2.5°C increase from pre-industrial levels) will still occur, with global temperatures peaking sometime between 2040 and 2060 before declining to stabilize at the Paris Agreement target[104]. This scenario is still associated with a high probability of multiple extreme heat events at least as intense as the 2003 European event over the remainder of the 21st century[102]. Notwithstanding global successes, or lack thereof, in halting climate change, adaptation will be critical to mitigate the projected healthcare burden. However, the technological advances, alterations to infrastructure, and socio-political reform required for adequate climate adaptation will likely take decades to implement[91]. Rapidly deployable and sustainable climate-adaptation strategies that account for individual-, community-, and population-level risk factors are therefore critical in the near-term to prevent or temper coming elevations in heat-related health disorders.

Heat exposure in vulnerable populations

The health impacts of extreme heat are not evenly distributed across all individuals but are instead concentrated in vulnerable sectors of the population. Heat-vulnerability is influenced by advanced age more than any other intrinsic risk factor[2,15,16]. During the European extreme heat event of 2003, for instance, mortality in France increased by 40-100% in individuals aged ≥65 years, with relatively modest elevations in middle-aged adults (~20-30%) and no effect in the young[107]. The full extent of the deleterious health impacts of extreme heat events is often difficult to determine. Elevated hospital admissions and deaths occur due to disorders in almost every organ system. This makes determination of exact extreme heat event morbidity and mortality difficult as patient intake forms and death certificates often do not list heat as a contributing factor[49]. Typically, the health impacts are not fully realized until excesses in all-cause and/or cause-specific morbidity and mortality during the extreme heat event are quantified relative to a control period (e.g., corresponding weeks or months of previous years).

There are also important extrinsic risk modifiers related to geographic factors and the built environment. For example, regions with lower annual temperatures experience greater increases in mortality during extreme heat events[108] and many of those locations are warming more rapidly than the global average. Mean temperatures in some areas of Western Canada, for instance, have increased by as much as 3°C[95] (or 2.5 times the global average temperature elevation). Increased heat-related disorders are also prevalent in cities[109], in which peak extreme heat event temperatures can be 1-2°C hotter than surrounding rural areas due to the urban heat island effect (i.e., elevated urban temperatures from increased waste heat production and altered heat capacity and albedo of the environment)[110,111]. Global urbanization is contributing to a greater number of people being exposed to heat islands every year, especially older adults, many of whom move to urban centres to be closer to essential services[112-114]. Other factors increasing one's risk include living on the top floor of an apartment complex, living alone, not leaving the home, being confined to a bed, and/or relying on the care of others[6-9,15]. Conversely, owning a working air-conditioner, a strong social-support system (e.g., participating in group activities, having friends in the area, etc.), access to transportation, and regularly visiting cooled locations (e.g., an air-conditioned lobby or cooling center) have all been associated with protection from extreme heat[6-9,15].

Heat vulnerability is therefore determined by complex interactions between multiple intrinsic and extrinsic factors. Some of the strongest protective factors noted above relate to behavioral modification of body temperature (e.g., turning on an air-conditioner). However, older adults may be unable to utilize appropriate behavioral responses due to reduced functional capacity and/or ability to sense their own thermal state[15,115,116]. In other cases, elderly individuals are unwilling to employ simple measures such as opening windows due to ambient noise and pollution or fear of crime[117-119]. These individuals must therefore rely more heavily on the autonomic control of body temperature and cardiovascular stability to maintain homeostasis and health during heat events.

2.2 Human autonomic thermoregulation

Basic thermoregulation

To maintain a stable internal environment conducive to health, the human body regulates body core temperature within a narrow range (~36.5-37.0°C). This requires a fine balance between the heat produced as a by-product of metabolism (metabolic heat production) and the dry (convection, radiation, conduction) and evaporative heat exchanges occurring between the individual and surrounding environment. During exposure to ambient heat stress (e.g., hot weather), elevated environmental heat gain will initially exceed the rate of heat loss, causing an increase in body heat storage that is further augmented by elevations in metabolic rate due to physical activity[22,120]. The resultant rise in body temperature is sensed by collections of high-density thermally sensitive neurons (i.e., thermoreceptors) located in the skin and throughout deeper body structures (e.g., brain, muscle)[121,122]. Thermoafferent feedback from these receptors is integrated in the central nervous system (preoptic anterior hypothalamus)[123], which triggers one or more specialized thermoeffector mechanisms to augment heat loss from the body in a bid to restore heat balance (i.e., equilibrium between heat gain and loss) and maintain body temperature within physiological limits[22,121,124,125].

Mechanisms of heat loss

Cutaneous blood flow

Control of the cutaneous circulation is essential to the regulation of body temperature and is the primary mechanism influencing heat exchange at rest in temperate environments[126,127]. During heat stress, elevated core and skin temperatures elicit neural- and locally mediated mechanisms that dilate the cutaneous blood vessels increasing the transfer of blood-borne heat to the skin[19-21]. The resultant increase in skin temperature facilitates dry heat loss in temperate environments by widening the skin-to-environment temperature gradient and buffers the rate of dry heat gain in hotter conditions[22,128]. The capacity for cutaneous vasodilation is substantial, supporting increases in skin blood flow from resting levels of ~0.3 L/min to values of up to ~7-8 L/min during extreme heat stress[52,129]. This is accomplished by the coordinated action of two populations of sympathetic nerves responsible for active vasoconstriction and active vasodilation[130]. Sympathetic vasoconstriction is mediated primarily via presynaptic release of noradrenaline, whereas active vasodilation occurs secondary to release of acetylcholine and as of yet unknown co-transmitters[19-21]. During heat stress, these nerves function in a sequential manner, with withdrawal of vasoconstriction providing the initial ~10-15% of the vasodilatory response and vasodilation supporting the remaining 85-90%[19-21].

Sweating

Increases in ambient temperature cause a narrowing of the skin-environment temperature gradient, placing greater reliance on sweat evaporation for facilitating heat loss[23,131]. Evaporative heat loss is facilitated by the expulsion of sweat on to the skin surface from the body's 2-3 million eccrine glands[132], which are activated via the binding of acetylcholine released from sympathetic cholinergic sudomotor nerves to muscarinic receptors on the gland surface[23]. Due to the high latent heat of vaporization of sweat, evaporative heat loss provides the greatest capacity for heat dissipation during heat stress and is, in fact, the only mechanism by which heat exchange can occur when ambient temperature exceeds that of the skin (i.e., ≥35°C)[22,128,131].

Modeling human heat exchange

The dynamic exchange of heat between the body and the environment is characterized using the human heat balance equation[22,128]:

$$\mathbf{S = M - (\pm W) \pm (C+R) - E}$$

where all terms are expressed in W/m^2 and,

S = rate of body heat storage
M = metabolic rate
W = rate of mechanical work
C = rate of convective and conductive heat loss from the skin (and respiratory tract)
R = rate of radiative heat loss from the skin
E = rate of evaporative heat loss from the skin (and respiratory tract)

As this equation illustrates, for the rate of body heat storage to be zero (i.e., body heat content and thereby core temperature is stable), total heat loss to the environment must balance the rate of metabolic heat production (a by-product of metabolism). Heat loss is facilitated via dry (i.e., convection, conduction, and radiation) and evaporative mechanisms, with the former dependent on the temperature gradient between the skin and the environment. Consequently, dry heat loss decreases as ambient temperature approaches skin temperature (~34˚C). In conditions where the ambient temperature exceeds that of the skin, dry heat loss becomes negative such that dry heat gain is experienced[22,128]. In contrast, evaporative heat loss (via sweating), which is dependent on the water vapour gradient between the skin and the environment, can only contribute to heat loss from the body and represents the primary avenue of heat loss during exposure to elevated ambient temperatures and/or physical activity[22,126-128,131]. However, this also means that increased ambient humidity reduces the effectiveness of sweat evaporation[133]. During heat stress, the body increases heat loss in an attempt to regain a state of heat balance such that the net heat load (as defined by the rate of heat gain via metabolism and the environment) is matched by total heat loss[22]. In practice, the individual components of the heat balance equation can be estimated with partitional calorimetry[134] or measured using a direct calorimeter[135].

Physiological integration of body temperature regulation during heat stress

Body temperature is under negative feedback regulation, such that increases in core and skin temperatures provide the stimulus for activation of heat dissipation, which in turn reduces the strength of the stimulus. This means that the rate of heat dissipation achieved in a given environment as well as the body temperatures at thermal equilibrium will depend on the balance between 1) the active (physiological) control of thermoeffector responses with increases in body temperature; and 2) the passive (physical) kinetics of heat exchange between the body and the environment (Figure 1).

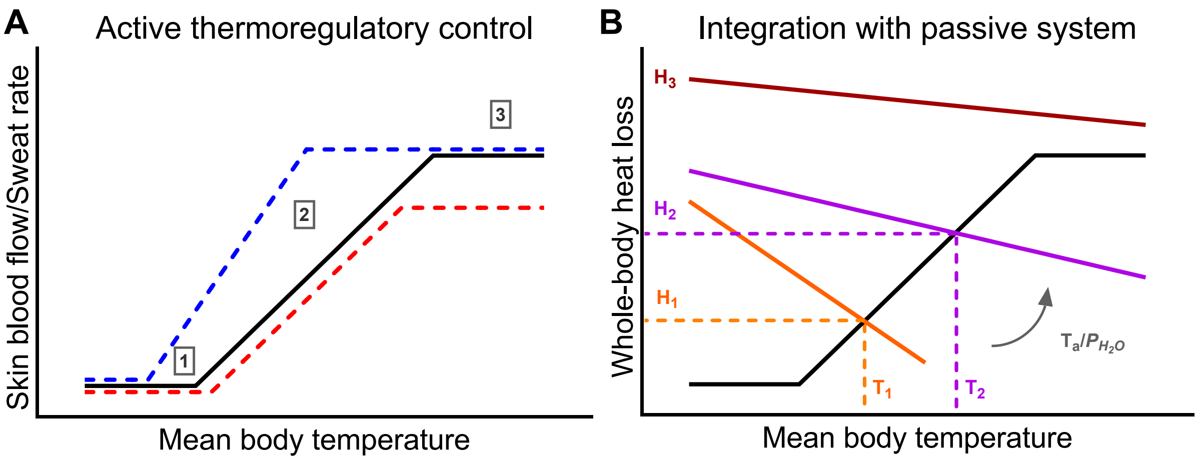


Figure 1. Regulation of body temperature during heat stress. *Panel A*: Increased mean body temperature elicits neurally-mediated elevations in skin blood flow (SkBF) and sweat rate (SR) to facilitate heat loss. This relation can be modelled by its: 1) onset, the body temperature threshold at which elevations in SkBF/SR first occur; 2) thermosensitivity, the linear relation between SkBF/SR and further increases in body temperature; and 3) plateau, the point at which no further increases in SkBF/SR occur despite continued elevations in body temperature, corresponding to the maximal achievable rate of heat dissipation. Note that alterations in onset and thermosensitivity are thought to represent central and peripheral alterations in the control of heat loss responses, respectively. Also note that two individuals can have different onsets/thermosensitivities but similar plateaus (dashed blue line) or vice-versa (dashed red line). *Panel B*: Thermoregulatory control is also dependent on passive (physical) heat exchange, which dictates heat transfer between the environment and the body independently of physiological modulation of heat dissipation (orange and purple lines), such that a higher rate of heat dissipation is associated with a lower body temperature and *vice versa*. Increases in ambient temperature (T_a) and humidity (P_{H_2O}) and other factors such as metabolic heat production (i.e., during physical activity) shift this relation up and to the right (grey arrow). The interaction between passive (physical) and active (physiological) heat exchange determines the rate of heat loss (H_1 and H_2) and body temperatures (T_1 and T_2) required for thermal equilibrium (i.e., heat balance) during compensable heat stress. In the case of uncompensable heat stress (H_3), the line describing the physical relation between heat exchange and the environment does not cross the line denoting the active control of heat loss. Thus, thermal equilibrium is not possible and body temperature continues to rise. Redrawn, in part, from Lamb et al.[24].

To express the integrated thermal stimulus from central and peripheral thermoreceptors during heat stress (i.e., exercise and/or heat exposure), a mean body temperature is often calculated based on simultaneous measurements of core temperature (typically esophageal and/or rectal) and the mean skin temperature across multiple body regions[136]. Activation of the thermoeffector responses to increases in mean body temperature follows three distinct phases: the onset threshold, the thermosensitivity and the plateau (Figure 1A)[19,137]. The onset threshold is the body temperature at which in increases cutaneous blood flow and sweating are initiated while thermosensitivity refers to the period following the onset threshold in which increases in the heat loss responses are proportional to progressive elevations in mean body temperature. Finally, a plateau in the stimulus-response relation will occur at the point where cutaneous vasodilation and sweating fail to increase with further elevation of body temperature. This represents the point at which the maximal capacity for heat loss has been exceeded.

The relation between body temperature and heat loss is also influenced by passive (physical) heat exchange between the body and the environment. This is primarily determined by ambient temperature (which dictates dry heat exchange) and metabolic heat production as well as factors that alter heat dissipation such as ambient humidity and clothing insulation (Figure 1B). In instances where whole-body heat loss (evaporative ± dry) is sufficient to offset metabolic heat production and dry heat gain (in hot environments), the rate of body heat storage will return to zero and body temperature will stabilize; albeit, at an elevated level depending on the relation between passive (physical) heat exchange with the environment and physiological control of the thermoeffector responses (e.g., H_1 and H_2 in Figure 1B)[24,35]. By contrast, hotter and more humid conditions with substantial solar (radiant) heat load promote dry heat gain and restrict sweat evaporation, which can cause the whole-body sweat rate required to attain heat balance to exceed the maximal rate of evaporation possible[138]. In such uncompensable conditions, continued exposure will cause a progressive rise in body heat storage and body temperature (e.g., H_3 Figure 1B) that can compromise health if left unchecked.

Importantly, this negative feedback model of human thermoregulation dictates that thermal equilibrium and the limits of compensability during exposure to a given environment will be determined by both the functional characteristics of active control of heat loss (i.e., onset, thermosensitivity, plateau) as well as any factors that alter the passive relationship between heat dissipation and body temperature (e.g., ambient temperature and humidity, metabolic heat production, clothing insulation, etc.). The effect of a given factor (e.g., age) on body temperature during heat exposure may therefore reflect either 1) an alteration in onset and/or thermosensitivity with no change in the maximal rate of heat dissipation, or 2) a reduction in the maximal rate of heat dissipation. Importantly, the former would result in thermal equilibrium at different body temperatures whereas the latter would mean differences in heat tolerance.

This means that when comparing integrated physiological responses between different populations, we need to consider both the active and passive characteristics of heat exchange as well as their temporal relation. During resting exposure to a hot environment, a sufficient amount of heat must first be stored before heat balance can be attained, as the resultant increase in body temperature is the stimulus for heat dissipation and ultimately the achievement of thermal equilibrium. Although two populations, young and older adults for example, may be able to achieve thermal equilibrium in such an environment, the amount of heat that would be stored before heat balance is achieved, and the time needed to store the heat, may not be equivalent in each group.

2.3 Integrated cardiovascular response to heat stress

Heat stress elicits profound cardiovascular adjustments to support body temperature regulation and maintain cardiovascular stability (i.e., arterial pressure and tissue perfusion). Cutaneous vasodilation can elevate skin perfusion from ~0.3 L/min at rest to as high as ~7-8 L/min during extreme heat stress (as assessed during whole-body heating induced by an encapsulated water perfusion garment)[50]. Compensating for this rise in peripheral cardiovascular demand presents a significant physiological challenge. To maintain blood pressure, cardiac output increases by up to 7 L/min, primarily through elevations in heart rate[52,53]. Stroke volume is maintained (or slightly elevated), despite falling central venous pressure and cardiac preload, via increased myocardial contractility[54-58]. Concurrent vasoconstriction of the splanchnic and renal vascular beds facilitates re-distribution of blood to central and cutaneous regions[50,59-61]. These alterations are coordinated by sympathetic activation in proportion to the magnitude of heat stress[139-141] and, in young adults, are typically sufficient to maintain cutaneous and systemic perfusion and central arterial pressure in the face of marked reductions in peripheral resistance[63,129].

CHAPTER 3 – THESIS ARTICLES

3.1 Thesis Article 1

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

Robert D. Meade[1], Ashley P. Akerman[1], Sean R. Notley[1], Ryan McGinn[2], Paul Poirier[3], Pierre Gosselin[4] and Glen P. Kenny[1,5]

AFFILIATIONS:
[1]Human and Environmental Physiology Research Unit, School of Human Kinetics, University of Ottawa, Ottawa, Ontario, Canada,

[2]Department of Anesthesiology and Pain Medicine, The Ottawa Hospital, University of Ottawa, Ottawa, ON, Canada

[3]Institut Universitaire de Cardiologie et de Pneumologie de Québec, Université Laval, Québec, Québec, Canada.

[4]Institut National de Santé Publique du Québec and Université Laval, Québec, Québec, Canada.

[5]Clinical Epidemiology Program, Ottawa Hospital Research Institute, Ottawa, Ontario, Canada.

Key words: aging, heatwaves, heat stress, chronic disease, climate change, thermoregulation

Number of tables: 2

Number of figures: 6

See Appendix B for the final published version of this article.

ABSTRACT

More frequent and intense periods of extreme heat (extreme heat events) 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 extreme heat events. 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. 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 consider how these impairments contribute to acute pathophysiological events common during extreme heat events (e.g., heatstroke, major adverse cardiovascular events, acute kidney injury) and discuss how age-associated chronic health conditions may further augment those impairments. Finally, we briefly consider the importance of physiological research in the development of climate-health programs aimed at protecting heat-vulnerable individuals.

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)[16,95]. Extreme heat events 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)[7,49,74,142]. 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)[6-8,143]. The global population is aging and the prevalence of age-associated disease is on the rise[4]. Coupled with more frequent and intense extreme heat events, 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[144].

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[15,16]. A critical step in realizing these goals is the identification and characterization of factors associated with heat-vulnerability[145]. 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[8,13,14,16]. 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[13,14]. A more complete understanding of the physiological basis of heat vulnerability would therefore aid healthcare officials and policy makers concerned with protecting heat-vulnerable sectors of the population.

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 consider how these impairments 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.

AGING AND INTEGRATED PHYSIOLOGICAL RESPONSES TO HEAT EXPOSURE

Heat-vulnerability is influenced by advanced age more than any other non-modifiable risk factor[15,16,95]. For instance, during the European extreme heat event 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)[47,107]. As previously reviewed, in brief, by Kenny et al.[8] and Kenney et al.[14], 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 (Figure 1) and how they are impacted by aging independent of the development of overt chronic health conditions (hereafter referred to as healthy aging) (Figure 2). Older adults are considered as individuals over the age of 65 years[4], with middle-age encompassing those aged 35-64 years. It should be noted, however, that the physiological alterations accompanying aging, and, by extension, heat vulnerability are progressive, complex and strongly related to genetic and lifestyle factors in addition to chronological age.

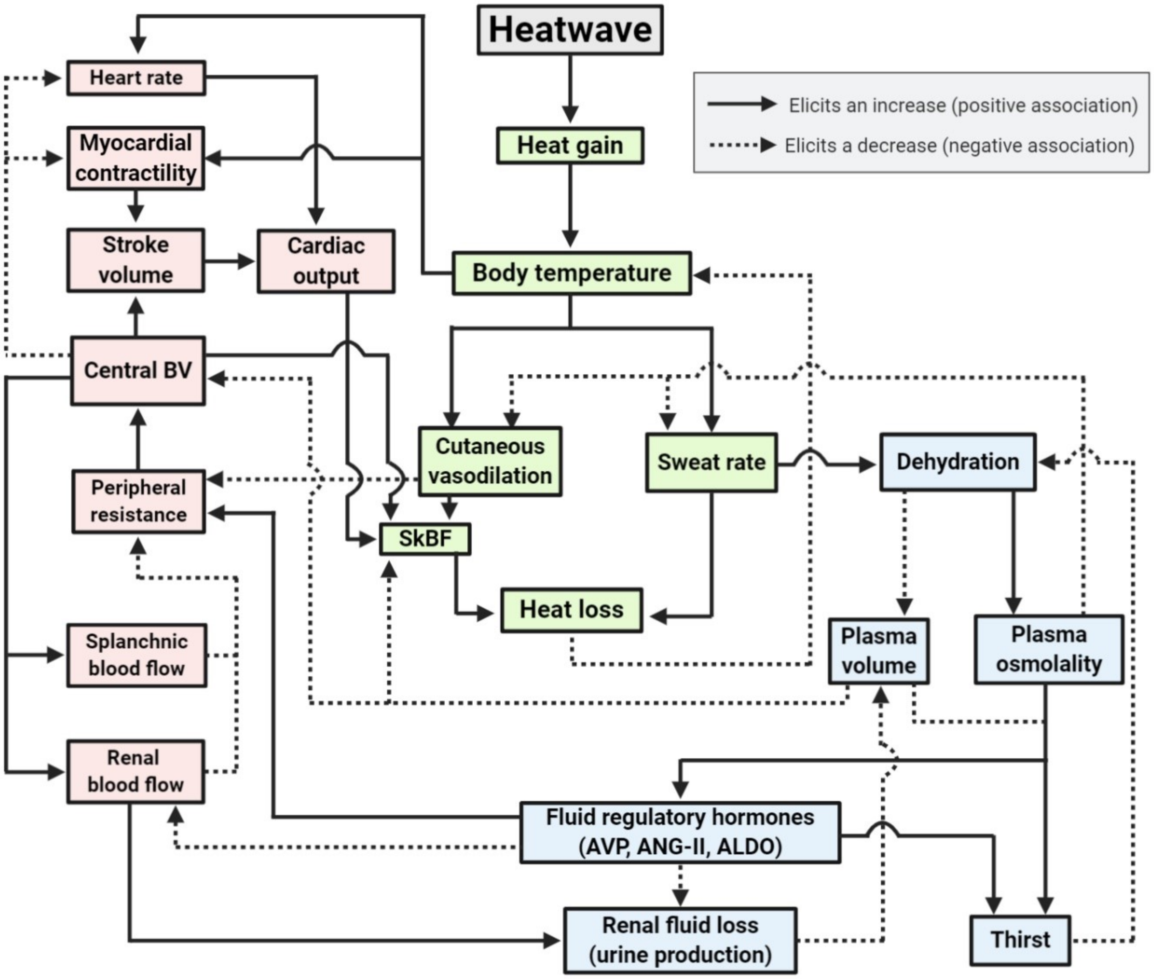


Figure 1. A schematic summary of the integrated physiological responses tasked with maintaining homeostasis during extreme heat events (heatwave). The green, red and blue boxes denote the thermoregulatory, cardiovascular and fluid regulatory systems, respectively. These broad classifications reflect 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).

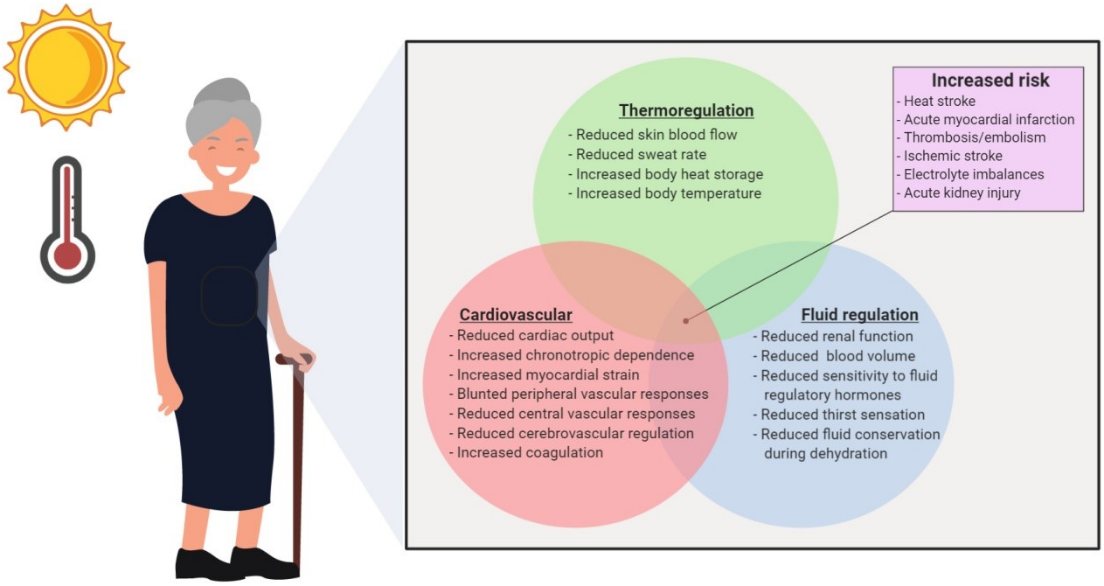


Figure 2. A Venn diagram summarizing the age-related impairments in the integrated physiological responses to heat stress thought to contribute to the increased risk of acute adverse health events in older relative to young adults during extreme heat events (see main text for details).

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 the 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[146]. Moving to a cooler location and use of air-conditioning, for example, have been linked to lower morbidity and mortality during extreme heat events[6-8,15]. However, some older adults may be unable to utilize appropriate behavioral responses due to impaired functional and cognitive capacity and/or ability to sense their own thermal state[115,116]. In other cases, elderly adults may be unwilling or unable to employ simple measures such as opening windows due to costs, ambient noise and pollution or fear of crime[117]. 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[22]. The resultant rise in body temperature is sensed by thermoreceptors located primarily in the central nervous system and skin[122]. Feedback from these receptors is integrated in the preoptic anterior hypothalamus[123], which triggers thermoeffector mechanisms to restore a balance between heat gain and loss to prevent continued rises in body temperature[22]. 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[22]. 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[132]. Sweat evaporation provides the greatest capacity for heat dissipation and is the primary avenue of heat loss during exposure to hot, dry environments[22]. 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[133].

In instances where heat loss is sufficient to offset heat gain (compensable conditions), the rate of body heat storage will return to zero and body core temperature will stabilize, albeit, at an elevated level (Figure 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[22]. In such conditions, termed uncompensable, continued exposure will cause a progressive rise in body temperature that can compromise health if left unchecked.

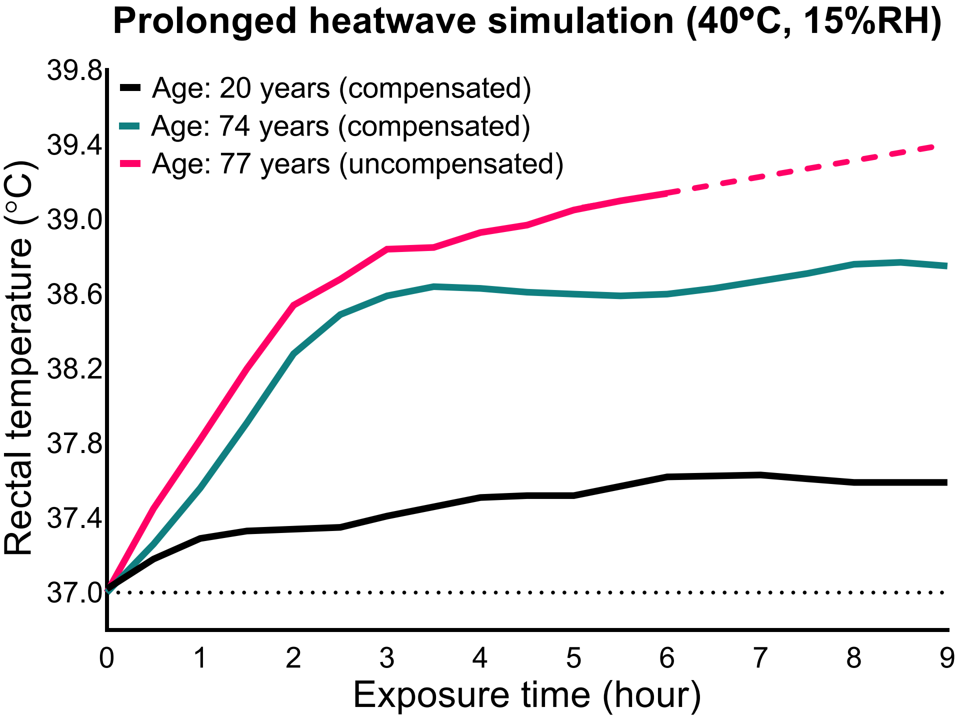


Figure 3. Unpublished data from our laboratory showing rectal temperature in one young and two older women over a 9-hour extreme heat event simulation (40°C, ~15% relative humidity; heat index: 38°C). These conditions were chosen to simulate the heat index experienced during recent extreme heat events 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 yrs; black line) and elderly (74 yrs; 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 hours due to feelings of light-headedness and nausea.

Thermoregulation in older adults

Recent years have seen marked advances in our understanding of age-related impairments in thermoregulatory function[26,35]. Early investigations in this domain led to the belief that aging was associated with increased skin blood flow during heat stress [147,148]. However, following seminal work by Kenney[149], 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[26]. This impairment is primarily owed to attenuated nitric-oxide (NO)-dependent vasodilation secondary to reductions in NO bioavailability resulting from elevated reactive oxygen species (ROS) and arginase activity[150,151]. Also contributing to compromised skin blood flow in heat-stressed older adults is blunted autonomic control of the cutaneous circulation[27] and reduced cardiac reserve[14].

Aging is also associated with reductions in sweat production. While the number of sweat glands responsive to thermal stimuli is unaffected by aging[152], the output from each gland for a given change in body temperature or in response to pharmacological stimuli is attenuated[153,154]. A reduced contribution of NO[151] and altered sweat gland potassium channel function[155] have been shown to contribute. The net effect is a reduction in whole-body sweat rate, limiting the potential for evaporative heat loss[35].

As a result of these alterations, activation of cutaneous vasodilation and sweating with increasing body temperature is blunted with aging[25,156]. 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.[40] 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[40]. 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 extreme heat events. Whether older adults experience progressive increases in heat storage and body temperature during extreme heat events remains to be evaluated; though, this hypothesis is supported by preliminary data from our laboratory (Figure 3).

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[b]	Exposure duration	Primary findings[d]
	n[a]	Age (years)[b]			
Drinkwater et al.[45]	10 women	38 (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.
	10 women	58 (2)			
Dufour & Candas[157]	15 men	24 (12)	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.
	15 men	45 (12)			
	15 men	68 (14)			
Hellon & Lind[148]	12 men	18-23	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.
	12 men	44-57			
Hellon & Lind[147]	6 men	17-26	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	41-57			
	6 men	17-26	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.
	6 men	41-57			
Kenny et al.[40]	30 adults	23 (3)	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.
	30 adults	62 (6)			
Miescher & Fortney[44]	6 men	26 (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.
	5 men	64 (2)			
Sagawa et al.[158]	10 men	27 (7)	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.
	6 men	66 (4)			
Shoenfeld et al.[159]	29 adults	24 (3)	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.
	14 adults	42 (1)			
	17 adults	63 (4)			
Stapleton et al.[41]	12 adults	21 (3)	36.5°C, 20% RH Heat index: 35°C	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.
	12 adults	65 (5)			
	12 adults	21 (3)	36.5°C, 60% RH Heat index: 50°C	120 min	Compared to younger adults, older adults stored 26% more heat (~125 kJ). Rectal temperature was 0.4°C greater in the older men.
	12 adults	65 (5)			

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. [b]Age is presented as a range or mean (standard deviation). [c]Environmental conditions indicate air temperature relative humidity (RH). [d]Data represent the change (Δ) in rectal temperature from baseline/resting to end-exercise (imputed when not provided).

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 ~7-8 L/min during extreme heat stress[50]. To compensate for the resultant fall in peripheral resistance, cardiac output increases by up to 7 L/min, primarily through elevations in heart rate[53]. Stroke volume is maintained (or slightly elevated), despite falling central venous pressure and cardiac preload, via increased myocardial contractility[58]. Concurrent vasoconstriction of the splanchnic and renal vascular beds facilitates re-distribution of blood to central and cutaneous regions[50,61]. These alterations are coordinated by sympathetic activation in proportion to the magnitude of heat stress[139,140] and, in young adults, are typically sufficient to maintain cutaneous perfusion and arterial pressure[63].

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[50]. 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[26] and the upstream peripheral arteries[160]. 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[161,162]. Central arteries stiffen with aging[66] 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[163]. 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[164], 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[50], likely due to attenuated beta-adrenergic responsiveness and altered cardiac mechanics[165], which limit maximal cardiac output[67]. Further, stroke volume is reduced for a given left ventricular filling pressure in non-heat stressed [166] and heat stressed conditions[50]. 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[167]. 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[14].

Finally, aging is associated with impaired autonomic regulation of blood pressure (e.g., baroreflex sensitivity)[68], which may further compromise the systemic cardiovascular response and maintenance of blood pressure during heat stress[168,169]. 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[50]. 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 extreme heat events (discussed in Section 4).

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/hour during resting heat exposure[40,170] and ≥2 L/hour during physical activity in a hot environment[171]. Since sodium and other electrolytes are reabsorbed during the production of sweat from the plasma-derived precursor fluid[172], heat-induced dehydration elicits a state of hemoconcentration[173], reduced circulating volume (hypovolemia), and elevated serum osmolality (hyperosmotic/hypernatremic)[174]. These alterations attenuate cutaneous vasodilation and sweating responses for a given body temperature[175,176], 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 maximal heat loss achievable[34], 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[177].

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[178]. 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 [179,180]. 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 induces release of aldosterone by the adrenal cortex to promote renal sodium retention[179]. Hemodynamic alterations sensed via low pressure baroreceptors located in the systemic veins and walls of the heart also influence vasopressin secretion[179] and thirst[181]. 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[182].

Aging and body fluid during heat stress

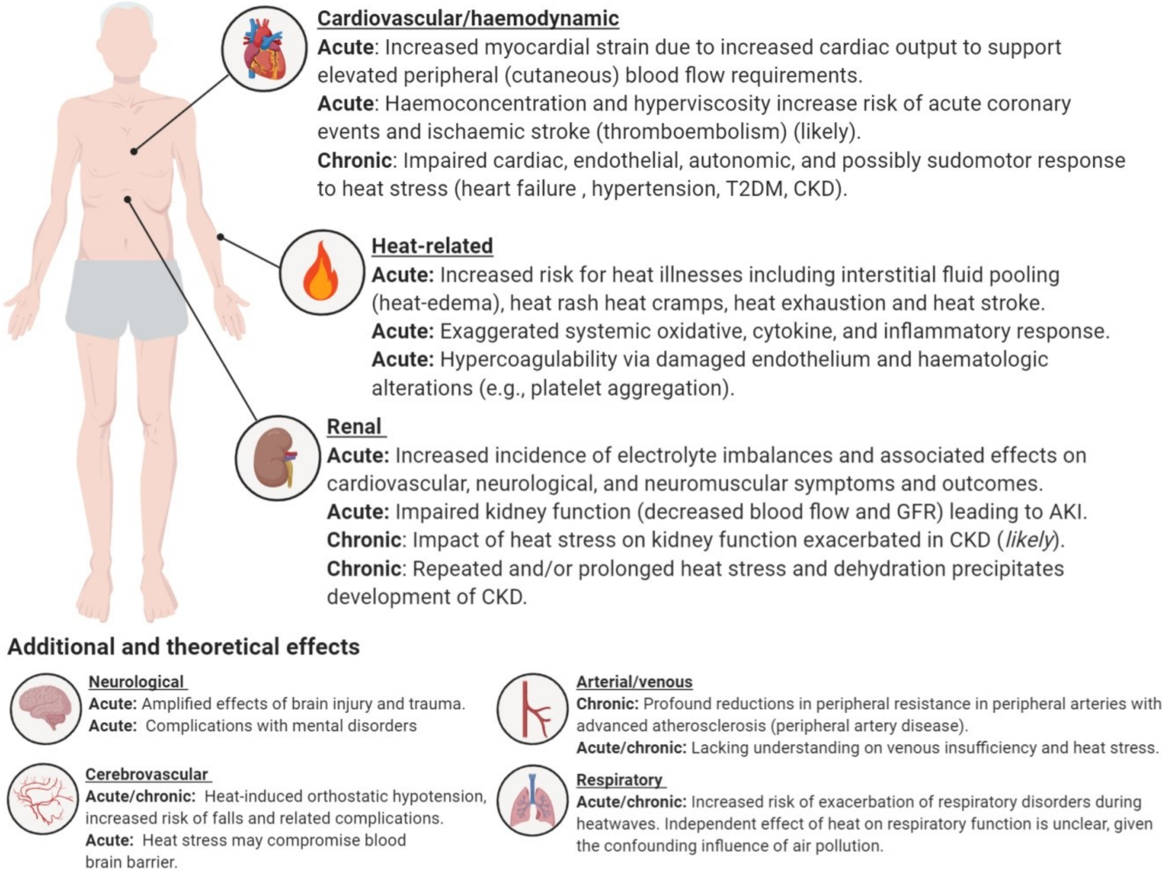
Aging may compromise body fluid regulation during extreme heat events via multiple mechanisms. Compared to the young, older adults have a diminished thirst response to dehydration[183,184], which may be explained by blunted sensitivity to elevations in plasma osmolality [185] and reduced involvement of the baroreflex[181]. Diminished thirst is compounded by impaired renal water conservation[186,187] resulting from blunted renal sensitivity to vasopressin[180] and attenuated RAAS activity[184,188]. Further, while dehydration has been consistently shown to attenuate whole-body sweat rate during heat stress in young adults[175,176], this effect appears blunted by aging[34]. 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[189] and intravascular volume[190]; a given absolute fluid loss represents a larger reduction in the volume of these compartments compared to younger adults. Despite this, the daily fluid intake of older adults is generally within normal range in non-heat stressed conditions[191]. Thus, community living older individuals are not typically hypohydrated, despite overstated reports to the contrary[192]. That said, it should be noted that older adults undergo greater voluntary dehydration during heat-exposure compared to their younger counterparts[184] and oral rehydration is delayed following heat stress and/or water deprivation[183]. Thus, even healthy older adults are at increased risk of dehydration during prolonged and repeated heat exposure, as occurs during an extreme heat event.

ACUTE AND CHRONIC DYSFUNCTION DURING EXTREME HEAT EVENTS

To summarize the preceding section, healthy aging causes myriad physiological alterations that limit the homeostatic response to heat exposure. Unsurprisingly, extreme heat events are associated with stark elevations in hospital admissions[3] and deaths[49] due to catastrophic failure of body temperature regulation (heatstroke). In many cases, however, acute injury during extreme heat events 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 (Figure 3). Since extreme heat events 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 Figure 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[193]. 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[194,195].



Cardiovascular/haemodynamic

Acute: Increased myocardial strain due to increased cardiac output to support elevated peripheral (cutaneous) blood flow requirements.

Acute: Haemoconcentration and hyperviscosity increase risk of acute coronary events and ischaemic stroke (thromboembolism) (likely).

Chronic: Impaired cardiac, endothelial, autonomic, and possibly sudomotor response to heat stress (heart failure , hypertension, T2DM, CKD).

Heat-related

Acute: Increased risk for heat illnesses including interstitial fluid pooling (heat-edema), heat rash heat cramps, heat exhaustion and heat stroke.

Acute: Exaggerated systemic oxidative, cytokine, and inflammatory response.

Acute: Hypercoagulability via damaged endothelium and haematologic alterations (e.g., platelet aggregation).

Renal

Acute: Increased incidence of electrolyte imbalances and associated effects on cardiovascular, neurological, and neuromuscular symptoms and outcomes.

Acute: Impaired kidney function (decreased blood flow and GFR) leading to AKI.

Chronic: Impact of heat stress on kidney function exacerbated in CKD (*likely*).

Chronic: Repeated and/or prolonged heat stress and dehydration precipitates development of CKD.

Additional and theoretical effects

Neurological

Acute: Amplified effects of brain injury and trauma.

Acute: Complications with mental disorders

Cerebrovascular

Acute/chronic: Heat-induced orthostatic hypotension, increased risk of falls and related complications.

Acute: Heat stress may compromise blood brain barrier.

Arterial/venous

Chronic: Profound reductions in peripheral resistance in peripheral arteries with advanced atherosclerosis (peripheral artery disease).

Acute/chronic: Lacking understanding on venous insufficiency and heat stress.

Respiratory

Acute/chronic: Increased risk of exacerbation of respiratory disorders during heatwaves. Independent effect of heat on respiratory function is unclear, given the confounding influence of air pollution.

Figure 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[196,197], cerebrovascular[168,198,199], arterial/venous[200] and respiratory[201]. These conditions worsen during heat exposure and/or extreme heat events, but mechanistic links are relatively undefined.

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	- 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 & Perreault[202]; Blachère et al.[203]; Westaway et al.[204].

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[96]. Many of these conditions are associated primarily with discomfort and contribute minimally to heat-related mortality. In this section, we focus on the deadliest heat-illness: heat stroke.

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 extreme heat events, older adults are at particular risk of classic heat stroke[205,206]. Mortality rates in those affected can reach >50%[205,207] and survivors often experience long-term functional limitations and an elevated risk of future morbidity and mortality[208,209]. The etiology of heat stroke is complex and the associated pathophysiological mechanisms have been detailed extensively[205,206]. 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 (Figure 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[206].

Older adults are also likely predisposed to SIRS, a key event in heatstroke pathogenesis, which occurs due to dysregulation of the inflammatory response[206]. The severity of SIRS can be magnified by accompanying endotoxemia that develops due to increased gastrointestinal permeability[210] secondary to oxidative and ischemic damage to the mesenteric epithelium[211]. 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[212,213]. Consequently, older 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[214] and animals[215,216].

Heat stroke can also lead to DIC, in which diffuse microvascular emboli develop[206], due to damage to the vascular endothelium[217]. 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 extreme heat event[218]. Elevated body temperatures and reduced central blood volume during heat stress elicit a state of hypercoagulability[219]. In older adults, this is compounded by endothelial dysfunction, vascular remodeling (e.g., atherosclerosis)[220], and hematological changes (e.g., increased platelet aggregation)[221] that promote thrombosis and the development of acquired coagulopathies[222] and, by extension, DIC. Thus, not only are older adults at elevated risk of extreme hyperthermia during extreme heat events, they are likely also pre-disposed to SIRS and DIC due to exacerbated activation of inflammatory, oxidative stress and coagulation pathways.

Major adverse cardiovascular events and cardiovascular disease

As much as 90% of extreme heat event-associated mortality is attributable to major adverse cardiovascular events (MACE; e.g., myocardial infarction, ischemic stroke)[49,142,198]. 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[14,223]. 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[43,224], yet little-to-no change, or even decreases, in cardiovascular-related hospitalizations[3,74,224].

The physiological basis for increased risk of cardiovascular events during extreme heat events has been discussed in depth by Kenney et al.[14] In general, increased incidence of MACE in older adults is thought to stem from reduced myocardial perfusion [59] and augmented myocardial strain[225,226]. Concurrently, impaired regulation of body temperature and fluid status are associated with hyperviscosity and hypercoagulability, increasing the risk for acute coronary events[227,228] and ischemic stroke[198]. Relatedly, hyperthermia may elevate the risk of atherosclerotic plaque rupture by exacerbating on-going inflammation or perhaps through more direct mechanisms[229,230]. It should be cautioned, however, that much of the support for these mechanisms is based on clinical and experimental (animal) observations in heatstroke victims[225,226,228]. Future work is therefore required to confirm the mechanisms through which protracted heat stress influences the etiology of MACE.

Cardiovascular diseases

More people die of CVD every year than of any other cause[231]. Perhaps unsurprisingly, pre-existing CVD has been reported to increase mortality risk during extreme heat events by as much as 6-fold compared to those without overt CVD[6,8]. 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[232,233], vascular[234,235] and autonomic function[236], and inflammatory status[237,238] 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 Figure 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 extreme heat events, those that are admitted have a worse prognosis[3,239]. As discussed, however, reduced hospitalizations for heart failure may reflect increased out-of-hospital incidents[224]. Chronic heart failure results in widespread changes in the structure[240] and function of the peripheral vasculature[241,242] along with over-activation of the RAAS[238]. Consequently, cutaneous vasodilation is attenuated in passive heating[241,243]. Further, heart failure, by definition, is associated with reductions in cardiac function that limit the appropriate haemodynamic adjustments to heat stress[244], likely increasing the risk of cardiovascular decompensation[245] and kidney injury (discussed below), especially in those undergoing treatment with diuretics (Table 2)[246].

Hypertension

Chronically elevated blood pressure is the leading risk factor for premature mortality globally[247]. Hypertension was common among those who died during the Chicago 1995 extreme heat event[117] and was associated with a ~24% greater risk of hospitalization[7], though this is not a universal finding[8]. 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[248]. Those with untreated hypertension exhibit endothelial dysfunction and attenuated cutaneous vasodilation during localized skin heating[249,250]. Similar responses have been observed during whole-body passive heating and have been partially attributed to elevated oxidative stress and upregulated arginase activity[251,252].

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[253,254]. 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 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[255], the 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).

Metabolic disorders

Obesity

Obesity is a global epidemic characterized by the accumulation of abdominal adiposity[256] and excess fat deposition in muscle[257] due to complex interactions between genetic, environmental and lifestyle factors[258,259]. Obesity is prevalent in older individuals and has been suggested to hasten the aging process and development of other age-associated chronic conditions[258,260]. Older adults living with overweight and obesity are also at greater risk for heat-related illness or injury[261]. Indeed, obese adults were twice as likely to die during the 2003 European heat event compared to their non-obese counterparts[143], findings consistent with observations of heatstroke occurring at a rate 3.5

times higher in individuals living with overweight and obesity relative to those of normal weight[262].

The increased risk of heat-related injury with 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[263,264]. Further, due to its lower thermal conductivity, increasing subcutaneous fat may impair core-to-skin heat transfer[265]. 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[266]; though, this effect is likely minor[267].

Individuals living with obesity are likely at greater risk of cardiovascular events during extreme heat events owing to structural and functional alterations to the cardiovascular system [268,269] and predisposition for cardiovascular disease[270]. Likewise, obesity has been linked to altered water homeostasis and dehydration[271], plasma hyperosmolality[272] and kidney dysfunction[273], 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 extreme heat events.

Type 2 diabetes

Type 2 diabetes mellitus (T2DM) is associated with acquired insulin resistance, hyperinsulinemia and dysglycemia, vascular inflammation, stiffening and atherosclerosis[274,275]. 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[276]. Heat exposure does not appear to alter the risk of T2DM-related complications. For instance, neither Bobb et al.[3] nor Semenza et al.[7] observed increased hospital admissions for diabetes-related causes (e.g., hyper- or hypoglycemia), whereas Vaidyanathan et al[74]. 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[7,8], 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*[275].

Individuals with T2DM exhibit impaired increases in cutaneous vasodilation in response to pharmacological stimulation[277,278], local skin heating and whole-body passive heat stress[279,280]. 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[275]. Reductions in sweat rate are also characteristic of the disease[281,282], typically manifesting 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[275]. While duration of diabetes, long-term glycemic control, and presence of neuropathy are thought to determine the progression of these alterations[283,284], even individuals with well-controlled T2DM exhibit a compromised ability to dissipate heat and regulate core temperature during moderate-to-high (exercise) heat stress[285,286]. 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[287]. Whether less active individuals with poor glycemic control or related comorbidities (e.g., neuropathy) display similar responses, is currently unknown.

Much of the general diabetes-related health burden stems from macrovascular and microvascular complications[288]. In fact, cardiovascular events comprise the most common cause of death in individuals with T2DM[289]. Compared with healthy aging, T2DM is also associated with altered cardiovascular and autonomic function[282,290], which can manifest as impaired blood pressure regulation[291]. These cardiovascular alterations are closely related to the extent of insulin resistance[292] and glycemic control[293]. T2DM is also associated with altered body water handling. Acute increases in blood glucose induce osmotic diuresis which may lead to hypovolemia[275] and those with T2DM are at increased risk of developing electrolyte disorders[294]. Along these lines, prolonged hyperglycemia causes kidney dysfunction and is a leading cause of chronic renal failure[295,296]. These conditions also disrupt fluid regulation, further increasing the risk of dehydration and associated deleterious health impacts (see below).

Fluid and electrolyte balance and kidney function

Emerging evidence clearly highlights the negative consequences of heat exposure and dehydration on kidney health[297]. This risk is likely greater in older adults due to structural and functional senescence in the kidney leading to impaired water and electrolyte handling[13,298]. Disorders of body water balance (e.g., electrolyte disorders) and kidney dysfunction during extreme heat events are well documented[3,7,74,299-302]. Protracted and/or repeated heat stress may also increase this risk of developing chronic kidney disease (CKD)[297]. This growingly 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[303,304].

Fluid and electrolyte imbalance

The incidence of electrolyte imbalances in older adults increases during extreme heat events[3,74]. 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[305]. 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[305]). 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[13,306].

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[172]. Progressive sweating-induced fluid losses thereby elicit a state of hypernatremic (hyperosmotic) hypovolemia; that is, sodium loss accompanied by a relatively greater loss of body water. This can lead to reductions in thermoregulatory and cardiovascular function and, if severe enough, can contribute to the development of heatstroke, MACE and kidney injury. Aging does not appear to influence sweat sodium reabsorption[307] but is associated with a reduced ability to concentrate urine[187]. 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[308,309] 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[310], severe hyponatremia causes significant morbidity[311]. 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[312]. As discussed, prolonged sweating elicits a *relative* hypernatremia as proportional water loss is greater than that of sodium; however, absolute extracellular sodium still decreases[174]. 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 several other age-associated contributing factors. For one, dietary sodium decreases in the summer[313] and is generally lower in older adults due to reduced caloric intake[314]. Additionally, senescent kidneys are less able to excrete excess free water[187]. As such, age-related risks for hyponatremia[315,316] 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).

Acute kidney injury

In addition to electrolyte imbalances, extreme heat is associated with elevations in morbidity and mortality due to kidney disorders[13,302]. This includes an increased incidence of acute kidney injury (AKI) particularly in older adults[299,300]. 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)[317,318]. Broadly speaking, AKI can be divided into three major classifications describing its etiology (pre-renal, intrinsic, post-renal)[319]. 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)[320]. 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[319]. However, marked and/or prolonged renal hypoperfusion can progress to intrinsic AKI, which is associated with tubular ischemia and injury[318] and can lead to potentially life-threatening conditions (e.g., hyperkalemia)[321].

Heat-stress and dehydration superimposed upon age-related alterations in renal autoregulation may explain the increased incidence of AKI in older adults during extreme heat events. During heat stress, reductions in renal blood flow occur due to sympathetically-mediated vasoconstriction[61]. Heat-induced renal vasoconstriction and reductions in renal blood flow are attenuated with aging[50]. However, basal renal blood flow also decreases by ~10% per decade after the 4th decade (from ~1200 ml/min)[322]. As a result, absolute renal blood flow is lower in older adults compared to their younger counterparts under both normal and heat-stressed conditions[50].

Renal hypoperfusion during heat stress is amplified by concurrent dehydration[323] via increases in sympathetic nervous system activity[324] as well as elevated circulating vasopressin and angiotensin II[325,326]. Although the systemic actions of these hormones are reduced in older adults[180,188,327], vasoactive sensitivity of the renal medulla to angiotensin II and other vasoconstrictors (e.g., adenosine) appears preserved or even increased[328,329] due to age-related oxidative stress[102,330]. Oxidative stress may also reduce renal production of NO and prostaglandins, which would normally act to oppose the actions of renal vasoconstrictors[327,331]. 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[318,332]. As ischemia progresses, microvascular injury contributes to sustained tissue hypoxia, inflammation, and oxidative stress, extending the tubular insult[318,319,332]. During extreme heat events, 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[333]. This pathway is thought to be a major contributor to the on-going epidemic of heat-nephropathy and CKD in agricultural workers[297] and has also been implicated in the age- and disease-related decline in kidney function[334,335]. 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[336].

In summary, multiple lines of evidence indicate that physiological alterations occurring during healthy aging may increase the risk of AKI during extreme heat events 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[319], older adults are also less able to resolve tubular injury and recover from AKI[337].

Chronic kidney disease (CKD)

The prevalence of overt kidney disease is rapidly increasing in older adults[273], progressing from asymptomatic reductions in renal function (chronically reduced GFR and azotemia) to end-stage kidney failure[338]. Diabetes, hypertension[273], inflammation and oxidative stress[339] as well as previous incidents of AKI[340] augment the risk of developing CKD. Currently, CKD is a leading cause of death globally and its burden is on the rise[341]. In fact, CKD now affects 24-36% of individuals aged ≥64 years[342] and as many as 50% of individuals over the age of 70 years[341].

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[343], 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[13], electrolyte imbalances[344] and AKI[338]. 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[344]. Similarly, impaired potassium excretion[345] and regulation of acid-base balance[346] can contribute to the development of hyperkalemia, which can lead to fatal arrhythmias. Finally, upregulation of coagulation pathways increases the risk of thrombotic complications[13,347]. While this is typically associated with patients with end stage renal failure[348,349], elevated levels of procoagulant factors (e.g., fibrinogen, d-dimer) have been observed in individuals with moderate CKD[347]. Both mechanisms are thought to have contributed to increased mortality in older adults during recent heat events[13].

NEXT STEPS: INTEGRATING PHYSIOLOGICAL RESEARCH AND PUBLIC HEALTH

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 environmental physiology[17,18]. Physiological research is inherently integrated[350], 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[351]. These tenets lend themselves to translational and integrated research approaches aimed at addressing pressing public health concerns[352].

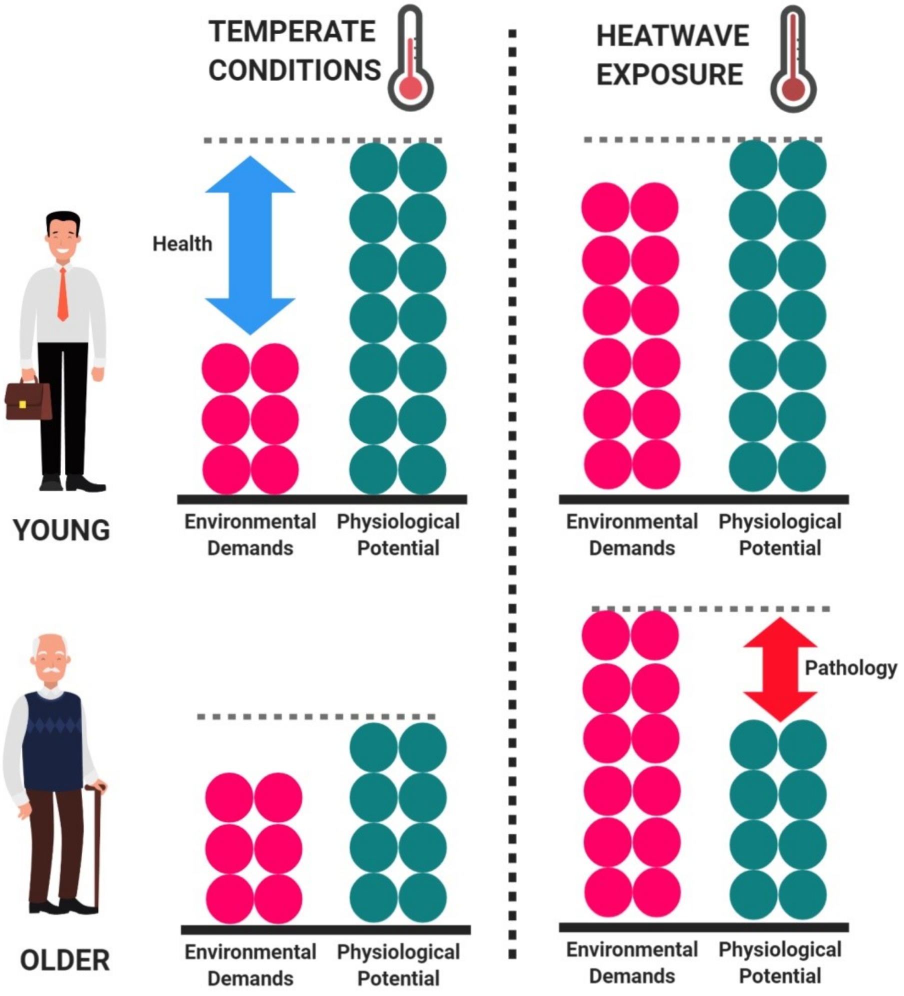


Figure 5. Bircher's model of health[353] applied to extreme heat events. In this example, health is seen as a *balance* between physiological potential (complex and adaptive interactions between physiological systems) and environmental demands (determined by the number and magnitude of environmental

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 extreme heat event conditions, integrated physiological responses in young adults (reflected in their elevated biological 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 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).

As a crucial first step, a move toward ecologically minded study design is warranted to improve our ability to utilize the results from physiological research to help generate and refine public health guidance during extreme heat events. 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[62], 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[53]. Further, because of the rapid transfer of heat through water (25 times greater thermal conductivity vs dry air)[71] and restricted sweat evaporation due to the encapsulated design, skin temperatures can reach upwards of ~40°C[50]. Highly elevated skin temperatures can exacerbate elevations in cutaneous vascular conductance by 1) activation of sympathetic cutaneous vasodilator activity, increasing skin blood flow[63] and 2) directly augmenting cutaneous venous capacitance[72]. Furthermore, since whole-body passive heating studies are often conducted with participants in the supine position, end-diastolic volume is maintained[59], supporting the marked elevations in cardiac output[53]

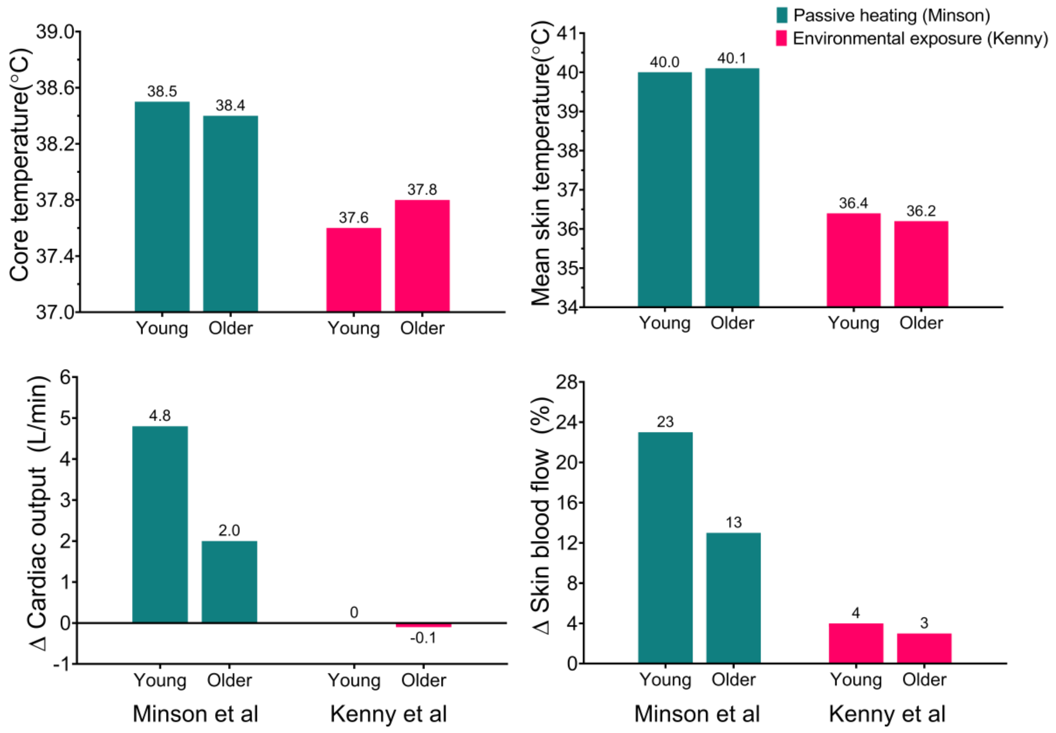


Figure 6. Differences in thermal and cardiovascular responses during whole-body passive heating and environmental exposure. Data presented are changes in core and mean skin temperatures, cardiac output and forearm blood flow in studies by Kenny et al.[40] Minson et al.[50] In the study by Kenny et al, 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 hours. 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 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.

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 Figure 6 for example). In that work, however, exposure duration has been relatively short (≤4 hour; Table 1) whereas extreme heat events, by definition, occur over extended periods (e.g., days to weeks). Further, most studies have employed conditions unrepresentative of extreme heat events. 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 48-65°C (median: 51°C), with the exception of the study by Stapleton et al.[41] (heat index: 35°C). By comparison, peak day-time outdoor conditions in several large extreme heat events from 1995-2012 were less severe ~36-51°C (median: 43°C)[48]. Furthermore, most people, especially older adults, spend ≥70% (average of ~17 hours/day) of their time in the home[78], 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[80]. 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 during extreme heat events.

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 extreme heat events. We also considered the role of age-associated chronic disease and other comorbidities in modifying that risk. Our understanding of the mechanistic links between extreme heat events and health are, in many cases, still insufficient. In our view, a move toward ecologically minded study design is required to better integrate physiological research in public health programs and climate-health models and improve our ability to protect the most vulnerable sectors of the population.

DISCLOSURES

There are no conflicts of interest, financial or otherwise, to disclose.

AUTHOR CONTRIBUTIONS

R.D.M., A.P.A., S.R.N and G.P.K conceived the review. R.D.M drafted the manuscript and created the figures. All authors critically revised the manuscript and approved the final version.

3.2 Thesis Article 2

Thermoregulatory and cardiovascular responses in young and older adults during a day-long simulated extreme heat event

ClinicalTrials.gov identifier: NCT04353076 (Intervention 1)

Key words: aging, heatwaves, heat stress, haemodynamics

Number of tables: 3

Number of figures: 4

ABSTRACT

Investigations of the physiological strain experienced by older adults during extreme heat events have typically employed short-duration exposures (≤3 hours), even though heat events occur over extended periods. This study was therefore designed to advance our understanding of whole-body heat exchange and the development of hyperthermia during a day-long exposure to simulated heat event conditions. Twenty young (19-31 years; 9 women) and 19 older (64-78 years; 7 women) adults rested in 40°C (~15% relative humidity; heat index of 38°C) ambient conditions for 9 hours; representative of exposure conditions experienced in recent extreme heat events in temperate continental climates (e.g., Ontario, Canada in 2018). During the initial and final 3 hours of exposure, whole-body heat storage was assessed as endogenous heat production (indirect calorimetry) minus whole-body heat loss (direct calorimetry). Rectal temperature was monitored continuously. During the first 3 hours of the 9-hour exposure, the older adults stored 87 kJ [95% confidence limits: 33, 141] more heat than their younger counterparts (241 [SD: 87] vs 328 [71] kJ; $P<0.001$). Over the final 3 hours, however, heat storage was not different between groups (41 [72] vs 43 [57] kJ; $P=0.998$). This was paralleled by a 0.4°C [0.2, 0.6] greater increase in rectal temperature in the older compared to younger adults that was maintained throughout the 9-hour exposure (1.0 [0.3] vs 0.6 [0.3]°C; $P<0.001$). These findings indicate that during prolonged extreme heat events, older adults experience sustained elevations in thermal strain that are greater in extent than those observed in their younger counterparts.

INTRODUCTION

Yearly heat-related mortality and morbidity is expected to rise over coming decades[92] due to global increases in the incidence, severity and duration of extreme heat events[11]. Already, these changes can be felt; in 2019 approximately 475 million more vulnerable individuals were exposed to extreme heat events compared to the turn of the century, with yearly heat-related fatalities increasing ~54%, from 150,000 to 296,000 globally, over this period[1]. Protecting vulnerable sectors of the population from extreme heat therefore represents a pressing public health concern. A critical step in developing targeted guidance is the identification and characterization of factors associated with heat-vulnerability[145]. It is well known that older adults are among the most at risk[1] due, in large part, to age-related deterioration of the physiological systems tasked with maintaining thermoregulatory and cardiovascular stability[93]. At present, however, the mechanistic links between age-related physiological perturbation and the adverse health impacts of extreme heat events are not fully clear.

While numerous studies have shown that aging is associated with attenuated heat dissipation during heat stress, due to lesser activation of skin blood flow and sweating in response to increasing core and skin temperatures[35,93], this work has primarily employed exercise-heat stress models[35]. These likely overestimate the level of thermal strain experienced during extreme heat events. That said, there have been some studies that have assessed age-related differences in physiological responses during passive exposure to a hot environment[40,41,44,45,158]. In a notable example, Kenny et al.[40] demonstrated that older adults stored ~70% more heat than their younger counterparts during a 3-hour exposure to extreme heat (44°C, 30% relative humidity). Importantly, the older group did not achieve a state of heat balance, where the rate of heat gain was offset by heat loss. Based on this, the authors posited that continual increases in body heat storage and temperature would have occurred, reaching potentially dangerous levels, if exposure duration was extended[40]. It is important to note, however, that in the report by Kenny and colleagues[40] and other studies employing passive heat stress[41,44,45,158], exposure duration was limited to relatively brief periods (≤3 hours). This highlights a critical problem in past designs since extreme heat events last over extended periods[42].

Older adults also exhibit attenuated cardiovascular responsiveness during heat stress, characterized by reduced increases in skin blood flow and cardiac output, due primarily to attenuated heart rate, compared to their younger counterparts[50,64,167]. Our understanding of the cardiovascular responses to heat stress comes mostly from studies employing whole-body passive heating using a water perfused suit[62,63]. The encapsulated nature of this design causes highly elevated skin temperatures (upwards of ~40°C)[50] and profuse fluid loss not consistent with exposure to hot ambient conditions due to restricted evaporation of sweat. This makes it difficult to translate findings from this research to what is experienced during exposure to a hot environment[93]. Unsurprisingly, studies employing passive heating have generally shown markedly greater cardiovascular burden compared to studies employing resting environmental heat exposure[40,50,158]. As discussed above, however, the intensity and duration of heat exposure in those latter studies was likely unrepresentative of extreme heat events[93].

Whether thermal and cardiovascular strain comparable to very extreme ambient heat exposure and/or encapsulated heat stress would eventually develop during an extreme heat event is currently unclear. This represents an important knowledge gap in our understanding of the physiological basis of heat-vulnerability in older adults. We therefore designed this proof-of-concept extreme heat simulation study to evaluate physiological responses in healthy young and older adults resting in conditions representative of recent deadly extreme heat events (9-hour exposure to 40°C, 15% relative humidity). We hypothesized that, in comparison to their younger counterparts, older individuals would exhibit reduced whole-body heat loss such that heat balance would not be achieved. As a result, greater hyperthermia (rectal temperature) and cardiovascular burden (heart rate, rate pressure product, cardiac output, etc.) would be observed in the older compared to young adults and these between-group differences would be exacerbated as exposure progressed.

METHODS

Ethical approval

This study was approved by the University of Ottawa Health Sciences and Science Research Ethics Board and conformed to the latest version of the Declaration of Helsinki. Written and informed consent was obtained from all volunteers prior to their participation. This study was prospectively registered as part of a larger clinical investigation (ClinicalTrials.gov identifier: NCT04353076; Intervention 1).

Participants

Twenty young (19-31 years, 9 women) and nineteen older (64-78 years, 7 women) adults participated. Participants were non-smokers with no history of metabolic or cardiovascular disease and were not taking prescription medications for these conditions.

Menstrual cycle phase was not controlled for in the young women and all older women were post-menopausal. Their characteristics are summarized in Table 1.

Experimental design

Each participant completed one preliminary session and one experimental session. The experimental session consisted of a prolonged simulated extreme heat event (9-hour exposure to 40°C and 15% relative humidity; heat index: 38°C). These conditions were chosen to simulate peak temperatures experienced during extreme heat events and are similar to peak heat index in recent events in North America in 2018 (41°C)[46] and Europe in 2003 (38°C)[48].

All participants were asked to avoid strenuous activity and alcohol for 24 hours and to eat a light meal 2 hours before each session. They were also instructed to consume ~500 ml of water the night before and morning of each session to ensure adequate hydration, which was verified before the experimental session (euhydration operationally defined as a urine specific gravity <1.025[354]). If participants exceeded this threshold, ~500 mL of tap water was provided, and urine specific gravity was tested again after ~30 min. Participants wore only athletic shorts and sandals (and a sport top for women).

Preliminary screening

The preliminary screening session was completed a minimum of 48 hours before the first experimental session. During this session, participants were familiarized with all experimental procedures and measurement techniques and completed the Get Active Questionnaire (GAQ) and the American Heart Association Pre-participation screening

Questionnaire to assess their eligibility to participate. The GAQ was also used to assess habitual activity levels[355]. Thereafter, physical characteristics were evaluated. Body height and mass were determined via a physician stadiometer (Detecto, model 2391, Webb City, MO, USA) and a high-performance weighing terminal (model CBU150X, Mettler Toledo Inc., Mississauga, ON, Canada), respectively, and from these measurements body surface area was calculated[356]. Body density was estimated via hydrostatic weighing and used to calculate body fat percentage[357].

Experimental session

Each session commenced between 07:00-08:00. Upon arrival to the laboratory, the participant provided a urine sample for the assessment of urine specific gravity, after which a measurement of nude body mass was obtained. Participants then inserted a temperature probe (Mon-a-therm General Purpose Temperature Probe, Mallinckrodt Medical Inc., St-Louis, MO, USA) for the continuous measurement of rectal temperature. Thereafter, participants were instrumented for the measurement of skin temperature (DS1922L Thermochron, OnSolution Pty Ltd, Australia).

Following instrumentation, baseline cardiovascular parameters were evaluated via a brief (~45 min) cardiovascular test battery, performed as follows. First, cardiac output was measured via inert gas rebreathing (Innocor, Innovision, Odense, Denmark). Brachial arterial systolic and diastolic pressures reconstructed from the pressure waveform measured at the right middle finger were then collected for 10-min (Finometer Pro, Finapress Medical Systems, Amsterdam, Netherlands) and subsequently used for evaluation of resting spontaneous cardiac baroreflex sensitivity (an index of cardiovascular autonomic function)[358,359]. Immediately thereafter, arterial systolic and diastolic pressures were measured in triplicate via manual auscultation, with each measurement separated by 30 s. A second measurement of cardiac output was then taken (allowing for ≥10 min between the first and second measurements to ensure full gas washout), after which forearm blood flow on the right side of the body was measured with venous occlusion plethysmography (Hokanson AI6, D.E. Hokanson, Inc., Bellevue, WA, USA). Throughout the test battery, participants remained quietly seated (slightly reclined) with both feet placed on the floor and their hands resting comfortably in their lap, except for during the measurement of forearm blood flow, where the instrumented limb was elevated to facilitate venous drainage. Following the battery, a venous blood sample and measurement of body mass were obtained.

Participants were then transferred to the Snellen whole-body air calorimeter chamber (a unique chamber providing the only gold standard measurement of whole-body dry and evaporative heat exchange[135]), which was regulated to 40°C and ~15% humidity (heat index of 38°C). The participant rested for 3-hours (hours 1-3) within the calorimeter chamber while whole-body heat production and exchange were measured continuously. At the 3-hour mark, the participant exited the calorimeter, and the brief cardiovascular test battery was repeated followed by a measurement of body mass. Hours 4-6 were then spent resting in the heat in the thermal chamber adjacent to the calorimeter. During this time, participants could consume a light (~300 g), self-provided lunch with low water content (e.g., peanut butter sandwich). Tap water was available ad libitum via a self-service insulated water cooler located in the thermal chamber (but out of direct sight of the participant). At the 6-hour mark, the participant re-entered the calorimeter where the final 3 hours were spent (hours 6-9). At the end of this period, the participants completed a fourth and final cardiovascular test battery and a venous blood sample and body mass measurement were procured. Participants were provided with water and/or a commercially available sports drink before dismissal from the laboratory.

Measurements

Whole-body heat exchange

Whole-body dry and evaporative heat loss were measured via the Snellen air calorimeter[135]. Calorimeter inflow and outflow values of air temperature and absolute humidity were measured at 8 second intervals using high precision resistance temperature detectors (Black Stack model 1560, Hart Electronics, UT, USA) and dew point hygrometry (RH Systems model 373H, Albuquerque, NM, USA), respectively. Air mass flow, equivalent to ~0.3 m/s where the participant is seated[360], was determined via differential thermometry over a known heat source in the effluent air stream. All data were displayed and recorded on a personal computer with LabVIEW software (Version 7.0, National Instruments, Austin, TX, USA). Dry heat loss was then determined using the outflow–inflow difference in absolute humidity, multiplied by air mass flow and specific heat capacity of air (1005 J/kg/°C). Heat loss via sweat evaporation was similarly derived from the outflow–inflow air temperature difference, air mass flow, and the latent heat of vaporization of sweat (2426 J/g). Since ambient temperature (40°C) was greater than that of the skin (~35-36°C), dry heat loss was negative, indicating heat gain from the environment. Hereafter, dry heat exchange is discussed in terms of a dry heat gain, with positive values indicating heat gain by the participant.

Metabolic energy expenditure was measured using indirect calorimetry. Expired oxygen and carbon dioxide content were measured using electrochemical gas analysers (AMETEK model S-3A/1 and CD 3A, Applied Electrochemistry, Bastrop, TX, USA). Expelled air was recycled back into the chamber to account for respiratory heat exchange. The gas analyzers and turbine ventilometer were calibrated ~30 min prior to each calorimetry measurement period (2 per experimental session). Endogenous metabolic heat production was assumed to be equivalent to metabolic energy expenditure since no external work was performed[22].

Body temperatures

Rectal temperature was monitored using a general-purpose thermocouple probe (Mon-a-therm General Purpose Temperature Probe) inserted ~12 cm past the anal sphincter. Skin temperature was assessed using surface temperature monitors (DS1922L Thermochron) placed in 8 locations as described in ISO 9886:2004: forehead, right scapula, upper left chest, upper right arm, right forearm, left hand, right anterior thigh, and left calf[361].

Cardiovascular responses

Arterial systolic and diastolic blood pressures were taken as an average of three values measured at the brachial artery (~30 s between measures) via manual auscultation. Cardiac output was taken as the average of duplicate values measured non-invasively using an inert gas (5% blood soluble N_2O, 1% and blood insoluble SF_6,) rebreathing system (Innocor). Forearm blood flow was determined as the average of a minimum of four measurements obtained via automated venous occlusion plethysmography (Hokanson AI6). Brachial systolic pressures were estimated from beat-to-beat recordings of the arterial pressure waveform measured at the right middle finger with the volume-clamp technique (Finometer Pro) and used to evaluate baroreflex sensitivity (an index of cardiac autonomic activity) using the provided software (PRVBRS, Fina-press Medical Systems, Amsterdam, Netherlands)[358,359]. Heart rate was also derived as an average of the final 5 min of the 10-min recording window.

Hydration-related variables

Baseline urine specific gravity was assessed with a hand-held total-solids refractometer (Reichert TS 400 total solids refractometer, Reichert, Depew, NY, USA). Changes in fluid status were evaluated via changes in body mass monitored using a high-performance weighing terminal (CBU150X). Venous blood samples were collected for determination of plasma volume responses (0 and 9 hours of exposure). Blood samples were transferred directly into plasma Vacutainer tubes (5.4 mg K2EDTA; BD, Franklin Lakes, NJ, USA). The K2EDTA blood was mixed by inversion and used to measure haematological parameters in duplicate (Ac·T diff, Beckman Coulter, Miami, FL, USA).

Data analysis

Continuous variables related to whole-body heat exchange measured via direct calorimetry (i.e., metabolic heat and dry heat gain and evaporative heat loss) were converted to averages of data collected over the last 15 min of each hour of each calorimetry sessions (e.g., a 15-min average at hours 0 (first 15 min), 1, 2, 3, 7, 8 and 9) and expressed relative to body surface area (W/m^2). Total heat gain (from the environment and metabolism) was derived as metabolic heat production plus dry heat gain. Body heat storage (kJ) was calculated as the temporal summation (of minute data) of total heat gain and evaporative heat loss over each hour and as a cumulative value for each calorimeter session (i.e., hours 1-3 and 7-9). Mean skin temperature was derived using the weightings: forehead (7%), right scapula (17.5%), upper left chest (17.5%), upper right arm (7%), right forearm (7%), left hand (5%), right anterior thigh (19%) and left calf (20%)[361]. Rectal and mean skin temperatures were converted to 15-min averages for each hour of the 9-hour exposure.

Heart rate was presented in absolute values and as a percentage of age-predicted maximum (calculated as 220-age). Rate pressure product, an index of myocardial work[362,363], was calculated as heart rate × systolic pressure. Stroke volume was derived as cardiac output ÷ heart rate × 1000. Body temperatures and cardiovascular responses were presented in absolute values and as a change from baseline (hour 0) at hours 3 and 9 of exposure. Due to technical difficulties, inert gas rebreathing was not used for 3 older adults, for whom cardiac output was instead estimated via model flow (Finometer Pro).

Fluctuations in fluid status, corrected for food consumption, were calculated from changes in body mass (% change from baseline) and presented at 3 and 9 hours of exposure. Haemoglobin and haematocrit were used to estimate changes in plasma volume using the technique by Dill and Costill[364]. Due to technical difficulties, we were not able to evaluate plasma volume responses for 1 young and 3 older adults.

Statistical analysis

An a priori power analysis determined that a total sample size of 19 participants in each group was required to detect a difference in the rate of whole-body heat storage between the young and older adults at the end of each calorimeter session (i.e., hours 3 and 9), with 80% statistical power. The standardized effect size (Cohen's d = 1.06) was calculated based on the difference in the rate of whole-body heat storage between young and older adults over the final 30-min of a 3 hour heat exposure protocol in our previous work (young: -2 [26] kJ/hour, older: 43 [54] kJ/hour) [40].

Variables related to whole-body heat exchange and storage as well as body temperature, cardiovascular, and fluid regulatory responses were evaluated using mixed-effects models with the factors of time and group. When main effects or interactions were statistically significant, post hoc multiple comparisons were performed according to Sidak's procedure. Homoscedasticity and normality of residuals were evaluated by visual assessment of residuals and Q-Q plots. For all analyses, the threshold for statistical significance was set at $P<0.050$. Statistical analysis and data visualization were performed with Prism (Version 8, GraphPad Software). Descriptive statistics were presented as mean (standard deviation) and comparisons between groups as means and 95% confidence interval [lower limit, upper limit].

RESULTS

Participant characteristics

Except for age and body fat percentage (both $P<0.001$), participant characteristics were not different between age groups (Table 1).

Table 1. Physical characteristics of the young (n=20) and older (n=19) adults.

	Young		Older		
	Mean (SD)	Min-max	Mean (SD)	Min-max	P-value[d]
Women/men (n)	9 / 11		7 / 12		
Age (years)	24 (4)	19 - 31	72 (4)	64 - 78	**<0.001**
Height (m)	1.69 (0.08)	1.55 - 1.84	1.69 (0.10)	1.45 - 1.90	0.979
Mass (kg)	69.2 (14.2)	48.2 - 95.2	70.5 (11.1)	47.6 - 91.2	0.749
A_D (m^2)[a]	1.8 (0.2)	1.4 - 2.2	1.8 (0.2)	1.4 - 2.1	0.793
Body fat (%)	18 (5)	8 - 26	30 (8)	18 - 47	**<0.001**
Body mass index[b]	24.1 (3.4)	18.7 - 29.4	24.8 (3.4)	18.7 - 30.0	0.537
Aerobic activity (min/week)[c]	247 (169)	40 - 720	155 (153)	0 - 420	0.470

Notes: [a]A_D, body surface area[365]; [b]body mass index calculated as body mass/height^2. [c]Self-reported aerobic activity (min/week) levels as defined by the Canadian Society for Exercise Physiology[355]. [d]P-values indicate results from an unpaired, two-tailed t-test.

Whole-body heat exchange

Whole-body heat exchange is presented in Table 2. Apart from the 3- and 8-hour time points (both P≥0.115), metabolic heat production was 7 W/m^2 [4, 11] lower in the older compared to younger adults. Dry heat gain was not different between groups (effect of condition: P=0.425). Total heat gain, however, was 10 W/m^2 [5, 16] greater in the young relative to older adults (P=0.004). Further, evaporative heat loss was elevated by 20 W/m^2 [8, 32] and 18 W/m^2 [6, 30] in the young at the start (hour 0) and first hour of exposure, respectively (both P<0.001), but not different between groups thereafter (all P≥0.139).

As a result of the differences in whole-body heat loss and gain, body heat storage was 77 kJ [45, 110] greater in the older relative to young adults over the first hour of exposure (P<0.001) but was not different between groups for the remainder of the 9 hours (all P≥0.949; Figure 1A). Similarly, the cumulative increase in body heat storage was 87 kJ [33, 141] greater in the older adults (P<0.001) during the first 3 hours but was similar in each group over the final 3 hours (P=0.998; Figure 1B).

Body temperatures

Rectal temperature (Table 3) was not different between groups at baseline (P=0.181), but was 0.2°C [0.0, 0.4] greater in the older relative to young adults after 3 (P=0.022) and 9 hours (P=0.018) of exposure. When analyzed as a change from baseline, the increase in rectal temperature was 0.4°C [0.2, 0.6] greater in the older adults throughout the 9-hour exposure (P<0.001; Figure 2B). By contrast, no differences in mean skin temperature were observed between age groups, whether analyzed in absolute values (Table 3) or as a change from baseline (effect of condition: P=0.358).

Table 2. Whole-body heat exchange (in W/m^2) in the young (n=20) and older (n=19) adults during the 9-hour extreme heat exposure.

		Hour of exposure							ANOVA P-values[b]		
Variable	Group	0	1	2	3	7	8	9	Time	Group	Int.
Heat production	Young	58 (8)	54 (7)	54 (8)	53 (8)	57 (6)	55 (6)	55 (7)	0.145	**<0.001**	**0.015**
	Older	47 (7)*	48 (7)*	48 (5)*	48 (7)	50 (6)*	50 (5)	48 (4)*			
Dry heat gain	Young	43 (9)	36 (7)	37 (6)	37 6)	39 (6)	37 (6)	35 (6)	**<0.001**	0.425	0.839
	Older	42 (7)	34 (6)	35 (6)	34 (7)	39 (6)	37 (5)	36 (5)			
Total heat gain	Young	101 (9)	90 (9)	92 (9)	90 (9)	96 (9)	92 (8)	90 (8)	**<0.001**	**0.002**	0.444
	Older	89 (9)†	82 (10)†	83 (10)†	82 (12)†	89 (10)†	87 (9)†	84 (7)†			
Evap. heat loss	Young	39 (28)	81 (7)	88 (9)	87 (8)	93 (9)	90 (10)	91 (9)	**<0.001**	**<0.001**	**0.017**
	Older	18 (16)*	62 (18)*	77 (13)	79 (13)	85 (12)	84 (11)	87 (12)			

Notes: Data presented as means (standard deviation). Data at hour 0 represents an average of the first 15 min of exposure whereas data presented at each hour thereafter represents an average of the final 15 min. Metabolic heat production was measured via indirect calorimetry. Dry heat gain and evaporative heat loss (Evap. heat loss) were measured via direct calorimetry Total heat gain was calculated as heat production + dry heat gain. [b]ANOVA P-values indicate results from a two-way mixed-effects model assessing the effects of time and age group. *Significantly different from young adults (at each time point). †Significantly different from young adults (collapsed across time); all P<0.050, exact P-values provided in text.

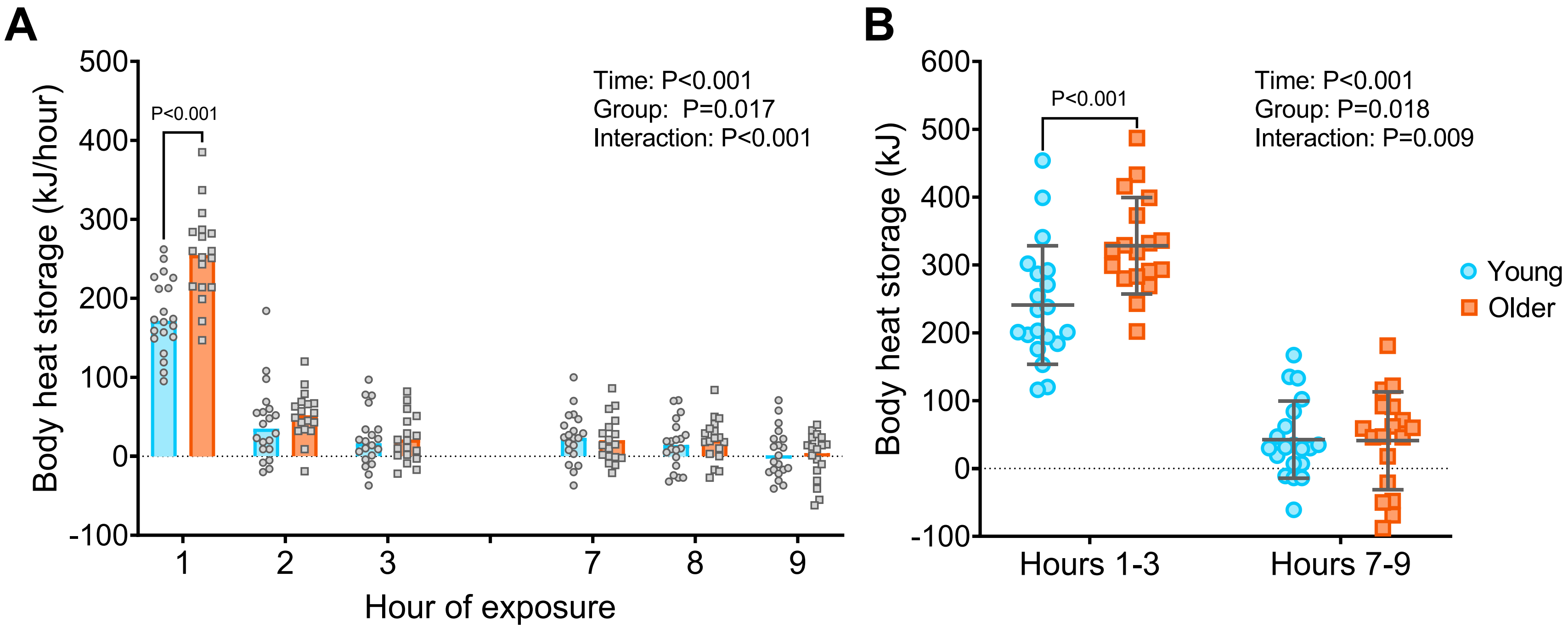


Figure 1. Whole-body heat storage for every hour (panel A) and as a cumulative increase (panel B) over each of the two calorimetry sessions (hours 1-3 and 7-9) in the young (n=20, blue symbols) and older (n=19, orange symbols) adults during the 9-hour extreme heat exposure (40°C, 15% relative humidity). Hourly data reported as mean (bars) and individual data whereas cumulative data is reported as mean ± standard deviation and individual data.

Table 3. Body temperature and cardiovascular responses in the young (n=20) and older (n=19) adults during the 9-hour extreme heat exposure.

		Hour of exposure			ANOVA P values[b]		
Variable	Group	0 (Baseline)	3	9	Time	Group	Int.
Rectal temperature (°C)	Young	37.1 (0.3)	37.6 (0.2)	37.7 (0.2)	**<0.001**	0.118	**<0.001**
	Older	36.9 (0.2)	37.8 (0.3)*	37.9 (0.3)*			
Mean skin temperature (°C)	Young	32.0 (0.6)	36.9 (0.3)	36.9 (0.4)	**<0.001**	0.650	0.361
	Older	32.1 (0.8)	36.8 (0.5)	36.7 (0.5)			
Heart rate (beats/min)	Young	69 (7)	81 (11)	83 (12)	**<0.001**	0.114	0.875
	Older	64 (9)	76 (13)	78 (13)			
Heart rate (% maximum)	Young	35 (4)	41 (5)	42 (6)	**<0.001**	**<0.001**	0.419
	Older	43 (6)†	51 (9)†	52 (10)†			
Cardiac output (L/min)	Young	5.8 (1.0)	6.1 (1.1)	6.1 (1.4)	0.428	**<0.001**	0.148
	Older	3.7 (0.6)†	3.6 (0.8)†	3.6 (0.6)†			
Stroke volume (mL/beat)	Young	85 (21)	77 (20)	76 (23)	**<0.001**	**<0.001**	0.960
	Older	59 (13)†	50 (14)†	48 (11)†			
Forearm blood flow (mL/100 mL tissue)	Young	1.5 (0.4)	4.4 (1.5)	4.4 (1.6)	**<0.001**	0.124	**0.025**
	Older	1.7 (0.5)	3.8 (1.6)	3.3 (1.6)*			
Systolic blood pressure (mm Hg)	Young	115 (10)	112 (13)	114 (11)	**<0.001**	0.065	**0.018**
	Older	127 (14)*	120 (13)	117 (16)			
Diastolic blood pressure (mm Hg)	Young	73 (7)	69 (9)	70 (7)	**<0.001**	0.587	0.285
	Older	74 (9)	67 (10)	68 (10)			
Rate pressure product (mm Hg·beats/min)	Young	7915 (1202)	9149 (1959)	9559 (2072)	**<0.001**	0.805	0.130
	Older	8152 (1616)	9046 (1873)	9078 (2117)			
Baroreflex sensitivity (ms/mm Hg)	Young	14.3 (6.3)	9.0 (4.5)	8.6 (4.5)	**<0.001**	**0.004**	**0.007**
	Older	6.6 (4.6)*	4.2 (2.9)*	4.1 (3.2)*			

Notes: Data presented as means (standard deviation). Data at hour 0 (Baseline) represents data taken in a thermoneutral room (~23°C) prior to heat exposure. [b]ANOVA P values indicate results from mixed-effects model assessing the effects of time and age group. *Significantly different from young adults (at each time point). †Significantly different from young adults (collapsed across time); all P<0.050, exact P-values provided in text.

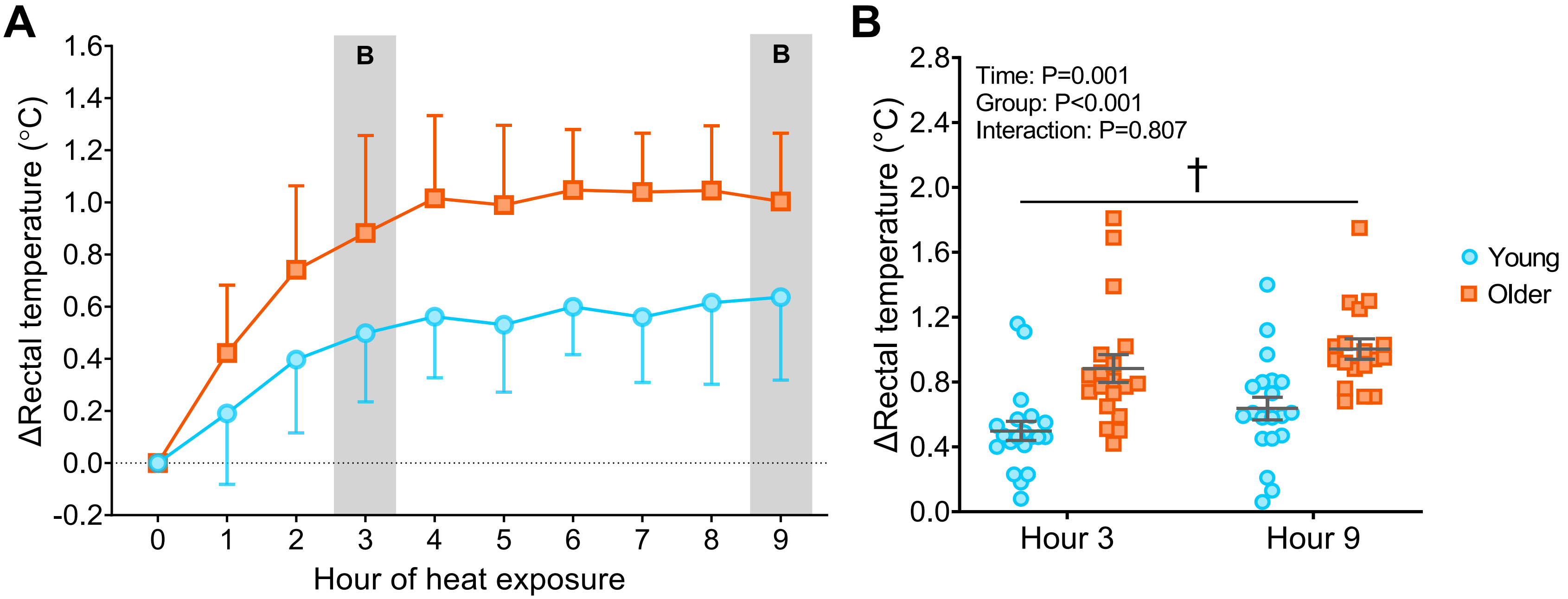


Figure 2. Time-dependent increases (Δ) in rectal temperature (Panel A) in the young (n=20, blue symbols) and older (n=19; orange symbols) adults over the 9-hour extreme heat exposure (40°C, 15% relative humidity). Individual data at the three- and nine-hour points of exposure are presented in Panel B. Data reported as mean ± SD and individual points. † indicates a difference between the young and older adults when data is averaged over time points (P<0.050; see main text in the results for exact P-values)

Cardiovascular responses

Absolute heart rate was not different between groups (Table 3). When presented as a percentage of age-predicted maximum, however, the heart rate response (Table 3) was 9% [5, 14] greater in the older adults throughout the experimental session ($P<0.001$) but this between-group difference was not observed when responses were presented as a change from baseline values (Figure 3A). Cardiac output and stroke volume (Table 3) were elevated by 2.4 L/min [1.8, 2.9] and 27 mL/beat [17, 38], respectively, in the young compared to older adults throughout exposure (both $P\leq0.020$), while the change from baseline was not different between groups (Figure 3B & C). Forearm blood flow (Table 3) was not different between groups at baseline or after 3 hours of exposure (both $P\geq0.486$) but was reduced by 1.2 ml/100 mL tissue [0.1, 2.2] at the 9-hour time-point in the older adults ($P=0.024$). The increase in forearm blood flow from baseline was 1.8 mL/100 mL tissue [0.1, 2.1] greater in the young adults ($P=0.025$; Figure 3D).

Systolic blood pressure (Table 3) was 12 mm Hg [2, 22] greater in the older compared to young adults at baseline ($P=0.019$) but was not different between age groups during exposure (both $P\geq0.221$). Expressed as a change from baseline, systolic blood pressure was reduced to a greater extent (7 mm Hg [2, 13]; $P=0.013$) in the older group (Figure 4A). By contrast, there were no between-group differences in diastolic pressure or rate pressure product whether presented in absolute values (Table 3) or as a change from baseline (Figure 4B & C). Cardiac baroreflex sensitivity (Table 3) was lower in the older compared to young adults by 7.7 ms/mm Hg [4.2, 11.1] at baseline and 4.8 ms/mm Hg [1.3, 8.3] and 4.5 ms/mm Hg [1.0, 8.0] after 3 and 9 hours of heat exposure, respectively (all P≤0.004). The reduction in baroreflex sensitivity during the heat exposure was 3.0 ms/mm Hg [0.5, 5.6] greater in the young adults (Figure 4B).

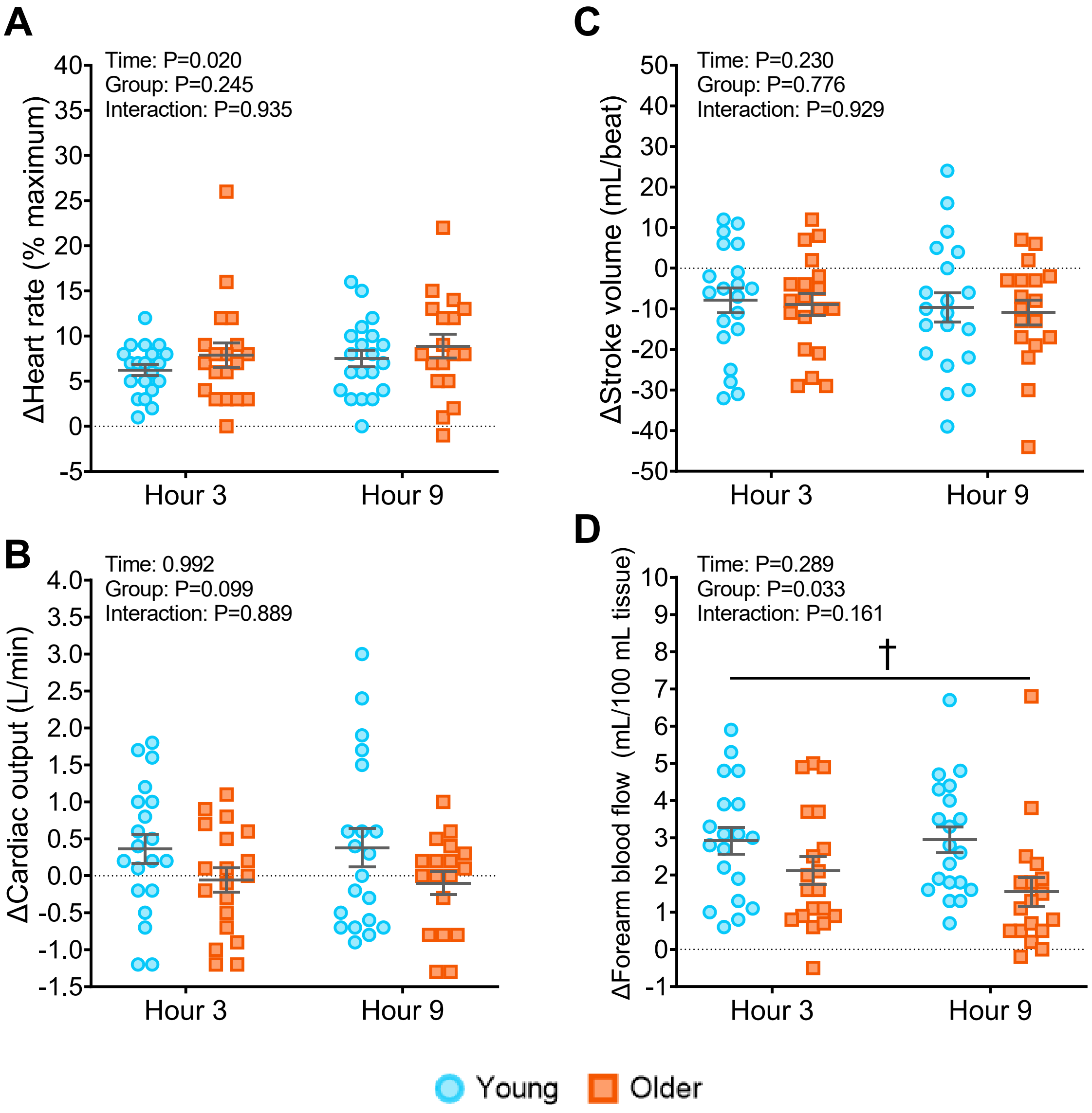


Figure 3. Change (Δ) in heart rate (percentage of age-predicted maximum, panel A), cardiac output (panel B), stroke volume (panel C), and forearm blood flow (panel D) from baseline values in the young (n=20, blue symbols) and older (n=19; orange symbols) at the 3- and 9-hour points of the 9-hour extreme heat exposure (40°C, 15% relative humidity). Data reported as mean ± standard deviation and individual points. † indicates a difference between the young and older adults when data is averaged over time (P<0.050; see main text in the results for exact P-values).

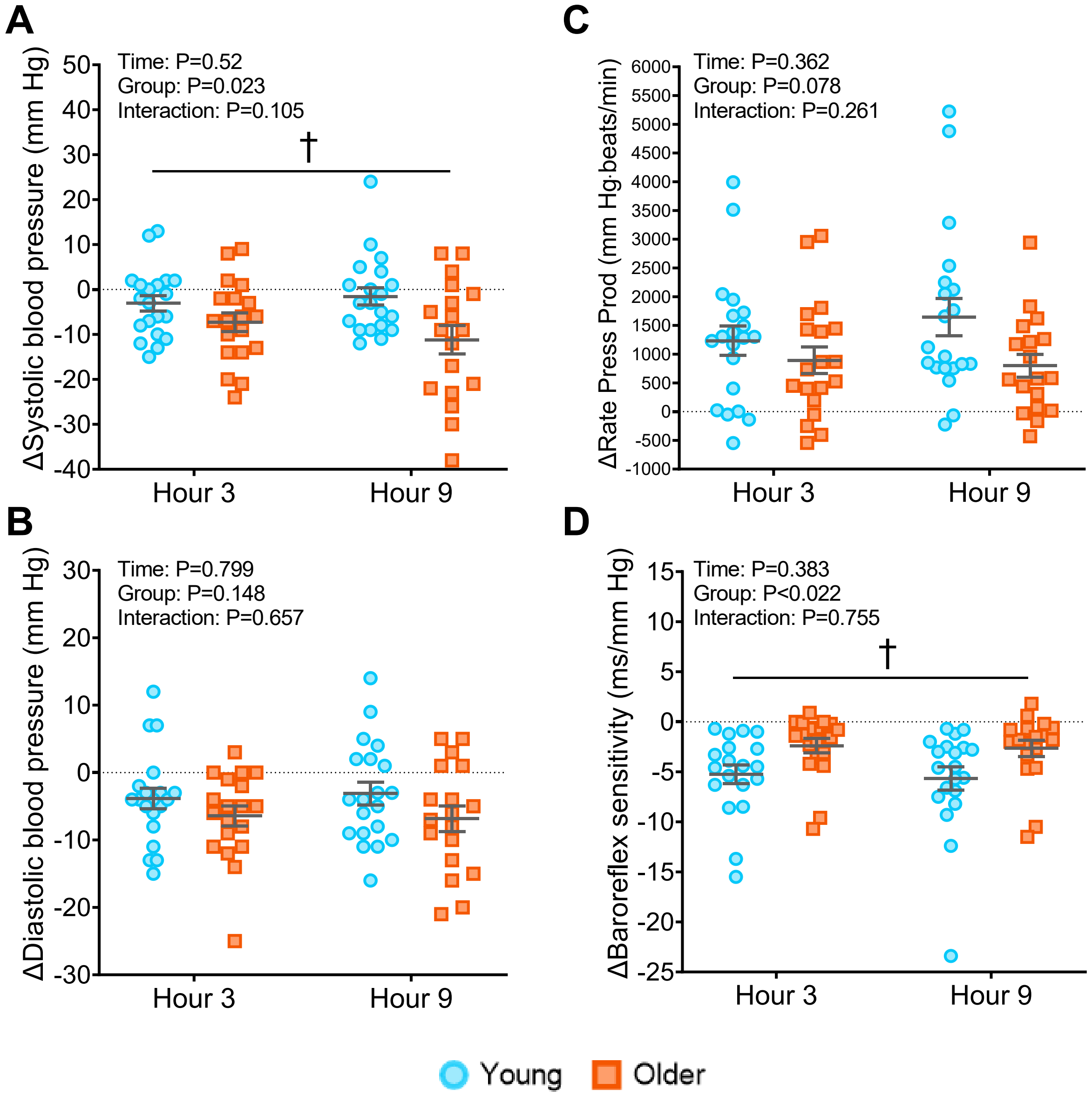


Figure 4. Change (Δ) in systolic blood pressure (panel A), diastolic blood pressure (panel B), rate pressure product (Rate press prod, panel C) and cardiac baroreflex sensitivity (panel D) from baseline values in the young (n=20, blue symbols) and older (n=19; orange symbols) at the 3- and 9-hour points of the 9-hour extreme heat exposure (40°C, 15% relative humidity). Data reported as mean ± standard deviation and individual points. † indicates a difference between the young and older adults when data is averaged over time (P<0.050; see main text in the results for exact P-values).

Hydration-related variables

There were no differences in net fluid loss between the young (hour 3: -1.2 [0.2]% body weight, hour 9: -1.6 [1.0]%) and older adults (hour 3: -1.4 [0.6]%, hour 9: -1.9 [0.9]%;

effect of age: P=0.074) over the 9-hour heat exposure. At end-exposure, the change in plasma volume was 5.1% [0.1, 10.3] greater in the older adults (-4.6 [6.0]% from baseline) compared to their younger counterparts (0.3 [8.6]%), though the difference did not reach the threshold for statistical significance (P=0.053).

DISCUSSION

The purpose of this study was to evaluate whole-body heat exchange and the resultant body temperature and cardiovascular responses in young and older adults during a prolonged, 9-hour exposure to simulated extreme heat conditions (40°C, 15% relative humidity). Over the first 3 hours of exposure, the older adults stored more heat than the young group; however, in contrast to our hypothesis, the older adults were able to attain heat balance and therefore stable body temperatures. As a result of early differences in the rate of body heat storage, rectal temperature in the older group was elevated by ~0.4°C compared to the young throughout heat exposure. Further, while we observed age-related differences in some cardiovascular responses, the magnitude was not altered as exposure progressed.

Heat balance in young and older adults during extreme heat exposure

The primary goal of this study was to evaluate the hypothesis that older adults would not attain a state of heat-balance, characterized by a rate of whole-body heat loss sufficient to offset heat gain via metabolism and the environment, during a prolonged simulated extreme heat event. This was based on a recent study by Kenny et al.[40], wherein a positive increase in heat storage over the final half hour of a 3-hour exposure (40°C) in older adults was observed. This postulate was also consistent with the findings of Stapleton et al.[41] who reported progressive increases in gastrointestinal temperature during a 2 hour exposure to hot-dry (36.5°C, 20% relative humidity) conditions (36.5°C, 20% relative humidity), that were exacerbated with an elevation in relative humidity (36.5°C, 60% relative humidity). During our 9-hour simulated extreme heat event the older adults were able to achieve a state of heat balance, evidenced by the lack of a significant increase in body heat storage over the final hours of exposure (Figure 1) and stable body temperatures from the 4-hour time-point onwards (Figure 2).

A likely explanation for our findings was that the thermal challenge was not sufficient to overwhelm the physiological capacity for heat dissipation in either age group. While previous research from our laboratory has observed age-related impairments in the maximal achievable rate of whole-body heat loss in adults as young as 40 years[32,35], those studies primarily employed exercise heat-stress models. The heat produced as a by-product of muscular work can quickly surpass that gained from the environment, even in extreme conditions. For example, we recently observed that the rate of metabolic heat gain was ~84% greater than that from the environment (129 vs 70 W/m^2) during very light intensity cycling (~25% of maximum oxygen consumption) in 45°C ambient conditions[37]. Thus, while previous work has observed age-related reductions in whole-body heat dissipation in response to an exercise-induced total heat gain of 200-250 W/m^2 [28-36], the rate of heat gain in the current study (80-100 W/m^2; Figure 2) was insufficient to overwhelm the thermoregulatory capacity of the older adults.

Thermal strain during extreme heat events

Although the older adults were able to attain heat balance, they still experienced greater thermal strain compared to their younger counterparts that was paralleled by an elevated burden on the cardiovascular system (discussed below). Specifically, the increase in body temperature from pre-exposure baseline was ~0.4°C greater in the older adults and this separation was maintained throughout the 9-hour extreme heat simulation (Figure 2). This was driven by slower increases in evaporative heat loss in the older adults (Table 2), resulting in greater body heat storage during the early hours of exposure (Figure 1). These findings are consistent with well-established age-related alterations in thermoregulatory function[25,156]. For example, Sagawa et al.[158] observed that cutaneous vasodilation and sweating were initiated at greater body core temperatures in a group of older (age: ~66 years) compared to younger adults (age: ~27 years) during 90-min of resting exposure to 40°C (40% relative humidity). This means that a greater increase in body temperature is *required* to activate heat loss to an extent sufficient to offset the elevated heat gain from the environment[35]. Thus, while the older adults in the current report were able to achieve a state of heat balance during the 9-hour extreme heat event, they did so at a greater level of thermal strain in comparison to the young adults.

Cardiovascular responses

During heat stress, increased core and skin temperatures elicit reflex vasodilation of the cutaneous vasculature to facilitate convective heat transfer to the skin, where it can be dissipated to the environment. This necessitates coordinated alterations in heart rate and cardiac output, which can increase by as much as 60-80 beat/min and 5-7 L/min, respectively, in healthy young adults[53,366,367]. Since most studies evaluating the effect of aging on these responses have done so using extreme, encapsulated heat stress[368], we felt it was important to assess cardiovascular responses during a simulated heat event. In a landmark study, Minson et al.[50] reported a smaller increase in forearm blood flow in older compared to young adults during whole-body passive heating using a water perfused suit (~13 vs 23 mL/100 mL tissue) and both Minson et al.[50] and Gagnon et al.[167] observed lesser elevations in cardiac output in older individuals (~2 vs. 5 L/min). While we observed attenuated increases in forearm blood flow in the older relative to young adults (Figure 3D), the magnitude of these adjustments in both groups were considerably smaller than those in the above studies and there were no-between group differences in the change in cardiac output (Figure 3B). These discrepancies are likely related to differences in the thermal strain experienced. In the studies by Minson et al.[50] and Gagnon et al.[167], participants were heated to a body core temperature of ~38.0-38.5°C while skin temperature reached ~39-40°C. By contrast, rectal and mean skin temperatures in the older adults in our study were ~37.9 and 36.8°C, respectively, after 9 hours of heat exposure (Table 3).

This underscores the necessity of a move toward ecologically minded studies for the evaluation of the cardiovascular burden experienced during extreme heat events, especially considering current theories regarding the mechanistic links between heat exposure and mortality are based on data from encapsulated study designs[14,73,93,369]. These theories posit that the elevated risk of heat-related cardiovascular deaths in older adults occurs due to increased myocardial work and reductions in coronary blood flow that place undue strain on the aging left ventricle[14,73,93,369]. In this regard, we observed that rate pressure product, an index of myocardial work, increased by ~926 mm Hg·beats/min (~11 % from baseline) in the older adults (Figure 4C), which is appreciably lower than the 1300 mm Hg·beats/min elevation that has been considered clinically relevant in other work[370].

We did, however, observe greater reductions in systolic blood pressure in the older adults (Figure 4A), with ~1/3 of the participants in this group (n=6/19) experiencing a >20 mm Hg drop in systolic pressure at the end of the 9-hour exposure. This coincided with reduced cardiac baroreflex sensitivity (an index of the autonomic regulation of arterial blood pressure; Figure 4D), though this only translated to reduced blood pressure in the older group. The contribution of this finding, if any, to the elevated risk of heat-related mortality and morbidity in older adults is currently unclear. It is important to note, however, that increased fluctuations in arterial blood pressure and severe hypotension can precipitate stroke and renal failure[371,372], which are common causes of mortality and morbidity during extreme heat events[93]. Likewise, autonomic nervous system dysfunction has also been implicated in sudden cardiac death[373].

Perspectives

Our findings, particularly when viewed in the context of previous work evaluating the thermoregulatory[40,41,44,45,158] and cardiovascular[50,64,167] effects of heat stress, highlight the need for more ecologically minded heat event simulation studies. Future studies should be conducted to evaluate the differences in physiological function in young and older adults in differing heatwave conditions (e.g., hot-humid) and using more precise measurements of cardiovascular function than were feasible in the current study (see the

Considerations section below). Further, given the stark reductions in blood pressure observed in the older adults (Figure 4A), thorough evaluation of cardiovascular autonomic function during simulated extreme heat events is an important direction for future research. This work should also be expanded to evaluate responses in individuals with chronic health conditions known to impact physiological function during heat exposure such as type 2 diabetes[93], particularly over multiple days as would occur in a natural heat event. This latter point is particularly important since our group has recently shown that a full day of heat exposure (in an occupational context) causes next-day impairments in fluid regulation and thermoregulatory function in older adults[374,375].

Prolonged extreme heat simulation studies will also be highly beneficial for the development of evidence-based personal heat mitigation strategies. Though national and international health agencies such as Health Canada[85] and the World Health Organization[86] currently advocate the use of electric fans and cooling centres (air-conditioned locations where individuals can spend a few hours during an extreme heat event) for preventing heat strain, epidemiological support for these strategies is not forthcoming[87,376]. This has been ascribed to difficulties in evaluating their effects on mortality/morbidity, leading some to suggest that extreme heat exposure studies, like the one employed in the current report, offer an important alternative solution[18]. The physiological impacts of electric fan use, however, have only been evaluated during short-term simulated heatwaves (120 min) and, even then, only in young adults[377]. Considering that rectal temperatures in the current study did not stabilize until the 4-hour mark (Figure 2), it is important that future work evaluate whether fans are effective over long durations of use in both young and older individuals. Likewise, the effect of cooling centres on physiological responses during an extreme heat event has yet to be delineated. Given growing global rates of heat-related mortality[1], such research is crucial to better protect heat-vulnerable sectors of the population.

Considerations

The current work is not without its considerations. The first relates to the conditions employed. A key operating principal for the Snellen calorimeter is that all produced sweat must be evaporated to obtain an accurate estimate of whole-body heat loss[22,135,378]. To ensure this, we employed low-humidity conditions (~15% relative humidity), but increased ambient temperature to approximate the level of heat stress experienced during recent extreme heat events in Ontario, Canada[46], where the study was conducted. It is possible that varying ambient temperature and humidity alter the thermoregulatory responses and increases in body temperature in older adults, potentially even for a given level of heat stress (i.e., a given heat index) due to the age-related alterations in skin blood flow and sweating[35,93]. However, this effect appears to be minor, as peak body core temperatures during 8 hours of rest in 36°C and 45% relative humidity (heat index: 41°C; peak core temperatures of ~37.8°C) in the second article of the thesis (see Section 3.3), were similar to those in this study (heat index: 38°C; peak core temperatures of ~37.9°C). Regardless, the independent and combined effects of elevated ambient temperature and humidity are important considerations for future extreme heat simulation studies.

Another important consideration is the methods used to measure the cardiovascular adjustments. Cardiac output and baroreflex sensitivity were estimated via inert gas rebreathing and reconstruction of arterial pressure waveforms (model flow analysis), respectively. While indirect indices of cardiac output and central haemodynamic function have been shown to underestimate direct measured (e.g., thermodilution), these observations have been made during encapsulated heating[379]. It would therefore be important that future studies employ more direct assessments of the cardiovascular responses to ecologically minded extreme heat exposures[93,368]. Importantly, this would allow for more detailed evaluations of the effect of aging on cardiac function during heat events (e.g., Frank-Starling relations[167] and systolic/diastolic function[55]).

CONCLUSIONS

Here, we assessed whole-body heat exchange and associated physiological responses in young and older adults during a prolonged, 9-hour exposure to simulated extreme heat conditions. While the older adults were able to attain a state of heat balance (i.e., thermal equilibrium), they did so at a ~0.4°C greater increase in body core temperature compared to the young adults and this separation was maintained throughout the 9-hour exposure. This was associated with altered blood pressure control, though the clinical significance of this finding remains to be explored. Regardless, this study represents an important step forward in the use of prolonged exposures for evaluating the effects of heat events on heat-vulnerable populations such as the elderly.

DISCLOSURES

There are no conflicts of interest, financial or otherwise, to disclose.

GRANTS

This research was funded by the Canadian Institutes of Health Research (Grant no. 39943; funds held by Glen P. Kenny). G. P. Kenny is supported by a University of Ottawa Research Chair. R.D. Meade is supported by the Human and Environmental Physiology Research Unit.

ACKNOWLEDGEMENTS

We thank all the participants who volunteered their time and Dr. Sean Notley, Dr. Ashley Akerman, Dr. Jeremy McCormick, Dr. Greg McGarr, Jeremy Nehme, Emma McCourt, Brodie Richards, and Emileigh Binet for their invaluable contributions to the project.

3.3 Thesis Article 3

The effect of indoor temperatures on body temperature and cardiovascular autonomic function in older adults

ClinicalTrials.gov identifier: NCT04348630

Key words: heatwaves, indoor temperature, cardiovascular autonomic function

Number of tables: 1

Number of figures: 4

ABSTRACT

Most heat-related fatalities occur in the home. While health agencies including Health Canada and the World Health Organization provide guidance for maximal indoor temperatures, there exists limited empirical evidence to support these guidelines. We therefore designed this study to evaluate physiological responses in older adults (n=8; age: 66-78 years) during an 8-hour exposure to a range of ambient conditions experienced indoors during extreme heat events: 22°C (COOL), 26°C (TEMP), 31°C (WARM), and 36°C (HOT). Relative humidity was maintained at 45% in all trials. Rectal temperature, heart rate and mean arterial pressure were monitored throughout. Cardiovascular autonomic function was assessed during the 7th hour of exposure with the Ewing's test battery (cardiovascular reflex tests). At the end of the 8-hour exposure, rectal temperature was not different between COOL and TEMP (P=0.300) but was elevated by 0.6°C [95% confidence limits: 0.2, 0.9] and 0.3°C [0.2, 0.4] in WARM compared to TEMP (P<0.001) and HOT compared to WARM (P<0.001), respectively. Heart rate increased by 4 beats/min [0, 7], from COOL to TEMP (P=0.020), 9 beats/min [3, 14] from TEMP to WARM (P=0.003), and 5 beats/min [2, 9] from WARM to HOT (P=0.004). Conversely, mean arterial pressure fell by 10 mmHg [1, 18] from COOL to TEMP (P=0.027), but reductions with further increases in ambient temperature were not statistically significant (both P≥0.078). The heart rate response to standing was blunted by 0.09 [0.03, 0.14] in COOL compared to TEMP (P=0.002), 0.09 [0.00, 0.11] in TEMP compared to WARM (P=0.045) and 0.06 [0.00, 0.11] in WARM compared to HOT (P=0.052). These findings indicate that indoor heat stress can increase body temperature and attenuate indices of cardiovascular autonomic function in older adults, even under conditions consistent with current indoor temperature guidelines.

INTRODUCTION

Protecting heat-vulnerable persons from rising global temperatures and the accompanying increases in the incidence and severity of extreme heat events represents a pressing public health concern. Most heat-related fatalities occur in the home[107,380], where individuals on average spend ≥70% of their time[78,79]. While targeted public health guidance to limit indoor heat stress is therefore an important strategy to reduce harmful exposures in vulnerable populations, there exists limited empirical evidence to guide the identification of upper indoor temperature limits to safeguard health and well-being[80,381]. Despite this, Toronto Public Health has recommended that the temperature of homes of vulnerable occupants should not exceed 26°C[81,82]. The World Health Organization also provides guidance for maximal indoor temperatures during extreme heat events but their day-time threshold is set considerably higher at 32°C[83].

Support for indoor temperature guidelines is largely indirect, based primarily on location-specific outdoor ambient temperature-mortality and morbidity relations[81,82]. This ignores that indoor and outdoor temperatures can diverge markedly depending on factors such as building design and insulation, and the presence of environmental control systems[381]. During the hot summer months, the temperature of the home can range from ≤22°C, if air conditioning is available, to ≥35°C in the case of poorly insulated and/or ventilated domiciles in densely populated neighborhoods[80]. In fact, the continual buildup of heat within the domicile during a prolonged heat event can result in indoor temperatures approaching or even exceeding peak outdoor conditions[382-384]. It follows that outdoor temperature is a poor predictor of the heat stress experienced indoors[385,386], and that the risk of heat-related mortality can vary widely amongst individuals experiencing the same heat event[387,388]. Ultimately, this limits the usefulness of city- or country level temperature-mortality/morbidity relations for defining indoor temperature guidance and highlights the need for improved characterization of the health impacts of indoor heat stress, particularly in vulnerable persons[381].

Another challenge is that existing guidelines generally offer a one-size-fits all solution and do not consider that the tolerable range of indoor temperatures may be restricted for some sectors of the population[381]. Older adults (individuals aged ≥65 years), for instance, are among the most affected by extreme heat due to age-related deterioration of the physiological responses to heat stress[93]. There is ample epidemiological data indicating that mortality begins to increase at lower threshold ambient temperatures in older adults[389] and that the slope of the temperature-mortality relation thereafter is steeper with increasing age[390,391]. Further, in a home-based study, Kim et al.[384] observed 0.2°C elevations in core body temperature and 3 mm Hg reductions in systolic blood pressure in older adults (aged ~70 years) for every 1°C increase in indoor temperature. The mean indoor temperature (31.5°C)[384] exceeded the yearly 99th percentile mean outdoor temperature for the study area (Seoul, Korea; humid continental climate), which has been associated with a ~4% greater risk of heat-related mortality in the general population compared to cooler conditions (25°C)[391]. Thus, indoor heat stress may perturb body temperature and blood pressure regulation and threaten health at temperatures below current guidelines.

These data highlight the need for improved characterization of the physiological impacts of heat stress in indoor environments in older adults. While some have attempted to address this knowledge gap directly by evaluating body temperatures and resting cardiovascular responses of free-living participants[384,385], the field-based nature of those studies precluded thorough evaluation of the physiological responses supporting health.

The purpose of this study was therefore to evaluate body temperature and cardiovascular responses in older adults resting for 8-hours in a range of ambient conditions reflective of those experienced indoors during extreme heat events in a temperate continental climate. Since most heat-related deaths and hospitalizations are of cardiovascular origin[93,392], and older adults are known to exhibit impaired cardiovascular responses to heat stress[93], including attenuated indices of autonomic blood pressure control[168,393,394] (3.2 Thesis Article 2), we also evaluated cardiovascular function using clinically validated tests selected to mimic the autonomic challenge experienced during activities of daily living. We hypothesized that body temperatures and resting cardiovascular responses (e.g., heart rate, mean arterial pressure, rate pressure product) would not be appreciably modified during rest below the currently recommended indoor temperature thresholds set by Toronto Public Health (22°C and 26°C). However, at higher temperatures (31°C and 36°C) elevated thermal and cardiovascular strain would be reflected in attenuated cardiovascular autonomic function.

METHODS

Ethical approval

This study was approved by the University of Ottawa Health Sciences and Science Research Ethics Board and the Health Canada and Public Health Agency of Canada Research Ethics Board and conformed to the latest version of the Declaration of Helsinki. The study protocol was prospectively registered (ClinicalTrials.gov identifier: NCT04348630).

Participants

Eight older adults (age: 66-79 years) participated. All were non-smokers and reported no history of metabolic or cardiovascular disease. Their characteristics are presented in Table 1.

Table 1. Physical characteristics of the older participants (n=8).

	Mean (SD)	Min-max
Women/men (n)	1 / 7	
Age (years)	71 ± 4	66 - 77
Height (m)	1.73 ± 0.05	1.65 - 1.81
Mass (kg)	73.9 ± 12.3	57.3 - 88.6
A_D (m^2)[a]	1.9 ± 0.2	1.7 - 2.1
Body fat (%)	28 ± 5	20 - 33
Body mass index[b]	24.5 ± 3.3	18.7 - 27.4
Aerobic activity (min/week)[c]	156 ± 147	0 - 420

Notes: [a]A_D, body surface area [365]; [b]body mass index calculated as body mass/height^2. [c]Self-reported aerobic activity (min/week) levels as defined by the Canadian Society for Exercise Physiology[355]. [d]P-values indicate results from an unpaired, two-tailed t-test.

Experimental Design

All participants were asked to avoid strenuous activity and alcohol for 24 hours prior to all preliminary and experimental sessions and to eat a light meal 2 hours before the start of each session. Participants were also asked to consume a minimum of 500 ml of water the night before and morning of each session to ensure adequate hydration, verified upon arrival to the laboratory on the day of the experimental sessions operationally defined as a urine specific gravity <1.025)[354]. If participants exceeded this threshold, ~500 mL of tap water was provided, and urine specific gravity was tested again after ~30 min. Participants wore an athletic shirt and shorts for each session.

Preliminary screening.

The preliminary evaluation was completed a minimum of 48 hours before the first experimental session. Participants were familiarized with all experimental procedures and measurement techniques and completed the Get Active Questionnaire (GAQ) and the American Heart Association Pre-participation screening Questionnaire to assess their eligibility to participate. The GAQ was also used to assess habitual aerobic activity levels[355]. Participant physical characteristics were then evaluated. Body height (Detecto, model 2391, Webb City, MO, USA) and mass (model CBU150X, Mettler Toledo Inc., Mississauga, ON, Canada) were determined via a physician stadiometer and a high-performance weighing terminal, respectively, and from these measurements body surface area was calculated[356]. Body fat percentage was estimated from measurements of body density made with the hydrostatic weighing technique[357].

Experimental sessions

Each experimental session began between 07:00-08:00. Upon arrival to the laboratory, hydration status was assessed via urine specific gravity and participants inserted a rectal temperature probe (Mon-a-therm General Purpose Temperature Probe, Mallinckrodt Medical Inc., St-Louis, MO, USA). A measurement of body mass (nude) was taken thereafter. Participants were then transferred to a thermal chamber regulated to 22°C (45% relative humidity). Following 10-min of supine rest, participants performed a specialized cardiovascular test battery to assess autonomic cardiovascular function (~60-75 min; described below). Following the battery, they rested in the seated position in a room adjacent to the thermal chamber (~22°C) for ~30 min and were instrumented with skin temperature sensors (DS1922L Thermochron, OnSolution Pty Ltd, Australia). Heart rate and arterial blood pressures were then measured in triplicate via oscillometry (UM-211, A&D Medical, Tokyo, Japan) and a venous blood sample was obtained.

While baseline measurements were being taken, the thermal chamber was heated to the conditions for that day's session. Each participant completed four separate sessions (separated by ≥2 days) in a randomized order (based on a pseudo-random sequence generated with commercially available spreadsheet software). These consisted of resting exposure to: i) 22°C, to simulate an air-conditioned environment (COOL); ii) 26°C, corresponding to recommended upper limits for indoor environments as set by Toronto Public Health (TEMP)[81,82]; ii) 31°C, similar to average daytime summer temperatures in Ontario and Quebec and slightly below World Health Organization recommended day-time indoor temperature limit during heat events (WARM, heat index: 32°C)[83]; and iv) 36°C, based on maximal indoor temperatures measured during extreme heat events in a temperate continental climate (HOT, heat index: 41°C)[80]. Relative humidity was maintained at 45% in all conditions.

Participants spent the next 8 hours seated in the chamber, except for during the 7th hour where they completed the cardiovascular test battery again. Rectal and skin temperatures were measured continuously. Tap water maintained at ~15-20°C was available ad libitum. Participants could eat a self-provided lunch (~300 g, low water content) between 1.5 h and 3.5 h of exposure. Heart rate and arterial blood pressures were measured in triplicate (UM-211, A&D Medical) at the end of each hour. Participants then stood and body mass was measured (WB-100A, Tanita Corporation, Tokyo, Japan), after which the participant could remain standing and perform light stretching if desired (max ~5 min). During the 7th hour of exposure, the cardiovascular battery was completed again. The participants were then seated in the chamber for the remainder of the 8-hour exposure. Following final measurements of heart rate and arterial blood pressure, a venous blood sample and nude body mass were procured, and the participant was given water and/or a commercially available sports drink before departing the laboratory.

Autonomic Cardiovascular Function Battery

The autonomic cardiovascular function battery performed at baseline and during exposure consisted of analysis of heart rate variability during supine rest and Ewing's battery (modified) for assessment of cardiovascular autonomic function. Prior to each battery, participants were instrumented with a 3-lead ECG (FE231 Bio Amp, ADInstruments, Colorado Springs, CO, USA) and non-invasive blood pressure monitor (NIBP, ADInstruments, Colorado Springs, CO, USA) for the integrated measurement of beat-to-beat heart rate and arterial blood pressure. The latter was estimated from the arterial pressure waveform measured at the right middle finger using the volume-clamp technique[358,359]. Throughout the battery, the arm was affixed to the chest using a medical sling with the finger held at the approximate level of the left ventricle. Participants were instructed to breathe normally and, without speaking, follow the instructions given by the test administrator (RDM). The test battery was performed twice in succession as follows:

- *Resting heart rate variability*. Heart rate variability was evaluated during 8-min of supine rest. Participants were instructed to breathe in time with a metronome set to 30 beats/min (15 breaths/min), to standardize the influence of respiratory sinus rhythm on cyclical fluctuations in heart rate and blood pressure. One minute of recovery (spontaneous breathing) was given prior to the start of the Ewing's battery.

- *Ewing's battery.* The modified Ewing's battery consisted of three tests (deep breathing, Valsalva maneuver, and lying-to-standing test) designed to assess autonomic control of heart rate (primarily parasympathetic) and blood pressure (primarily sympathetic)[395,396]. Consistent with the optimal sequence identified by Stranieri et al.[397], the battery was performed as follows:
    - First, participants performed 1 min of deep diaphragmatic breathing at a rate of 6 breaths/min (metronome set to 12 beats/min). Breathing was performed to vital capacity; that is, through a maximal inspiration and expiration. Five minutes of recovery was given before the next test.
    - The next test was the Valsalva maneuver. While in the supine position, participants exhaled against a closed glottis into a narrow vinyl tube connected to an electronic pressure transducer used to provide constant feedback on the generated expiratory pressure. The participant was instructed to maintain a pressure of 40 mm Hg for 15 s. Throughout expiratory straining, air was vented via a small bleed to prevent generation pressure using the mouth. Upon release, heart rate and blood pressure were monitored for 1 min.
    - The final test was the lying-to-standing test. The test began with 1-min of rest in the supine position. At this point the participant was instructed to quickly (but safely) assume a standing position directly beside the bed. The participant then stood quietly for 3 min.

Measurements

Body temperatures

Body core temperature was estimated by rectal temperature recorded continuously using a thermocouple probe (Mon-a-therm General Purpose Temperature Probe, Mallinckrodt Medical Inc) inserted ~12 cm past the anal sphincter. Skin temperature was measured using surface temperature monitors (DS1922L Thermochron) placed in 8 locations as described in ISO 9886:2004: forehead, right scapula, upper left chest, upper right arm, right forearm, left hand, right anterior thigh, and left calf[361].

Cardiovascular measurements

Heart rate and arterial systolic and diastolic blood pressures were taken in triplicate (~30 s between measures) via oscillometry (UM-211, A&D Medical). In the specialized cardiovascular test battery, beat-to-beat blood pressure was estimated from recordings of the arterial pressure waveform measured at the right middle-finger using the volume-clamp technique (NIBP, ADInstruments)[359] and heart rate was derived from R-R intervals measured continuously via an integrated 3-lead ECG (FE231 Bio Amp, ADInstruments). Arterial blood pressure and R-R interval data were continuously sampled at 1 kHz using an analog-to-digital converter (Powerlab, ADInstruments) and stored offline for subsequent analysis (LabChart Pro v8, ADInstruments).

Hydration-related variables

Urine specific gravity was assessed when the participants arrived at the laboratory using a hand-held total-solids refractometer. (Reichert TS 400 total solids refractometer, Reichert, Depew, NY, USA). Participants presenting to the laboratory with urine specific gravity <1.025 were considered adequately hydrated to begin the experimental session[354]. Fluid loss was estimated from the change in nude body mass from the start to the end of the experimental session (corrected for food consumption) using a high-performance weighing terminal (model CBU150X). Venous blood samples were collected for determination of changes in plasma volume. Blood was transferred directly into plasma (5.4 mg K2EDTA) Vacutainer tubes (BD, Franklin Lakes, NJ, USA), mixed by inversion, and used to measure haematological parameters in duplicate (Ac·T diff, Beckman Coulter, Miami, FL, USA).

Data analysis

Body temperatures were averaged over the final 15 min of each hour of exposure. Mean skin temperature was calculated using the weightings: forehead (7%), right scapula (17.5%), upper left chest (17.5%), upper right arm (7%), right forearm (7%), left hand (5%), right anterior thigh (19%) and right calf (20%)[361]. Heart rate and arterial pressures were presented as an average of the 3 measurements at the end of each hour. Mean arterial pressure was calculated as 2/3 diastolic pressure + 1/3 systolic pressure. Rate pressure product, an index of myocardial work[362,363], was derived as heart rate × systolic pressure. The change in plasma volume was calculated from the blood samples obtained at the start and end of each session[364].

Time-domain and non-linear estimates of HRV were calculated from R-R intervals using dedicated software (LabChart HRV, ADInstruments)[398]. The former included the square root of the variance of successive R-R intervals (i.e., SDRR), an index of overall variability; and the root mean squared of the standard deviation (RMSSD), which is more reflective of short-term high frequency fluctuations in heart rate (mediated primarily by the parasympathetic nervous system)[399]. In addition, non-linear fluctuations in heart rate were estimated via Poincaré standard deviations, SD_1 and SD_2, reflective of short- and long-term variation, respectively. These were used to calculate the cardiac vagal index ($Log_{10}[16 \cdot SD_1 \cdot SD_2]$)[400,401]. One participant displayed normal rhythm but interspersed with more 2-4 heart beats in more rapid succession, causing inflated heart rate variability (e.g., RMSSD ~8 SD from the mean in the COOL). The data from this participant was excluded and statistical analysis of HRV metrics was conducted with a reduced sample (n=7).

The Ewing's battery tests were analyzed according to the recommendations of Spallone et al.[396]. Deep breathing was analysed as the difference in heart rate between the average of the three lowest and three highest values recorded during inspiration and expiration, respectively (E/I HR_{Diff}). The Valsalva ratio was calculated as the longest R-R interval during recovery divided by the shortest R-R interval during the Valsalva Maneuver. The Valsalva maneuver was performed prior to the COVID-19 pandemic but was removed from the battery thereafter due to concerns over aerosol generation. The analysis was therefore conducted with a reduced sample size (n=6). Finally, the lying to standing test was analyzed via the 30:15 ratio, which represents the longest R-R interval measured between the 25-35th heartbeat upon standing divided by the shortest R-R interval between the 10-20th beat after standing. Additionally, the systolic response to standing (SR_{stand}) was taken as the 1-min average of systolic blood pressure after the second min of standing minus systolic pressure during the pre-stand supine resting period (i.e., the reduction in systolic pressure upon assuming a standing position). Analyzed values for each test were taken as the average of each of the two recorded values.

Statistical analysis

An a priori power analysis determined that a total sample size of 16 older adults was required to detect a difference in rectal temperature between groups with 80% statistical power, after adjusting for multiple comparisons. The effect size (Cohen's d=1.0) was determined based on a practically meaningful difference of 0.3°C between conditions, assuming a standard deviation of 0.3. The mean difference was chosen based on previous suggestions of clinically meaningful changes in body core temperature during heatwaves[170] as well as the daily variation in resting core temperature[402]. The standard deviation was determined from studies demonstrating a 0.2 (SD 0.3)°C and 0.0°C (0.3)°C difference in rectal temperature between young and older adults[40], and between older adults with and without type 2 diabetes[287], respectively, following 3 hours of rest in a hot environment. Due to the on-going global pandemic (COVID-19), we were not able to meet these numbers for this report. The findings should therefore be considered exploratory, requiring further support in larger-scale experimental trials.

Body temperatures and cardiovascular responses at the end of the 8-hour exposure as well as the autonomic functional tests of the cardiovascular battery at hour 6 were evaluated using a mixed-effects model with the repeated factor of environmental condition and baseline values included as a continuous covariate (except for measures calculated as a change from baseline: body mass and plasma volume). Statistical dependency arising from repeated measures was accounted for by including each ‘subject’ as a random effect. Pre-planned post hoc comparisons via Sidak’s procedure were employed to identify differences between adjacent conditions (COOL vs TEMP, TEMP vs. WARM, WARM vs. HOT). This was done to limit a large family of comparisons. Statistical analysis was performed using the nlme[403] and emmeans[404] packages for R (Version 3.6.1, R Development Core Team, 2018). Data was visualized using Prism (Version 8, GraphPad Software). The threshold for statistical significance was set at *P<0.050*. Descriptive statistics were presented as mean (standard deviation) and comparisons between conditions (model estimated marginal means) as means and 95% confidence interval [lower limit, upper limit].

RESULTS

Body temperatures

At the end of the 8-hour exposure, rectal temperature (effect of condition: P<0.001; Figure 1A & B) was not different between COOL and TEMP (P=0.300) but was elevated by 0.6°C [0.2, 0.9] in WARM compared to TEMP (P<0.001) and by 0.3°C [0.2, 0.4] in HOT compared to WARM (P<0.001). Mean skin temperature (effect of condition: P<0.001; Figure 1C & D) increased from COOL to TEMP (1.5°C [0.8, 2.2]; P<0.001), TEMP to WARM (2.0°C [1.3, 2.7]; P<0.001), and WARM to HOT (1.1°C [0.4, 1.8]; P=0.002).

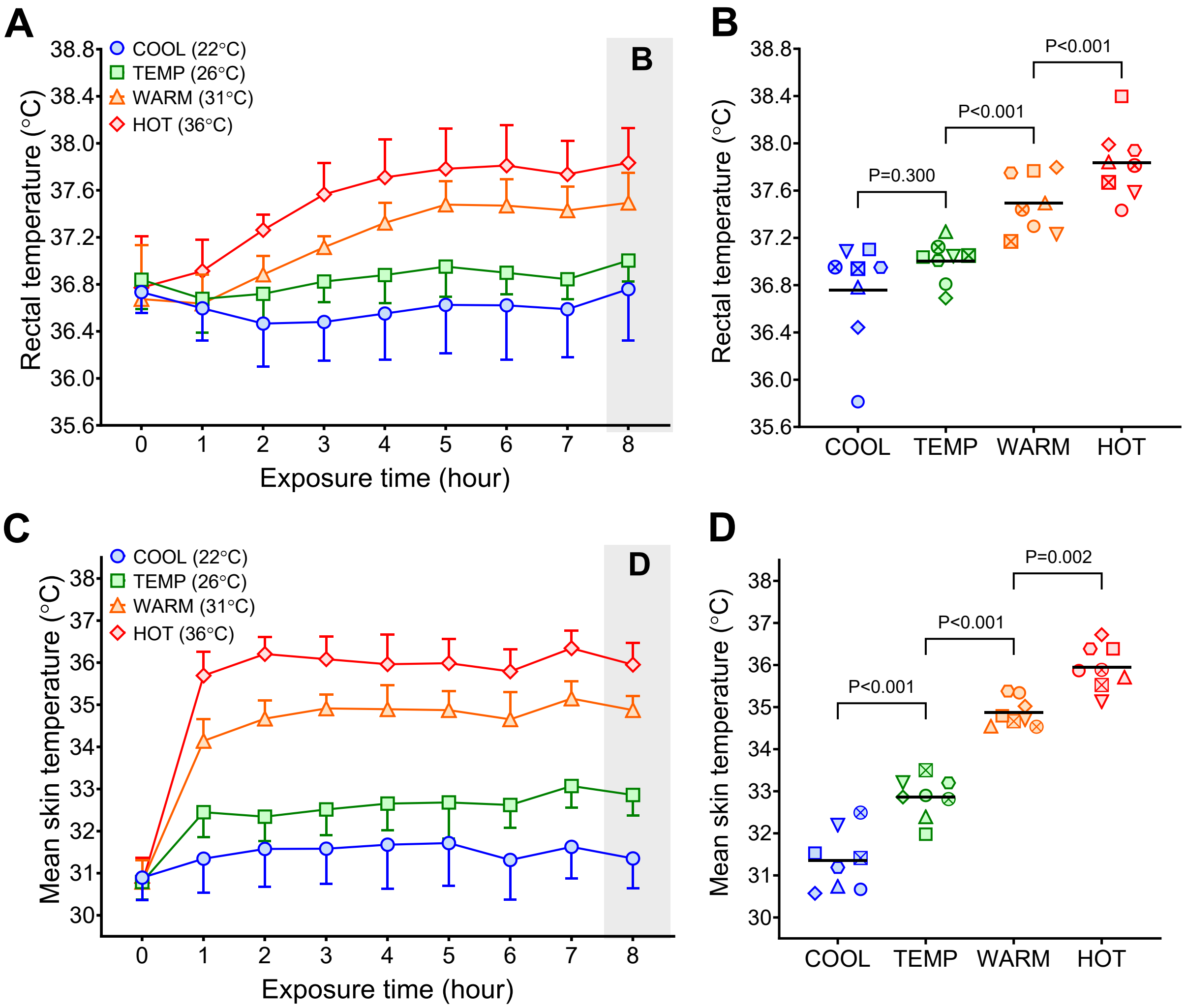


Figure 1. Time-dependent responses of rectal (panel A) skin temperature (panel C) in the older adults (n=8) over the 8-hour exposure to COOL (22°C), TEMP (26°C), WARM (31°C) and HOT (36°C) conditions (relative humidity of 45% in each condition). Individual data at the end of each exposure are presented in panels B and D. Data reported as mean ± SD and individual points. P-values indicate post hoc comparisons between model estimated marginal means (adjusted for baseline values) of adjacent conditions (following detection of a significant effect of condition).

Resting cardiovascular responses

Heart rate (effect of condition: $P<0.001$; Figure 2A & B) increased by 4 beats/min [0, 7], 9 beats/min [3, 14], and 5 beats/min [2, 9] from COOL to TEMP ($P=0.020$), TEMP to WARM ($P=0.003$), and WARM TO HOT ($P=0.004$), respectively. Conversely, mean arterial pressure (effect of condition: $P<0.001$; Figures 2C & D) fell by 10 mmHg [1, 18] from COOL to TEMP ($P=0.027$), but reductions from TEMP to WARM ($P=0.078$) and WARM to HOT ($P=0.444$) were not statistically significant. Rate pressure product did not differ between conditions (effect of condition: $P=0.435$; Figure 2E & F).

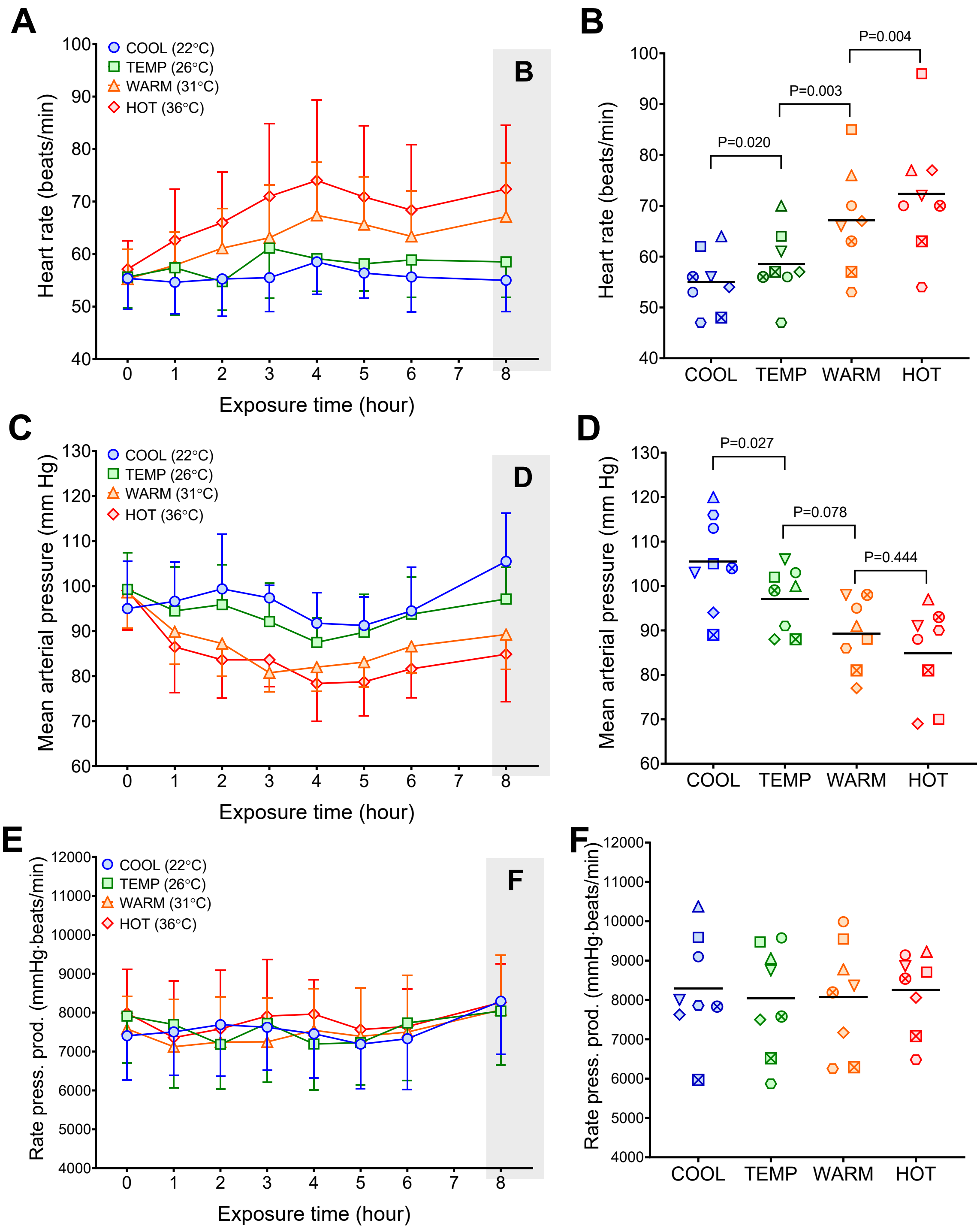


Figure 2. Time-dependent responses of heart rate (panel A) mean arterial pressure (panel C) and rate pressure product (panel E) in the older adults (n=8) over the 8-hour exposure to COOL (22°C), TEMP (26°C), WARM (31°C) and HOT (36°C) conditions (relative humidity of 45% in each condition). Individual data at the end of each exposure are presented in panels B, D and F. Data reported as mean ± SD and individual points. P-values indicate post hoc comparisons between model estimated marginal means (adjusted for baseline values) of adjacent conditions (following detection of a significant condition effect).

Cardiac autonomic function

Heart rate variability

While a main effect of condition was detected for SDRR (P=0.002; Figure 3A), there were no statistically significant differences between adjacent thermal conditions at the end of the 8-hour exposure (all P≥0.314). By contrast, RMSSD (effect of condition: P=0.014; Figure 3B) was reduced by 6 ms [3, 9] from COOL to TEMP (P<0.001), 5 ms [0, 10] from TEMP to WARM (P=0.042), and 4 ms [1, 7] from WARM to HOT (P=0.014). Despite an effect of condition (P<0.001; Figure 1C) cardiac vagal index was not different between adjacent thermal conditions (all P≥0.152).

Ewing's battery

Effects of condition were observed for the E/I HR_{Diff} (P=0.023; Figure 4A) and Valsalva ratio (P=0.040; Figure 4B) but, in general, no differences were observed between adjacent thermal conditions (all P≥0.139) except for the Valsalva ratio between TEMP and WARM (0.21 [0.02, 3.11]; P=0.023). The heart rate response to standing (30:15 ratio, effect of condition: P<0.001; Figure 4C) was reduced by 0.09 [0.03, 0.14] from COOL to TEMP (P=0.002), 0.09 [0.00, 0.11] from TEMP to WARM (P=0.045) and 0.06 [0.00, 0.11] from WARM to HOT, though the latter comparison was not statistically significant (P=0.052). Finally, while an effect of condition was observed for the systolic response to standing (P=0.011; Figure 4D), comparisons between adjacent thermal conditions were not statistically significant (all P≥0.169).

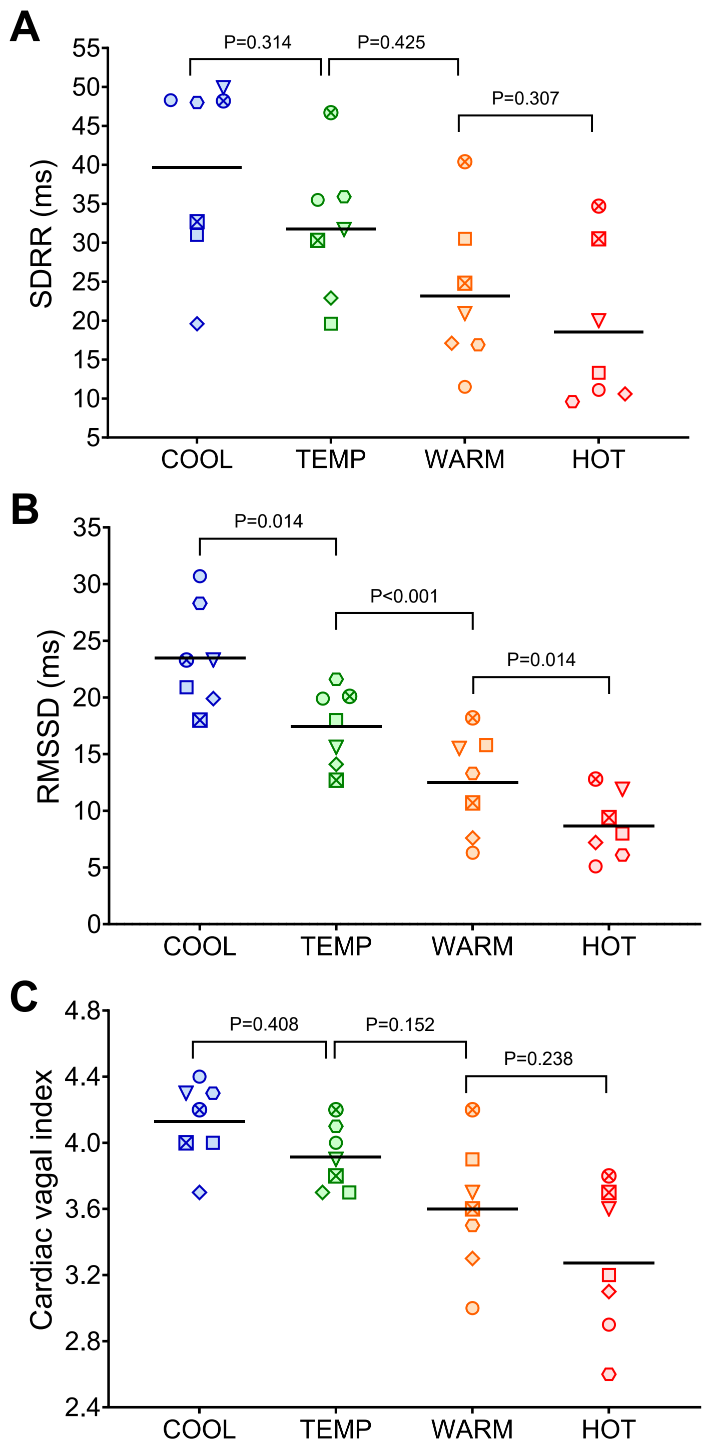


Figure 3. Indices of heart rate variability for the older adults (n=8) at the end of the the 8-hour exposure to COOL (22°C), TEMP (26°C), WARM (31°C) and HOT (36°C) conditions (relative humidity of 45% in each condition). These included the squared root of the variance of R-R intervals (SDRR), an index of overall variability; the root mean squared of the standard deviation (RMSSD), reflective of short-term high frequency fluctuations in heart rate (mediated primarily by the parasympathetic nervous system) and the cardiac vagal index. P-values indicate post hoc comparisons between model estimated marginal means (adjusted for baseline values) of adjacent conditions (following detection of a significant condition effect).

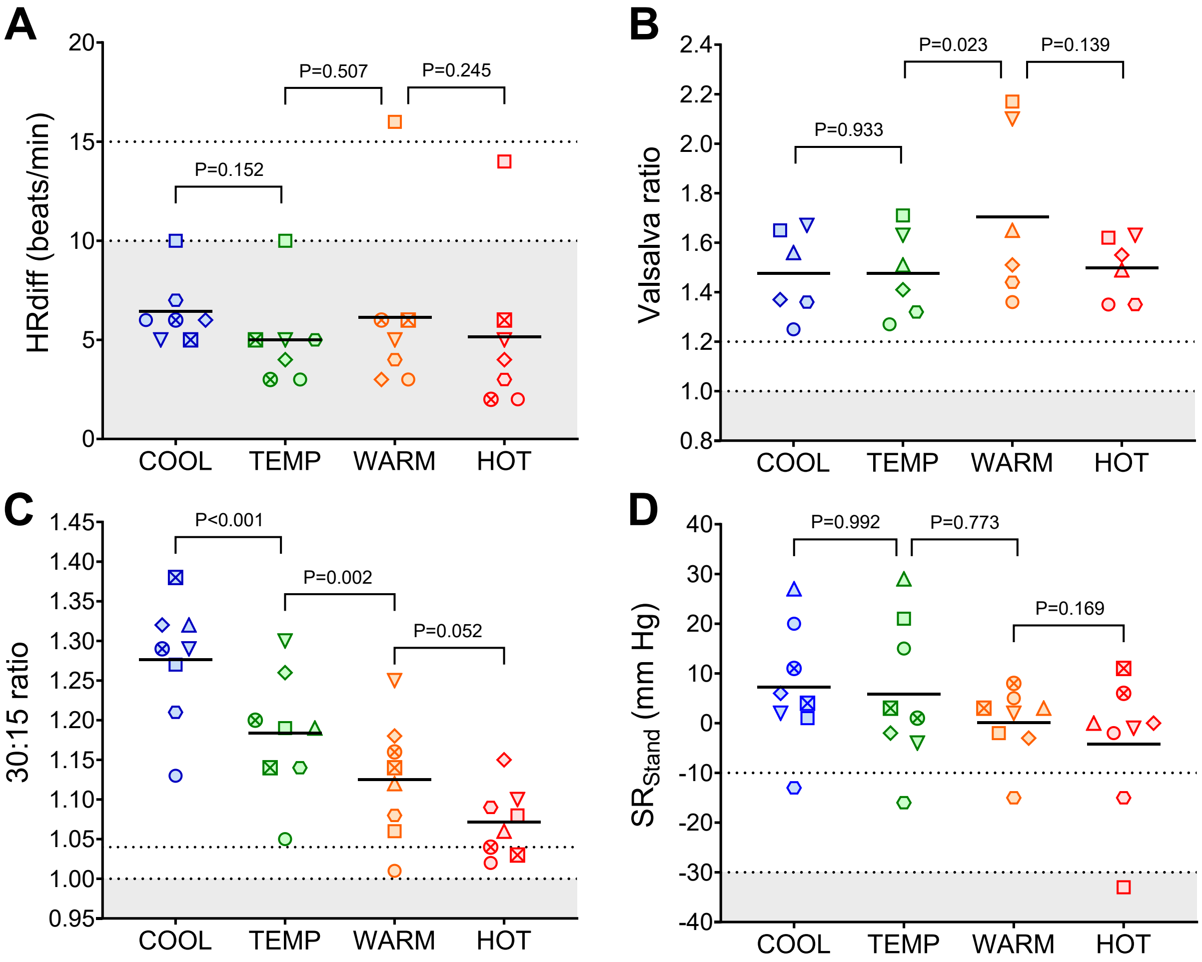


Figure 4. Ewing's battery tests for the older adults (n=8) at the end of the 8-hour exposure to COOL (22°C), TEMP (26°C), WARM (31°C) and HOT (36°C) conditions (relative humidity of 45% in each condition). These included the expiration-inspiration difference in heart rate (HRdiff), the ratio of the longest R-R interval during recovery divided by the shortest R-R interval during the Valsalva Maneuver (Valsalva ratio), the longest RR interval measured between the 20-40th heart beat upon standing from a supine position divided by the shortest RR interval between the 5-25th beat after standing (30:15 ratio) and the change in systolic blood pressure between supine and standing (systolic response to standing; SR_{Stand}). The white area between the dotted lines indicates a 'borderline abnormal' test, while the grey area indicates an 'abnormal' test, consistent with impaired autonomic function[395]. P-values indicate post hoc comparisons between model estimated marginal means (adjusted for baseline values) of adjacent conditions (following detection of a significant condition effect).

Hydration-related variables

The change in body mass (effect of condition: P=0.001) was 0.63% [0.2, 1.1] greater in HOT (-1.56 [0.78]%) compared to WARM (-0.96 [0.74]%; P=0.005) but was not different between WARM and TEMP (-0.76 [0.63]%; P=0.914) or TEMP and COOL (-0.78 [0.5]%; P>0.999). By contrast, the change in plasma volume (effect of condition: P=0.010) increased to a greater extent (4.0% [0.4, 7.6]) in WARM (2.7 [3.3]%) compared to TEMP (-1.3 [2.7]%; P=0.026) but was not different between TEMP and COOL (-2.4 [2.3]%; P=0.845) or WARM and HOT (-0.4 [3.1]%; P=0.103).

DISCUSSION

Here we assessed body temperature and cardiovascular responses in older adults resting in a range of conditions representative of those experienced indoors during extreme heat events in a temperate continental climate. While no differences in rectal temperature were observed between the cooler conditions (22°C and 26°C), participants experienced progressive elevations in body core temperature as ambient temperature increased (31°C and 36°C). Heart rate and mean arterial pressure were augmented and attenuated, respectively, with rising indoor ambient temperatures. Similarly, indices of autonomic function (as assessed by resting heart rate variability and Ewing's battery tests) were generally progressively blunted across the range of temperature conditions. These data indicate that, even under currently recommended indoor temperature guidelines, warm (>26°C) indoor environments may negatively impact the physiological responses supporting homeostasis and health.

Effect of indoor temperatures on body temperature responses

Most heat-related fatalities occur in the home[107,380]. It follows that guidance to limit indoor heat stress represents an important public health strategy to reduce the risk of heat-related mortality and morbidity in vulnerable populations[381]. Given the noted difficulties translating city- and/or country-level temperature mortality relations, which often form the basis for indoor temperature limits, to heat-related health risks for the individual, we felt an evaluation of the body temperature and cardiovascular responses of older adults resting in a range of simulated indoor conditions consistent with those experienced during extreme heat events was a warranted addition to the literature. In line with our hypothesis, the rectal temperature of older adults was not different between conditions below the Toronto Public Health recommended limit (≤26°C)[81,82]. Above this threshold, however, we observed progressive elevations in heat strain. Rectal temperature reached ~37.5°C during 8-hours of exposure to 31°C (WARM) and ~37.8°C during exposure to 36°C (HOT; Figure 1A & B); equivalent increases of 0.7°C and 1.1°C respectively, from the 22°C condition (COOL).

Based on our previous study, which employed a similar level of heat stress (3.2 Thesis Article 2), the stark increase in rectal temperature during the 36°C condition was not surprising. However, the elevation in thermal strain in the WARM condition is an important finding as this condition was below the World Health Organizations recommended day-time indoor temperature limit for extreme heat events (32°C), which they indicate *"… is especially important [to follow] for infants or people who are over 60 years of age or have chronic health conditions"*[83]. Although the level of hyperthermia in this condition was relatively modest (rectal temperature of ~37.5°C), it is possible that it could increase the risk of heat-related complications if sustained over multiple days[93]. While there currently little data to support this hypothesis, it is important to note that this thermal strain was associated with elevated cardiovascular burden (discussed below).

Indoor temperature and cardiovascular function

Resting cardiovascular responses

Elevations in body temperatures in the warmer indoor environments were accompanied by modulation of resting cardiovascular responses. Specifically, heart rate was elevated progressively with ambient temperature (Figure 2A & B), from 55 beats/min in COOL to 72 beats/min in HOT. Conversely, mean arterial pressure showed the reverse response, falling 16 mm Hg from COOL to WARM and another 3 mm Hg to HOT, though the difference between the latter two conditions was not statistically significant (Figure 2C & D). Regardless, the reductions in blood pressure were similar in magnitude to those observed in free-living older adults by Kim et al. (~3 mmHg/°C increase in indoor temp)[384]. Interestingly, however, rate pressure product, calculated as systolic blood pressure multiplied by heart rate and thought to be reflective of myocardial work[362,363] was not influenced by ambient conditions (Figure 2E & F).

These findings are consistent with our previous work, in which we demonstrated minor elevations in rate pressure product in older adults resting for 9 hours in simulated peak heat event conditions (3.2. Thesis Article 2). As we discussed in that report, the small increase in rate pressure product conflicts with current hypotheses on the impact of extreme heat events on the cardiovascular system, which suggest that elevated demand on the aging left ventricle precipitates the increases in cardiovascular mortality seen in older adults during extreme heat events[14,73,93,369]. In that study (3.2 Thesis Article 2), we did however observe large reductions in arterial pressure in 6 of 19 participants. The current findings therefore extend that work by demonstrating that heat-induced reductions in arterial pressure also occur, albeit to a lesser extent, in ambient conditions consistent with Toronto Public Health (26°C)[81] and the World Health Organization (32°C)[83] indoor temperature limits (Figure 2B & C).

Autonomic function

We also evaluated the influence of simulated indoor environments on cardiovascular autonomic function. Short-term blood pressure regulation is primarily under control of the autonomic baroreflex, which, under normal conditions, maintains blood pressure within a narrow range by adjusting heart rate (and peripheral resistance) in response to minute variations in central arterial and venous pressures[405]. In the current study, we delineated the effect of indoor heat stress on the functioning of this system by evaluating resting heart rate variability and through the clinically validated tests of the Ewing's battery. Regarding the former, we observed progressive reductions in RMSSD (Figure 3B), and the cardiac vagal index (Figure 3C), indicative of reduced parasympathetic modulation of heart rate[399,400]. While these findings are consistent with previous observations of heat stress-induced attenuations in heart rate variability in older adults resting in extremely hot conditions (44°C, 35% relative humidity)[393], this study is the first to demonstrate that these occur progressively with increasing ambient temperature.

These alterations were reflected in changes in the Ewing's battery tests of cardiovascular autonomic function. Specifically, the heart rate response to standing

(30:15 ratio) was blunted with increasing heat stress, with borderline abnormal values observed in 1 (12.5% of sample) and 3 (37.5%) participants in WARM and HOT, respectively (Figure 4C)[395]. While we did not detect any large effects on the group mean systolic blood pressure response to standing, 1 older adult had a severe reduction in blood pressure during this test in the hottest condition (Figure 4D) and could not maintain the standing position, and another participant indicated they felt very dizzy at the end of the 3-min stand. Again, these findings are consistent with the idea that older adults can experience disruptions in cardiac autonomic function during exposure to indoor heat stress that may place them at risk of heat-related falls or adverse cardiovascular events. However, the functional consequences of these findings to blood pressure control in free-living older adults requires further scrutiny (see Perspectives section below).

Perspectives

Our findings are consistent with previous observations of heat-induced blunting of autonomic cardiovascular function[406-408], which likely acted to compound age-related attenuation of heart rate variability[409] and blood pressure regulation[68]. However, blood pressure generally remained well-regulated during orthostatic challenge (Figure 4D). Given this study was conducted as a ‘proof-of-concept’, we specifically recruited relatively healthy and habitually active older adults, which may have preserved autonomic cardiovascular function from the natural age-related deterioration. In this respect, both SDRR (an index of overall heart rate variability[399]) and the heart rate response to standing (30:15 ratio) in the COOL condition exceeded the age-predicted mean in all but one participant[396,410]. It is crucial that future work be conducted to elucidate autonomic function in those with chronic health conditions, as these individuals are more susceptible to the adverse effects of extreme heat[93] and also exhibit attenuated indices of cardiovascular autonomic function in comparison to healthy age-matched controls[410]. Increased blood pressure variability and severe hypotension can lead to stroke and renal failure[371,372] and autonomic nervous system dysfunction may contribute to sudden cardiac death[373]. Furthermore, slower correction of mean arterial pressure following standing has been associated with reduced cerebral blood flow in normothermic older adults[394]. A further heat-induced blunting of this response, particularly in individuals with baseline reductions in function, may reduce orthostatic tolerance[168], thereby contributing to a greater risk of falls. The consequences of heat-induced deterioration of autonomic cardiovascular function in vulnerable population groups represents an important line of future inquiry.

Finally, it is likely that while a single day of heat exposure carries only moderate risk of heat-related mortality and morbidity in vulnerable groups, this risk is compounded over multiple days of exposure[381]. Indoor temperatures can rise steadily over the course of extreme heat events as heat is stored within the building during peak conditions and high night-time temperatures prevent its release[411]. There is also evidence to suggest that body temperature regulation may be perturbed over multiple days of heat exposure in older adults[374,375]. Beyond this, multiple days of heat exposure may have adverse effects on other facets of health. For example, sleep is sensitive to environmental conditions and elevated ambient temperature can lead to frequent sleep disturbances, especially in the elderly[412,413]. For instance, a 1°C increase in indoor temperature has been associated with a ~24% increase in sleep disturbance in healthy older adults[413]. Poor sleep quality is, in turn, associated with increased risk of mortality[414]. It is crucial that future work be conducted to determine the effects of elevated indoor temperatures on the health and well-being of vulnerable individuals over multiple days of exposure.

Considerations

A primary consideration of the current study was the environmental conditions employed. To ensure a standardized environment, we utilized set ambient temperatures and humidity in each trial. However, rising ambient humidity is associated with increased heat-related mortality[99] as well as elevated body heat storage and temperature[41]. Despite this, humidity is not considered in current indoor temperature guidelines[81]. While beyond the scope of any single study, it will be important for future work to evaluate the thermoregulatory and cardiovascular consequences through the *spectrum* of possible indoor ambient conditions (considering temperature, humidity, solar radiation, ventilation, etc.). With enough data, this would allow for more accurate determination of the conditions in which potentially dangerous body temperatures and cardiovascular responses begin to present.

As discussed in the perspectives, our findings are also limited to those without chronic health conditions linked with heat vulnerability such as type 2 diabetes and hypertension[93]. Future studies should therefore evaluate the effect of such conditions on the physiological responses to indoor heat stress. This would allow for more targeted indoor temperature guidelines for protecting all sectors of the population during extreme heat events, as current guidelines do not explicitly consider the factors contributing to heat vulnerability in older adults[81,83].

CONCLUSIONS

Indoor heat stress can increase body temperature and attenuate indices of cardiovascular autonomic function in healthy older adults, even at temperatures consistent with current recommendations. To inform the creation of more encompassing guidelines, it is important that future work explore the consequences of these findings to health and well-being, particularly in individuals with common chronic conditions that may limit their ability to appropriately respond to heat stress.

DISCLOSURES

There are no conflicts of interest, financial or otherwise, to disclose.

GRANTS

This research was funded by a research contract with Health Canada (Contract no.4500387992, funds held by Glen P. Kenny). G. P. Kenny is supported by a University of Ottawa Research Chair. R.D. Meade is supported the Human and Environmental Physiology Research Unit.

ACKNOWLEDGEMENTS

We thank all the participants who volunteered their time and Dr. Ashley Akerman, Dr. Sean Notley, Dr. Jeremy McCormick, Dr. Greg McGarr, Brodie Richards, and Emileigh Binet for their invaluable contributions to the project.

3.4 Thesis Article 4

Efficacy of a cooling-centre intervention for limiting thermal and cardiovascular strain in older adults exposed to a 9-hour simulated extreme heat event

ClinicalTrials.gov identifier: NCT04353076 (Intervention 2)

Key words: cooling centre, public health, aging, heatwaves, heat stress

Number of tables: 2

Number of figures: 2

ABSTRACT

Numerous national and international health agencies recommend that vulnerable individuals without home air-conditioning visit cooled locations (e.g., cooling centres) for 1-3 hours during extreme heat events. This short-term ambient cooling (STAC) is thought to *"…help [their] body stay cooler when [they] go back into the heat*". Despite this widespread guidance, there is little direct empirical evidence to support the effectiveness of cooling centres for protecting health. We therefore designed this study to assess the effectiveness of STAC for limiting elevations in body core temperature in older adults during a day-long simulated heat event. We hypothesized that while STAC would provide reprieve from hyperthermia, core temperature would rise rapidly upon re-exposure, quickly reaching levels similar to individuals not exposed to STAC. Nineteen older adults (72 [SD 4] years; 7 women) rested in ambient conditions of 40°C (~15% relative humidity) for 9 hours (no-cooling group). Another 8 older adults (71 [5] years; 3 women) were exposed to the same conditions but were moved to an air-conditioned room from hours 4-6 (~23°C; STAC group). Rectal temperature was monitored continuously. Rectal temperature at the end of the initial 3 hours was statistically equivalent (within ±0.3°C) in the STAC and no cooling groups (37.7 [0.3] vs 37.8 [0.3]°C; P=0.030). STAC reduced rectal temperature by 0.8°C [95% confidence limits: 0.6, 1.0] compared to the non-cooled group at the 6 hour time-point but rectal temperature was again equivalent in each group by the end of the 9-hour exposure (37.8 [0.3] vs 37.9 [0.3]°C; P=0.011). These results indicate that short-term cooling provides reprieve from hyperthermia in older adults during a day-long simulated extreme heat event, but only transiently. Core temperature quickly returns to pre-cooling levels upon re-exposure to the heat.

INTRODUCTION

With climate change, the global population is increasingly exposed to protracted periods of extremely hot temperatures[1]. Epidemiological data clearly highlight that hot weather and extreme heat events are accompanied by elevations in heat-related fatalities and hospitalizations, particularly in older adults (aged ≥65 years)[1,392] who exhibit a limited ability to cope with temperature extremes due to physiological[93] and socio-behavioral[6,9] maladaptations. Without progress toward climate adaptation the World Health Organization (WHO) predicts an additional 250,000 heat-related deaths per year globally in older individuals by 2050[12]. Mitigating the adverse health impacts of extreme heat in vulnerable populations such as the elderly is therefore a pressing public health concern.

The most effective means of protection from heat stress is household air-conditioning[6] but this strategy is cost-prohibitive and inaccessible to many individuals[415]. National and international health agencies including Health Canada[85], the United States Centres for Disease Control (CDC)[87] and WHO widely recommend that if access to prolonged cooling is not possible, a minimum of 1-3 hours per day be spent in an air-conditioned area (e.g., a cooling centre) to *"…help your body stay cooler when you go back into the heat*"[86]. Cooled common areas are also an accepted heat mitigation strategy used in long-term care and retirement facilities. The Ontario Long-Term Care Act, for example, requires a designated cooling area for every 40 residents for homes without central air-conditioning[416]. While there is support for the notion that those able to visit cooled locations are less likely to die during an extreme heat event[6,9], direct evidence linking the use of short-term ambient cooling with reduced mortality and morbidity is lacking[87]. Despite this, the CDC still recommends the use of cooling centres on the basis of a ‘high biological plausibility’ for their effectiveness[87]. However, the lack of empirical evidence for this claim makes it difficult to discern whether the protective value of visiting cooled locations is related to body cooling *per* se or other associated factors. For example, cooling centres may provide basic medical care[87] and those able to travel and access cooled locations are less likely to possess physical or psychological limitations preventing them from leaving the home or rendering them reliant on the care of others[417] – factors associated with increased risk of death during heat events[6,9].

The difficulty in evaluating the effectiveness of cooling centres has been ascribed to the unpredictable nature of extreme heat and challenges associated with surveilling usage by vulnerable groups[87]. This underscores the need for alternative strategies to gauge their effectiveness. One such strategy would be to directly assess whether short-term ambient cooling provides lasting reprieve from elevated body temperatures, as suggested by WHO[86]. We therefore designed this study to evaluate the efficacy of short-term cooling for limiting physiological strain in older adults. This was accomplished by comparing body temperature and cardiovascular responses in a group of older adults exposed to a simulated extreme heat event (40°C and ~15% relative humidity) for 9-hours, to a separate age-matched group removed from the heat to spend 2 hours resting in an air-conditioned environment midway through exposure (hours 5-6).

It was hypothesized that while short-term ambient cooling would provide reprieve from hyperthermia, this response would be transient. This is because body temperature is regulated through a negative feedback system in which elevations in core and skin temperatures elicit proportional activation of cutaneous vasodilation and sweating to facilitate heat loss and stabilize body temperature[24,35]. Thus, reductions in body temperature with cooling would suppress heat loss. Upon return to a hot environment, heat would be rapidly gained until body temperature rose to an extent sufficient to activate heat loss and re-attain thermal equilibrium.

METHODS

Ethical approval

This study was approved by the University of Ottawa Health Sciences and Science Research Ethics Board and conformed to the latest version of the Declaration of Helsinki. Written and informed consent was obtained from all volunteers prior to participation. This study was registered as part of a larger clinical investigation (ClinicalTrials.gov identifier: NCT04353076; Intervention 2).

Participants

Twenty-seven older adults (age: 64-78 years, 10 women) were recruited for the study and allocated to either the short-term ambient cooling (n=8) or no cooling (n=19) interventions. The latter group is the same as presented in Thesis Article 2 (Section 3.2). Participants were non-smokers and reported no history of metabolic or cardiovascular disease and were not taking prescription medications for these conditions. Their characteristics are summarized in Table 1.

Experimental design

The study involved one preliminary and one experimental session, the latter consisting of a 9-hour simulated extreme heat event (40°C and 15% relative humidity).

The no-cooling group was exposed to these conditions for the entire 9 hours whereas the short-term ambient cooling group completed the same protocol but were removed from the heat to spend 2 hours (hours 5-6) in an air-conditioned environment (~23°C). Participants were instructed to avoid strenuous activity and alcohol for 24 hours prior to all sessions. They were also asked to eat a light meal 2 hours before laboratory visits and to consume a minimum of ~500 ml of water the night before and morning of each session to ensure adequate hydration. This was verified upon arrival, with euhydration operationally defined as a urine specific gravity <1.025[354]. ~500 mL of tap water was provided to participants who exceeded this threshold, and urine specific gravity was tested again after ~30 min. For each session, participants wore only athletic shorts and footwear (women also wore a sport top).

Preliminary screening

The preliminary screening session was completed at least 48 hours prior to the first experimental session. Participants were familiarized with all experimental procedures and measurement techniques. They also completed the Get Active Questionnaire (GAQ) and the American Heart Association Pre-participation screening Questionnaire to assess their eligibility to participate. The GAQ was also used to assess habitual activity levels[355]. Participant physical characteristics were then evaluated. Body height was determined via a physician stadiometer (Detecto, model 2391, Webb City, MO, USA) and mass was measured with a high-performance weighing terminal (model CBU150X, Mettler Toledo Inc., Mississauga, ON, Canada). Body surface area was calculated from these measurements[356] while body fat percentage was estimated via hydrostatic weighing[357].

Experimental session

The experimental sessions commenced between 07:00-08:00. After arriving to the laboratory and providing a urine sample, participants inserted a rectal temperature probe (Mon-a-therm General Purpose Temperature Probe, Mallinckrodt Medical Inc., St-Louis, MO, USA) and were instrumented for the measurement of skin temperature (DS1922L Thermochron, OnSolution Pty Ltd, Australia). Baseline cardiovascular responses were then measured with participants resting quietly in the seated (but slightly reclined) position with both feet placed flat on the floor. To start, arterial pulse waveforms were measured at the right middle finger for 10 min (Finometer Pro, Fina-press Medical Systems, Amsterdam, Netherlands) and subsequently used for evaluation of resting cardiac output and spontaneous cardiac baroreflex sensitivity (an index of cardiovascular autonomic function)[358,359]. Arterial systolic and diastolic pressures were then measured in triplicate via manual auscultation.

Participants then entered the Snellen whole-body air calorimeter (a unique device allowing for the direct measurement of whole-body heat exchange[135,360]). The calorimeter was regulated to 40°C and ~15% humidity (heat index: 38°C), conditions chosen to simulate peak temperatures experienced during extreme heat events and were similar to peak conditions measured during recent events in North American in 2018 (heat index: 41°C[46]) and Europe in 2003 (heat index: 38°C[48]). During the first 3 hours (hours 1-3) participants rested within the calorimeter chamber while whole-body heat production and exchange were measured continuously. The participant exited the calorimeter after 3 hours and cardiovascular responses were measured again.

The short-term ambient cooling group were removed from the heat to spend hours 5-6 seated in an air-conditioned (23°C, ~50% relative humidity) room. The no-cooling group remained seated within the heated thermal chamber housing the calorimeter during this time (40°C, 15% relative humidity). Both groups were able to consume a light (~300 g), self-provided lunch with low water content (e.g., peanut butter sandwich) and tap water was available ad libitum. Cardiovascular responses were evaluated again at the end of this period. The final 3 hours (hours 6-9) were spent resting while seated within the calorimeter. Thereafter, a fourth and final set of cardiovascular measurements were taken before the participant was provided with water and/or a commercially available sports drink prior to departure from the laboratory.

Measurements

Whole-body heat exchange

The Snellen direct air calorimeter was used to measure rates of whole-body dry and evaporative heat loss[135,360]. Calorimeter inflow and outflow values of air temperature and absolute humidity were measured every 8 seconds with high precision resistance temperature detectors (Black Stack model 1560, Hart Electronics, UT, USA) and dew point hygrometers (RH Systems model 373H, Albuquerque, NM, USA), respectively. Air mass flow, equivalent to ~0.3 m/s where the participant is seated[360], was measured using differential thermometry over a known heat source placed in the effluent air stream. Data were displayed and recorded with LabVIEW software (Version 7.0, National Instruments, Austin, TX, USA). Dry heat loss was derived as the outflow–inflow difference in absolute air temperature, multiplied by air mass flow and specific heat capacity of air (1005

J/kg/°C). Dry heat loss was negative since ambient temperature (40°C) was greater than that of the skin (~35-36°C) and will therefore be referred to as a dry heat gain hereafter (positive values indicating heat gain). Evaporative heat loss (heat loss via sweating) was similarly derived from the outflow–inflow humidity difference, air mass flow, and the latent heat of vaporization of sweat (2426 J/g).

Metabolic energy expenditure was measured via indirect calorimetry. Oxygen and carbon dioxide concentrations of expired air drawn from a 6 L fluted mixing box located within the calorimeter were assessed with electrochemical gas analysers (AMETEK model S-3A/1 and CD 3A, Applied Electrochemistry, Bastrop, TX, USA). Expelled air was recycled back into the chamber to account for respiratory heat exchange. The gas analyzers and turbine ventilometer were calibrated ~30 min prior to each calorimetry measurement period. Metabolic heat production was assumed to be equivalent to metabolic energy expenditure since no external work was performed[135].

Body temperatures

Rectal temperature was monitored continuously with a thermocouple probe (Mon-a-therm General Purpose Temperature Probe) inserted ~12 cm past the anal sphincter. Skin temperature was assessed at 8 locations, as described in ISO 9886:2004 (forehead, right scapula, upper left chest, upper right arm, right forearm, left hand, right anterior thigh, and left calf)[361], using surface temperature monitors (DS1922L Thermochrons).

Cardiovascular responses

Triplicate measures of arterial systolic and diastolic blood pressures were taken at the brachial artery via manual auscultation (~30 s between measures). Data was presented as an average of those three measurements. Cardiac output was determined via model flow analysis of beat-to-beat recordings of arterial pressure waveform measured at the right middle finger (Finometer Pro)[358,359]. These were also used to determine cardiac baroreflex sensitivity, an index of cardiac autonomic modulation, using provided software (PRVBRS, Fina-press Medical Systems, Amsterdam, Netherlands)[358]. Heart rate was taken as an average the final 5 min of the 10-min recording window.

Data analysis

Cumulative body heat storage during each calorimeter session was derived as the summation of total heat gain (metabolic heat production + dry heat gain) minus evaporative heat loss. Mean skin temperature was calculated using the weightings: forehead (7%), right scapula (17.5%), upper left chest (17.5%), upper right arm (7%), right forearm (7%), left hand (5%), right anterior thigh (19%) and left calf (20%)[361]. Rectal and mean skin temperatures were converted to 15-min averages for each hour of exposure. Mean body temperature was derived as 0.9 × rectal temperature + 0.1 × mean skin temperature[22]. From the cardiovascular data, mean arterial pressure was calculated as 2/3 diastolic pressure + 1/3 systolic pressure whereas rate pressure product, an index of myocardial work[362,363], was calculated as heart rate × systolic pressure. Stroke volume was determined as cardiac output ÷ heart rate × 1000.

Statistical analysis

An a priori power analysis determined that a sample size of 18 older adults in each group (36 participants total) was required to confirm whether rectal temperature responses were *equivalent* within upper and lower bounds of +0.3°C and -0.3°C, respectively, with 80% power. This corresponds to an effect size (Cohen's *d*) of 1.0, based on a pooled-standard deviation of 0.3°C, determined from published data from our laboratory demonstrating a 0.2°C (SD 0.3) and 0.0°C (SD 0.3) difference in rectal temperature between young and older adults[40] and older adults with and without type 2 diabetes[287], respectively, following 3 hours of rest in a hot environment. The goal was to recruit 40 total participants, to ensure equal sample sizes with the older group from Thesis Article 3 (Section 3.3). We were not able to meet this target for the current report due to the COVID-19 pandemic. The findings should therefore be considered exploratory.

Baseline participant characteristics and body temperatures (rectal, mean skin and mean body) were compared between groups using two-tailed independent t-tests. The cumulative body heat storage was analyzed with a mixed-effects model with the factors of time (repeated; 2 levels: first and final 3 hours) and group (independent; 2 levels: no-cooling and short-term ambient cooling group). Homoscedasticity and normality of residuals were evaluated via visual assessment of residual and Q-Q plots. Post hoc multiple comparisons were performed according to Sidak's procedure.

Two one-sided tests were employed to assess the equivalence of the body temperature and cardiovascular responses at each of the following time points: baseline (hour 0), end of the initial exposure (hour 3), end of the short-term ambient cooling intervention (hour 6), and end of extreme heat simulation (hour 9). Briefly, this procedure involves two one-sided tests to evaluate whether a between-group mean difference is i) greater than a pre-specified lower bound and ii) smaller than pre-specified upper bound[418]. For our primary outcome of interest, rectal temperature, these bounds were set to ±0.3°C. This value corresponds to the typical day-to-day variation of resting body core temperature[402] and has been suggested to reflect a clinically meaningful change in body temperatures in a recent study assessing the influence of cooling strategies on physiological strain in young adults[377]. For the exploratory analysis for the other physiological variables, the equivalence threshold was set as the pooled between-group standard deviation over the first 3 hours of heat exposure (i.e., ±1 Cohen's *d*). The null hypothesis is taken as a meaningful difference between groups and its rejection therefore constitutes a functional equivalence of means.

Statistical analysis was performed using Prism (Version 8, GraphPad Software) and the TOSTER package[418] for R (Version 3.6.1, R Development Core Team, 2018). The threshold for significance was set at $P<0.050$. For the equivalence testing, the P-value corresponds to the greater of the two values comparing the between group mean difference to the upper and lower bounds. Descriptive statistics were presented as mean (standard deviation) and comparisons between groups were presented as mean and 95% confidence interval for null-hypothesis significance testing (i.e., mixed effects model) and mean and 90% confidence interval for equivalence testing [lower limit, upper limit].

RESULTS

Participant characteristics

The short-term ambient cooling and no-cooling groups did not differ significantly in any evaluated characteristic (Table 1).

Table 1. Physical characteristics of the participants in the short-term cooling (n=8) and no-cooling (n=19) groups.

	Short-term cooling group		No-cooling group		
	Mean (SD)	Min-max	Mean (SD)	Min-max	P-value[d]
Women/men (n)	3 / 5		7 / 12		
Age (years)	71 (5)	67 - 78	72 (4)	64 - 78	0.535
Height (m)	1.69 (0.08)	1.57 - 1.76	1.69 (0.10)	1.45 - 1.90	0.912
Mass (kg)	78 (17.6)	59.8 - 116.2	70.5 (11.1)	47.6 - 91.2	0.171
A_D (m^2)[a]	1.9 (0.2)	1.7 - 2.3	1.8 (0.2)	1.4 - 2.1	0.264
Body fat (%)	29 (8)	20 - 39	30 (8)	18 - 47	0.571
Body mass index[b]	27.1 (4.7)	21.7 - 37.5	24.8 (3.4)	18.7 - 30.0	0.161
Aerobic activity (min/week)[c]	119 (102)	0 - 300	155 (153)	0 - 420	0.551

Notes: [a]A_D, body surface area[356]; [b]body mass index calculated as body mass/height^2. [c]Aerobic activity (min/week) levels as self-reported time spent performing moderate-to-vigorous physical activity (i.e., exercise, work, or sports), as defined by the Canadian Society for Exercise Physiology[355]. [d]P-values indicate results from an unpaired, two-tailed t-test.

Whole-body heat storage

Cumulative heat storage was not different between groups over the first 3 hours of the 9-hour extreme heat exposure (P=0.798; Figure 1B). After short-term cooling, heat storage over the final 3 hours was 240 kJ [155, 324] greater compared to the group of older adults not removed from the heat (P<0.001; Figure 1C).

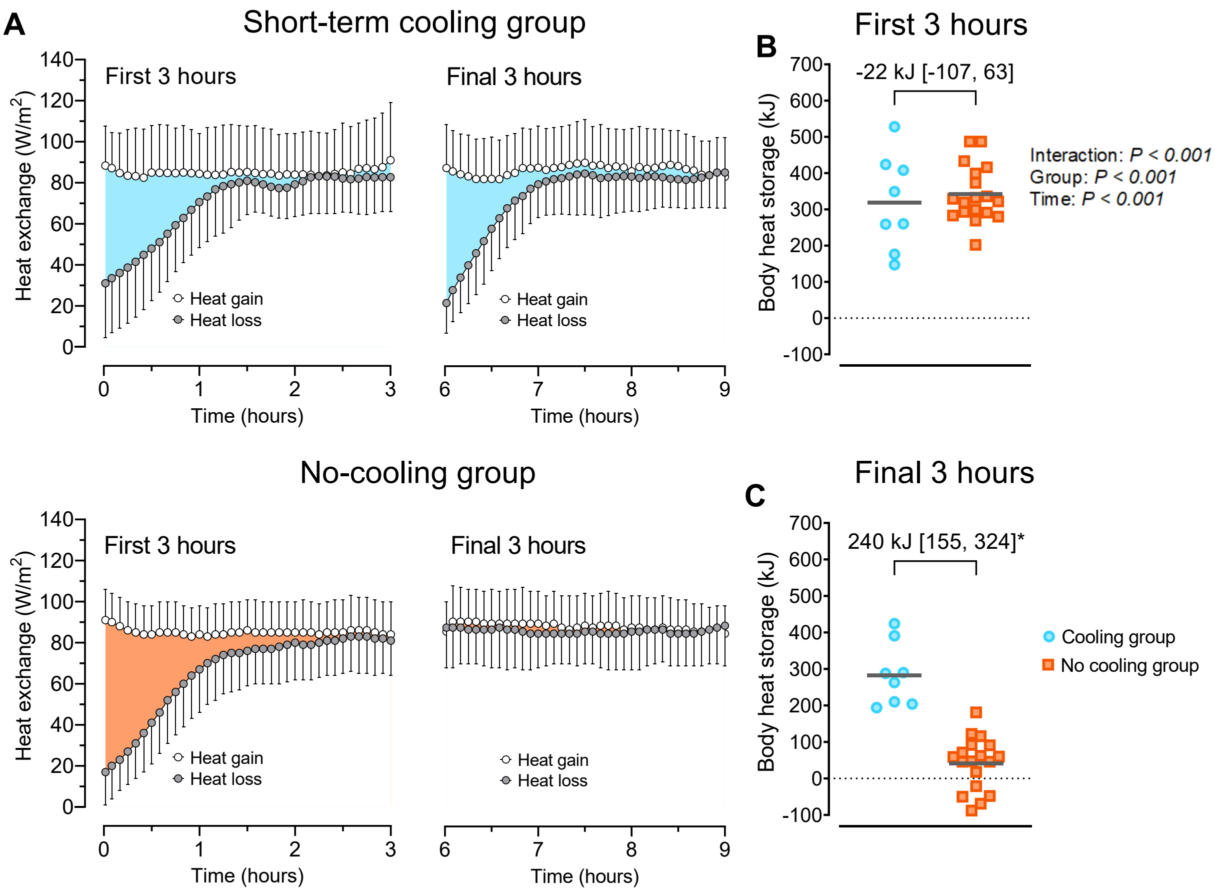


Figure 1. Time-course changes (mean ± standard deviation) in whole-body heat gain (metabolic heat production + dry heat gain) and heat loss (evaporative heat loss) in the short-term ambient cooling groups (n=8, top panel A, blue) and the no-cooling (n=19, bottom panel A, orange) during the first and final 3-h of resting heat exposure (40°C, ~15% relative humidity). Data are presented as mean ± standard deviation. Also depicted is the cumulative increase in body heat storage in the no-cooling (orange symbols and shaded area) and short-term ambient cooling groups (blue symbols and shaded area) over the first (panel B) and final (panel C) 3 hours. *, significant difference in heat storage between groups (P<0.001).

Body temperature responses

No differences in rectal (short-term ambient cooling: 36.9 [0.2] vs no-cooling: 37.0 [0.3]°C; P=0.123), mean skin (31.6 [0.3] vs 32.1 [0.8]°C; P=0.135) or mean body temperature (36.5 [0.4]°C vs 36.4 [0.2]°C; P=0.511) were observed between groups at baseline. After the first 3 hours of exposure, rectal temperature (Figure 2A & B) was equivalent within 0.3°C in each group (P=0.030). Short term ambient cooling reduced rectal temperature by 0.8°C [0.6, 1.0] but by the end of the 9-hour exposure rectal temperature was equivalent in each group (P=0.011). Similarly, while ambient cooling reduced mean skin temperature (Figure 2C & D) and mean body temperature (Figure 2E & F) by 4.2°C [3.8, 4.6] and 1.1°C [1.0, 1.3], respectively, responses in each group were equivalent within 0.5°C (P=0.026) and 0.3°C (P=0.016) at the end of exposure.

Cardiovascular responses

At the end of the day-long heat exposure, heart rate, rate pressure product, and baroreflex sensitivity were equivalent in the no-cooling and short-term ambient cooling groups within 11 beats/min (P=0.022), 1815 mm Hg·beats/min (P=0.032), and 4 ms/mm Hg (P=0.001), respectively. By contrast, cardiac output (threshold: ±0.8 L/min, P=0.483), stroke volume (±13 mL/beat, P=0.269), and mean arterial pressure (±9 units mm Hg·beats/min, P=0.133) responses in each group were not statistically equivalent.

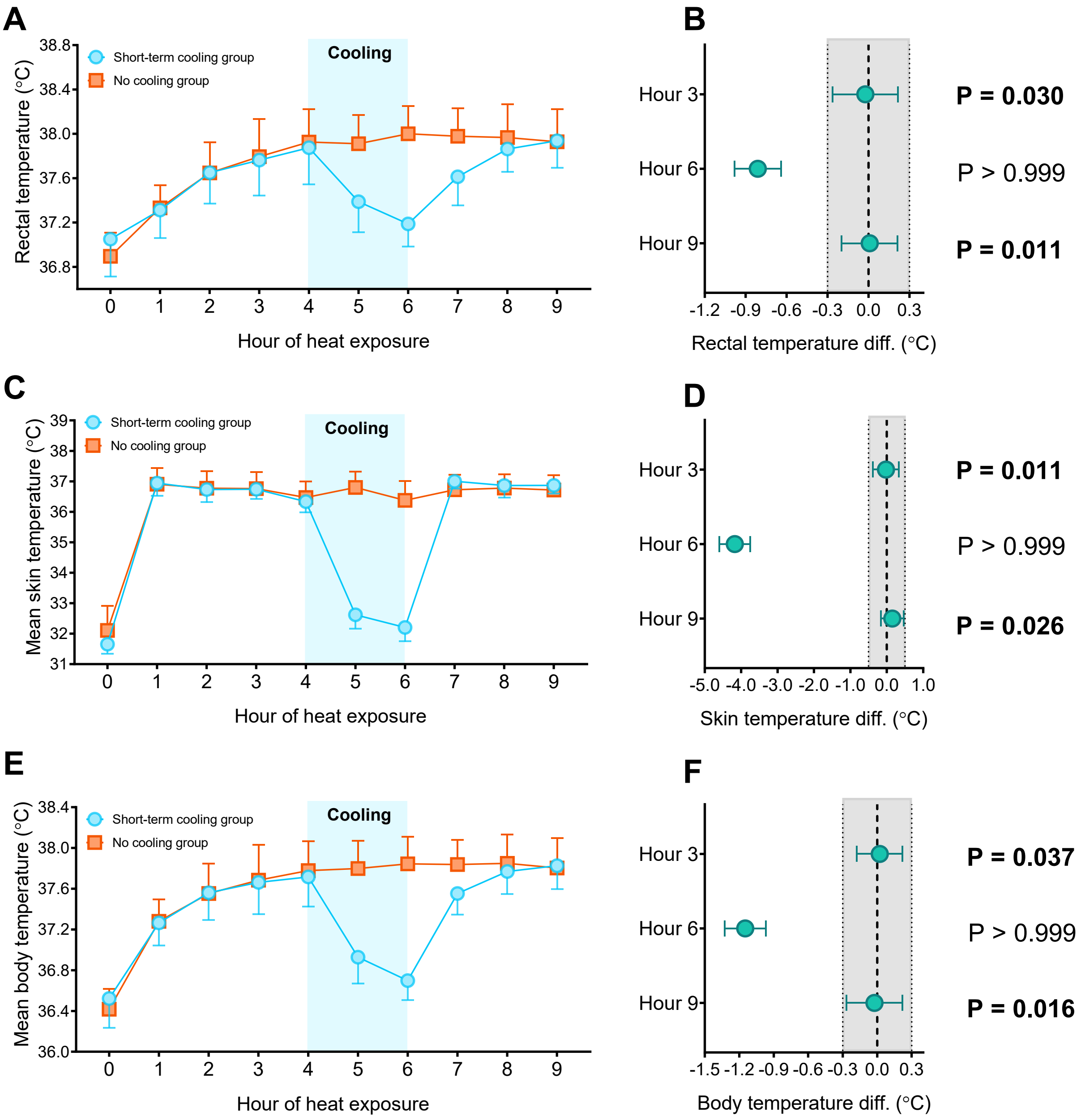


Figure 2. Time-course changes (mean ± standard deviation) in rectal (panel A), mean skin (panel C) and mean body (panel E) temperature in the no-cooling (n = 19, orange symbols) and short-term cooling groups (n = 8, blue symbols) over the 9-hour resting heat exposure (40°C, ~15% relative humidity). Also depicted is the mean ± 90% confidence interval for the between-group difference at 3, 6 (during cooling) and 9 hours time points (panels B, D and F). P-values represent the results from an equivalence test (two one-sided tests). For rectal temperature, equivalence was set at the pre-determined threshold of 0.3°C. For mean skin temperature and mean body temperature, the threshold was set as the between-group pooled standard deviation for each response over the first 3 hours of exposure.

Table 2. Cardiovascular responses in the short-term cooling (n=8) and no-cooling (n=19) groups during the 9-hour extreme heat exposure.

Variable	Time	Short-term cooling group	No-cooling Group	Mean diff[a]	NHST[b]		Equivalence Test[c]		
					95% CI	P-value	90% CI	P-value	Bounds
Heart rate	Baseline	65 (7)	64 (9)	1	-6, 8	0.786	-5, 7	**0.002**	± 11
beats/min	3 hours	76 (9)	76 (13)	1	-10, 11	0.451	-8, 9	**0.020**	
	6 hours	68 (7)	77 (14)	-9	-19, 1	**0.031**	-17, -1	0.295	
	9 hours	78 (10)	78 (14)	0	-11, 11	0.404	-9, 9	**0.022**	
Cardiac output	Baseline	4.2 (0.7)	3.6 (0.6)	0.6	0.1, 1.1	**0.028**	0.2, 1.0	0.232	± 0.8
L/min	3 hours	4.5 (0.9)	3.7 (0.8)	0.8	0.1, 1.5	**0.029**	0.2, 1.4	0.509	
	6 hours	4.7 (1.0)	4.2 (0.7)	0.5	-0.2, 1.2	0.162	-0.1, 1.10	0.206	
	9 hours	4.4 (1.3)	3.6 (0.6)	0.8	0.1, 1.5	**0.040**	0.2, 1.4	0.483	
Stoke volume	Baseline	66 (14)	58 (12)	8	-3, 19	0.135	-1, 17	0.196	± 13
mL/beat	3 hours	61 (15)	51 (14)	10	-3, 22	0.116	-1, 20	0.295	
	6 hours	70 (17)	55 (12)	14	3, 26	**0.017**	5, 24	0.602	
	9 hours	57 (18)	48 (11)	9	-2, 21	0.098	0, 19	0.269	
Mean arterial pressure	Baseline	92 (8)	92 (9)	0	-7, 8	0.945	-6, 7	**0.023**	± 9
mL/beat	3 hours	85 (8)	85 (10)	0	-9, 8	0.957	-7, 7	**0.032**	
	6 hours	88 (7)	81 (8)	14	3, 26	**0.041**	5, 24	0.856	
	9 hours	87 (8)	84 (11)	3	-6, 12	0.505	-4, 11	0.133	
Rate pressure product	Baseline	8167 (1008)	8152 (1616)	13	-1268, 1294	0.981	-1049, 1076	**0.004**	± 1815
mm Hg·beats/min	3 hours	8554 (1652)	9046 (1873)	-456	-2032, 1121	0.526	-1763, 852	**0.042**	
	6 hours	8306 (705)	9005 (1894)	-699	-2133, 735	0.325	-1888, 491	0.058	
	9 hours	9191 (1222)	9078 (2117)	119	-1526, 1764	0.905	-1245, 1484	**0.021**	
Baroreflex sensitivity	Baseline	5.4 (1.2)	6.6 (4.6)	-1.2	-4.6, 2.2	0.525	-4.0, 1.6	**0.045**	± 4
ms/mm Hg	3 hours	4.6 (3.1)	4.2 (2.9)	0.4	-2.2, 3.	0.776	-1.8, 2.6	**<0.001**	
	6 hours	5.8 (1.9)	4.8 (4.5)	1.0	-2.4, 4.4	0.616	-1.9, 3.8	**0.002**	
	9 hours	4.5 (3.0)	4.1 (3.2)	0.4	-2.3, 3.1	0.792	-1.8, 2.7	**0.001**	

Notes: Data presented as mean (standard deviation). Cardiovascular responses presented a baseline (hour 0) and at 3, 6 and 9 hours of the resting heat exposure (40°C, ~15% relative humidity). Older adults in the no-cooling group (n = 19) remained in the heat for the entire 9 hours, while participants in short-term cooling group (n = 8) were removed from the heat to spend hours 4-6 in an air-conditioned room. [a]Mean difference (mean diff.) calculated as short-term cooling group – no cooling group. [b]Null hypothesis significance test (NHST) analysis reported as 95% confidence interval (95% CI) for the mean difference between groups and P-value for a two-tailed independent t-test. [c]Equivalence analysis reported as 90% confidence interval (90% CI) for the mean difference between groups and P-value for two one-sided tests comparing the mean difference to pre-specified bounds (set as the pooled standard deviation for data measured at the 3-hour point). Statistical significance was set at P<0.050 for both analyses.

DISCUSSION

Here, we evaluated the efficacy of short-term ambient cooling, as experienced in a cooling centre, for limiting hyperthermia and cardiovascular burden during a 9-hour simulated extreme heat event (45°C, 15% relative humidity). As hypothesized, cooling reduced core and skin temperatures but heat was rapidly stored in the body upon re-exposure and body temperatures in the older adults exposed to the cooling intervention quickly returned to levels similar to age-matched controls who remained in the heat. These findings indicate that while cooling centres provide reprieve from hyperthermia during an extreme heat event, the effect is temporary.

Short-term ambient cooling and body temperature regulation

With the increasing incidence and severity of extreme heat events and growing global rates of heat-related mortality[1], there is burgeoning interest in the development of evidence-based cooling strategies for protecting the health and well-being of those exposed to extreme heat, particularly vulnerable individuals such as older adults[17,18]. For those without access to air-conditioning, national and international health agencies including Health Canada[85], CDC[87], and WHO[86] suggest that 1-3 hours per day be spent in an air-conditioned environment such as a cooling centre. This recommendation is based primarily on observational data indicating that those able to visit cooled locations are less likely to die during an extreme heat event[6,9], rather than direct evidence linking the use of cooling centres with reduced mortality and morbidity. Since epidemiological data are not forthcoming[87], alternative methods to gauge the effectiveness of cooling centres and other personal heat-mitigation strategies are required.

We therefore designed this study to evaluate whether cooling centres provide lasting reprieve from elevated body temperatures, as suggested by WHO and the CDC[86], during a prolonged, simulated extreme heat event (9 hours, 40°C, 15% relative humidity). Short-term ambient cooling caused a ~0.9°C and ~2.0°C reduction in rectal and mean skin temperatures, respectively (Figure 2). Upon re-exposure, however, heat was rapidly stored within the body (Figure 1) and body temperatures quickly returned to levels equivalent to the group that remained in the heat (Figure 2). While this study is the first to evaluate the impact of short-term ambient cooling during a simulated extreme heat event, ample research has assessed the effect of similar interventions in other contexts. For example, whole-body pre-cooling is thought to benefit endurance exercise performance by delaying the development of hyperthermia[419]. As with our data, however, this effect is transient. Booth et al.[420] and Zimmerman et al.[421] observed that while pre-cooling reduced body core temperature by ~0.7-0.9°C, this effect had abated by the end of the 30 and 38 min exercise bouts in the respective studies.

The transient impact of cooling is related to the physiological organization of the human thermoregulatory system. During heat stress, elevated metabolic and/or environmental heat gain causes an increase in core and skin temperatures, which activate reflex cutaneous vasodilation and sweating to facilitate heat loss. Because this system operates in a negative feedback loop, body temperature and heat loss will increase in tandem until the latter matches the rate required to offset heat gain[24,35]. That is, while an increase in heat loss is needed to prevent potentially dangerous levels of hyperthermia during heat stress, the accompanying elevation in body temperature is required to activate heat loss to an extent sufficient to do so. This is clearly evidenced by our findings of the rapid increase in heat storage following the cooling intervention (Figure 1), which caused core temperature to return to levels equivalent to the group of older adults not removed from the heat (Figure 2). Likewise, both Booth et al.[420] and Zimmerman et al.[421] observed that the activation of sweating was delayed following the onset of exercise in the pre-cooling compared to control (no-cooling) condition. As a result, heat was gained more rapidly in the former and core temperatures in each condition converged as exercise progressed[420,421]. All this to say that the increase in body temperature during exposure to a given environment is physiologically determined. Cooling is therefore only effective for limiting hyperthermia for as long as it is applied.

Cooling and cardiovascular responses

We also explored whether short-term ambient cooling was effective for reducing cardiovascular strain (Table 2). Cooling attenuated heart rate and increased mean arterial pressure and stroke volume compared to the no cooling group. By the end of exposure, however, heart rate, rate pressure product, and baroreflex sensitivity were equivalent between groups. While cardiac output, stroke volume and mean arterial pressure were not equivalent following return to the heat, none except for cardiac output reached the threshold for a statistically significant difference between groups (Table 2). This was unsurprising given that the cardiovascular adjustments to heat stress are primarily driven by elevations in core and skin temperatures[63]. Though these findings support our hypothesis that ambient cooling does not have a lasting effect on cardiovascular responses, the exploratory nature of this analysis must be considered (see Considerations section below). Given that up to 90% of fatalities during extreme heat events occur due to causes of cardiovascular origin (e.g., cardiac arrest, stroke)[93], studies are needed to more firmly elucidate whether short-term ambient cooling lessens cardiovascular burden during extreme heat events.

Perspectives

While numerous national and international health agencies advocate the use of cooling centres[85-87], direct evidence for their effectiveness for reducing heat-related mortality and/or morbidity is unavailable[87]. This recommendation is instead based on observational studies linking visiting cooled locations with a reduced risk of dying during extreme heat events[6,9]. The CDC further justifies the use of cooling centres by citing a high biological plausibility for their effectiveness[87]. Accessible, cooled common areas is also the standard method for protecting residents of long-term care and retirement facilities from heat stress when air-conditioning is not available or feasible for individual domiciles[416]. In this report, we have demonstrated that the physiological impacts of cooling centres are transient. While this does not necessarily indicate that visiting a cooled location is an ineffective means for protecting vulnerable groups from the adverse health impacts of extreme heat (see Considerations section below), our findings are inconsistent with the published guidance that "*even a few hours spent in an air-conditioned place can help your body stay cooler when you go back into the heat*"[86].

In light of the absence of direct evidence to support the effectiveness of cooling centres, this discrepancy highlights the need for further research before cooling centres can be advocated as an evidence-based public health strategy. First and foremost, the causal links between visiting cooled locations and reduced risk of dying during an extreme heat event[6,9] must be firmly delineated; it is not currently clear whether this association is related to cooling *per se* or related factors. For example, visiting public locations presumably increases the likelihood that an individual experiencing an adverse reaction to heat stress receives medical attention. Indeed, increased social contact has been associated with a reduced risk of mortality during extreme heat events[9]. Further, older adults confined to the home or reliant on the care of others are at elevated risk of death during extreme heat events[6,9] and are also less likely to visit cooled locations such as cooling centre or cooled common areas[88,417]. The contribution of these potentially confounding factors to the purported benefits of short-term ambient cooling during extreme heat events represents an important knowledge gap.

Future extreme heat simulations can be used to compliment traditional epidemiological research evaluating the effectiveness of personal heat mitigation strategies. Such a holistic approach is warranted, as the health impacts of extreme heat events are notoriously difficult to quantify. Often, the full extent of the damage is not known until retrospective analysis reveals increased mortality and morbidity during the heat event relative to a control period (e.g., corresponding months of previous years)[47]. The effectiveness of public health interventions is evaluated similarly. For example, reductions in heat-related mortality in the 1999 compared to 1995 extreme heat events in Chicago and St. Louis in the United states[422] have been taken as evidence for improved public health response between the two events[423]. However, such analyses do not allow for discrimination of the specific strategies (e.g., cooling centres, heat warnings) that were most effective and whether they reached the most vulnerable sectors of the population. By allowing for direct evaluation of the physiological responses supporting health, increased use of extreme heat simulations will allow public health practitioners to more quickly identify and implement efficacious cooling strategies where epidemiological study has elsewise proven difficult. It is our view that this holistic approach will increase precision and reduce the lag time in implementing effective and targeted guidance to protect vulnerable persons from extreme heat, ultimately saving lives.

Considerations

A key limitation of the current report is that our analysis was primarily exploratory, with the thresholds for the equivalence tests mostly based on the distribution (pooled standard deviation) of physiological responses over the first 3 hours of exposure. Ideally, these thresholds would be set at an a priori determined minimal clinically important difference[424] – that is, the cooling centre-induced reduction in heart rate or mean arterial pressure (for example) that would confer some benefit to health upon re-exposure to the heat. While other studies employing short-term extreme heat exposure to evaluate the effect of personal heat mitigation strategies (electric fan use) have contextualized their findings in reference to clinically meaningful thresholds, these were based on outcomes in patients with heart failure and soldiers[370] or the supporting information was not provided[377]. Thus, an important step for future work is the determination of context-specific clinically meaningful differences for incorporation into future extreme heat simulation studies, increasing their usefulness for informing public health guidance.

Finally, while our findings indicate that cooling centres do not provide prolonged respite from elevated body temperatures, there are other mechanisms through which they may protect health. For instance, we employed a static model where environmental conditions were fixed throughout the 9-hour exposure. However, visiting a cooled location mid-day may protect individuals from the peak day-time hours during a natural extreme heat event. It is also possible that the reprieve from elevated body temperatures has a positive influence on other determinants of health and well-being known to be impacted by extreme heat, but not measured in the current study. For example, future work should be conducted to evaluate the effect of cooling centres on body fluid and electrolyte balance, oxidative stress, inflammatory status[93], and sleep quality[412,413], particularly over multiple days of heat exposure as occurs during an extreme heat event. In this regard, we recently showed that a full day of heat exposure causes next-day impairments in fluid regulation and thermoregulatory function in older workers[374,375]. Whether similar effects occur during extreme heat events remains to be seen.

CONCLUSIONS

In this study we demonstrated that short-term ambient cooling, as experienced in a cooling centre, provides transient reprieve from hyperthermia during a day-long extreme heat simulation. Upon return to a hot environment, however, body temperatures rose rapidly, quickly returning to pre-cooling levels. These findings are inconsistent with guidance on cooling centre use published by WHO and CDC. More research is therefore required to determine whether visiting cooled locations is efficacious for protecting the health of heat-vulnerable older adults during an extreme heat event.

DISCLOSURES

There are no conflicts of interest, financial or otherwise, to disclose.

GRANTS

This research was funded by the Canadian Institutes of Health Research (Grant no. 39943; funds held by Glen P. Kenny). G. P. Kenny is supported by a University of Ottawa Research Chair. R.D. Meade is supported the Human and Environmental Physiology Research Unit.

ACKNOWLEDGEMENTS

We thank all the participants who volunteered their time and Dr. Sean Notley, Dr. Ashley Akerman, Dr. Jeremy McCormick, Dr. Greg McGarr, Emma McCourt, Brodie Richards, and Emileigh Binet for their invaluable contributions to the project.

CHAPTER 4 – THESIS DISCUSSION

4.1 Summary of findings

With increasing global temperatures and growing incidence, severity, and duration of extreme heat events, the development of evidence-based strategies to protect vulnerable sectors of the population from heat stress is critically important[1,2]. This has led to calls for increased use of physiological study to compliment public health research on the effects of climate change on health[17] and effectiveness of heat mitigation strategies[18]. To date, however, our understanding of the physiological responses to heat stress in vulnerable groups such as older adults has come primarily from studies employing exposures not representative of what is actually experienced during heat events[93]. This thesis was therefore designed as a first step in the development of ecologically minded extreme heat simulation studies for assessing the effectiveness of heat exposure guidelines and mitigation strategies for protecting vulnerable groups such as older adults.

The first article of the thesis (3.1 Thesis Article 1) was a comprehensive narrative review evaluating our current understanding of age- and chronic disease-related impairments in thermoregulatory, cardiovascular, and fluid regulatory responses to heat stress, and how these may contribute to the increased risk of heat-related injury that occurs with aging[93]. Given the diverse impacts of heat stress on these physiological systems and health more generally, this work was performed as a collaborative effort with physicians working in clinical and public health contexts. During this process it became clear that most studies that have evaluated the effect of aging (and chronic disease) on the physiological adjustments supporting health employed exercise-heat stress, whole-body encapsulated heating, or short-duration exposure to extreme ambient temperatures above that typically experienced during heat events.

This led to the first study of the thesis (3.2 Thesis Article 2), which aimed to assess whole-body heat exchange and its impacts on body temperature and cardiovascular responses in young (age: 19-31 years) and older adults (age: 64-79 years) during a 9-hour exposure to conditions representative of those experienced during recent heat events in temperate continental climates. The key finding was that older adults stored more heat than their younger counterparts during the early hours of exposure, leading to a 0.4°C greater increase in body core temperature that was maintained throughout exposure. Systolic blood pressure was also reduced to a greater extent in the older participants. This work provided the basis for the remaining thesis studies, which employed simulated heat event conditions to assess the impacts of indoor heat stress and cooling centre exposure on physiological responses in older adults.

While Thesis Article 2 was the first study to evaluate physiological responses in older adults during day-long (9-hour) heat exposure, the conditions employed were chosen to simulate peak conditions experienced during an extreme heat event. However, most individuals, and older adults in particular, spend most of their time in the home[78,79]. The second study of the thesis (3.3 Thesis Article 3) was therefore designed to assess body temperature and cardiovascular responses in older adults exposed to a range of conditions experienced indoors during extreme heat events – from an actively-cooled environment (22°C), through indoor temperature thresholds recommended by Toronto Public Health (26°C)[81] and the World Health Organization (31°C)[83], to a poorly insulated and ventilated domicile (36°C)[80]. To better quantify the effect of heat stress on the cardiovascular system, this study also included clinically validated functional tests selected to mimic the autonomic challenge experienced during activities of daily living[395,396]. The key finding of this work was that older adults can experience elevated body temperatures and attenuations in cardiovascular autonomic function, even during exposure to indoor conditions below current guidelines.

In the final study of the thesis (3.4 Thesis Article 4), the goal was to demonstrate how extreme heat simulation studies can be used to compliment public health research on the efficacy of commonly recommended heat mitigation strategies. Specifically, we studied the effectiveness of short-term ambient cooling (as experienced when visiting a cooling centre) for limiting hyperthermia and associated cardiovascular burden in vulnerable groups during a 9-hour simulated extreme heat event. While short-term ambient cooling provided transient reprieve from hyperthermia, body temperatures rose rapidly upon return to the hot environment, quickly reaching levels similar to a group of older adults not removed from the heat. Importantly, these findings are inconsistent with the World Health Organization published guidance that "*even a few hours spent in an air-conditioned place can help your body stay cooler when you go back into the heat*"[86] Although indirect, this study is the first to provide empirical evidence regarding the effectiveness of cooling centres for limiting hyperthermia during extreme heat events.

In all, the studies of this thesis provide important and novel information regarding the effect of extreme heat events on the physiological responses supporting health in older adults. More broadly, this work also highlights the effectiveness and potential uses of laboratory-based extreme heat simulation studies as an alternative means for evaluating the physiological basis of heat-vulnerability in older adults and those with chronic health conditions and for quantifying the effectiveness of current heat-mitigation strategies where population-based study has elsewise proven difficult.

4.2 Delimitations and limitations

The studies of the thesis are the first to assess the physiological responses of young and older adults during day-long exposures to conditions representative of extreme heat events in a temperate continental climate. However, there are still some important limitations to note. For one, all participants were healthy and sedentary or habitually active adults aged 19-31 (young) and 64-79 (older) years. As such, the results may not be directly applicable to those with age-associated co-morbidities that may further diminish heat tolerance (e.g., type 2 diabetes, cardiovascular disease)[6-8]. Further, given the age-groups employed, the outcomes may not be applicable to children, adolescents, or the very old (≥80 years). Further, the experiments performed did not permit the assessment of the interaction of age and sex on thermoregulatory and cardiovascular responses. Finally, behavioral factors in large part determine one's risk of mortality and morbidity during extreme heat events[6-8]. While the thesis provides novel information on the physiological responses to heat stress, it must be remembered that defining risk is a multi-faceted endeavour, larger in scope than any one series of studies in a given domain. In this regard, there is a need to evaluate the effects of prolonged elevations in body temperature and cardiovascular dysfunction on other facets of health including (but not limited to) hydration and electrolyte balance, oxidative stress, inflammatory status[93], and sleep quality[412,413], particularly over the course of an extreme heat event, which, by definition, occurs over multiple days[42].

4.3 Implications and future directions

Throughout the narrative review and three experimental studies of the thesis, the mechanistic underpinnings of the age-related impairments in the thermoregulatory and cardiovascular responses to heat stress and extreme heat events were discussed at length. Rather than repeat that information here, I have devoted this section to highlighting what I believe is the important role that physiological research can play in the broader context of climate change and health. Also included are a few examples of where this work can be integrated within existing frameworks in the medium-to-long term.

Environmental physiology and climate-health research

The long-standing notion of independent pathways in the development of pathology is no longer tenable. As recently highlighted by Sturmberg et al.[194], health and disease are perhaps better viewed as emergent states arising from complex and adaptive interactions between the physiological systems governing gene expression, hypothalamic-pituitary-adrenal axis activity, autonomic nervous system function, mitochondrial bioenergetics, endothelial function and inflammatory and oxidative stress pathways (among others)[425-430] and their top-down constraint by environmental and sociocultural factors. That is, structural and functional biological interactions provide the framework for health while the environment limits the number of possible health states[194]. In this view, an organism's ability to maintain internal consistency in the face of environmental perturbations is central to health[353,431] (3.1 Thesis Article 1, Figure 6).

The importance of environmental stressors in health and disease has long been appreciated. Environmental fluctuations can decrease or increase the physiological stress on an organism, causing internal perturbations leading to beneficial or pathological changes in the physiological systems highlighted above. Whether conferring positive (e.g., parks, green spaces)[432] or negative (e.g., industrial pollution, hazardous waste)[433,434] influences on health, the impact of environmental stressors are, in most instances, relatively fixed. However, climate change can bring rapid and severe changes in environmental conditions in the form of extreme heat events, floods, droughts, and fires, which can abruptly alter the magnitude and character of ambient stressors such as temperature, air pollution, and pathogen exposure[2,16]. This has led to the suggestion that a more integrated research approach drawing from disciplines outside of those traditionally employed in medicine and public health is crucial to maintaining the health of vulnerable populations in the era of climate change[17,18,93].

The burden brought about by rapid swings in ambient conditions lends itself to environmental physiological research, which is interested in quantifying the effect of relatively acute environmental perturbations on the functioning of physiological systems and health. Physiological research is inherently integrated[350], spanning the divide between assessing homeostatic regulation in isolated cells and organs to evaluating the effects of a multitude of environmental stressors on the organism as a whole in order to inform public health and policy[351]. Seals[352] acknowledged how these tenets lend themselves to translational research approaches aimed at addressing public health problems. Below, I extend this line of reasoning to discuss two key areas where I believe physiological research designs can be readily expanded and integrated with existing public health research frameworks.

Mechanisms of heat-related mortality and morbidity

There is ample epidemiological data to show that extreme heat events are associated with stark increases in mortality and morbidity, particularly in vulnerable groups such as older adults[1,2]. Despite this, the contributing mechanisms remain poorly defined. While heat stress overwhelming the bodies physiological capacity for heat dissipation is well known to precipitate a myriad of extreme pathological conditions (e.g., heat exhaustion and heat stroke), it does not explain the heat event hospitalizations and deaths that occur due to causes not directly related to extreme hyperthermia (e.g., major adverse cardiovascular events, acute kidney injury) (see 3.1 Thesis Article 1). This is not to say that impaired regulation of body temperature does not contribute to the associated pathology. Age-related alterations in the functional characteristics of the heat loss responses of skin blood flow and sweating mean that, even if conditions are compensable, heat balance will be maintained at higher body temperatures in older adults compared to their younger counterparts during heat exposure (see 3.2 Thesis Article 2). Since heat events last several days to weeks, low-to-moderate levels of hyperthermia may be sustained over protracted periods.

To fully appreciate the etiology of heat-related health disorders, we must therefore consider the physiological effects of prolonged and/or repeated ‘subclinical’ elevations of body temperature, as these will contribute to the development of strain and dysfunction in sensitive bodily systems in vulnerable persons such as the elderly and those with pre-existing chronic health conditions. This can be illustrated using Rothman’s multiple sufficient cause model of disease[194,195]. In his model, distinguished epidemiologist Kenneth Rothman argues that multiple different ‘cause-components’ combine to form a 'sufficient cause' for pathology (Figure 1A)[195]. Using heat events as an example (Figure 1B and C), generally benign physiological alterations associated with heat stress (e.g., dehydration; cause-component A) and aging (e.g., renal inflammation; cause-component B) can combine to produce acute pathology (e.g., acute kidney injury), especially in the presence of subclinical or overt disease (e.g., chronic kidney disease; cause-component C) and virtually countless other factors that may increase heat vulnerability (e.g., acute illness, medication use, sleep deprivation, etc.).

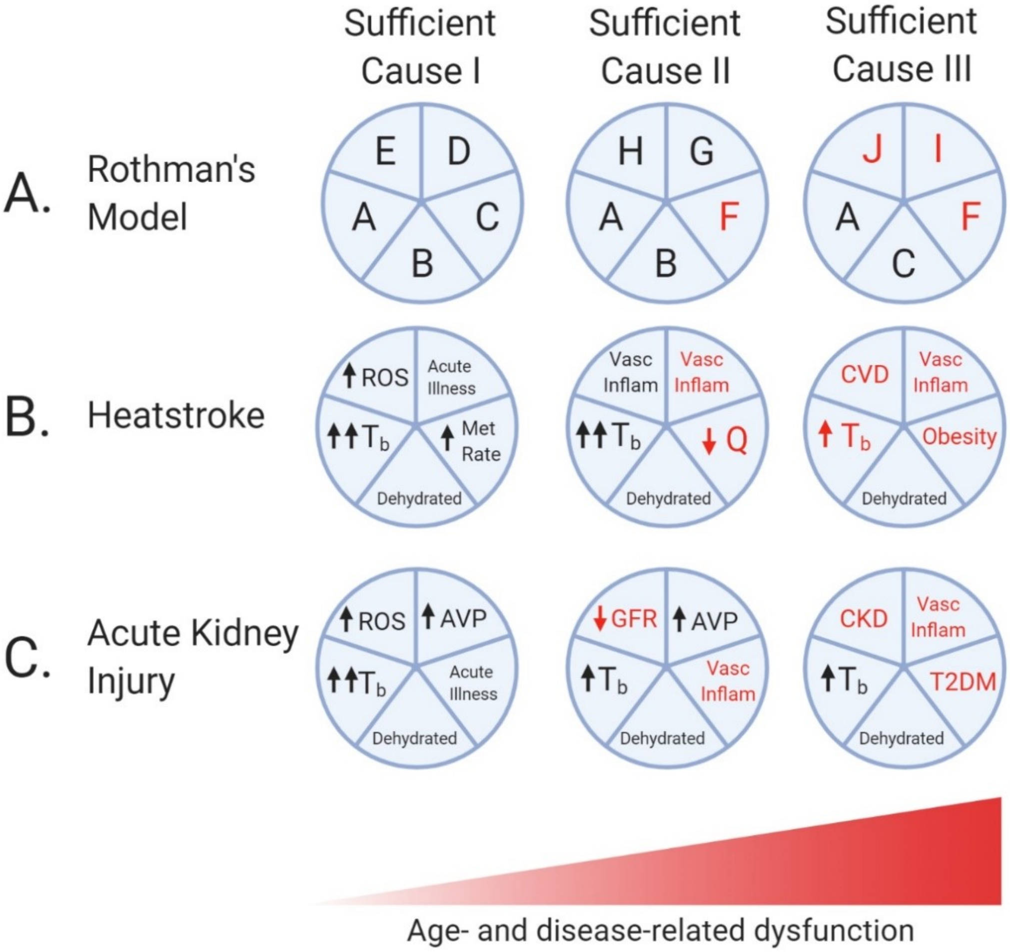


Figure 1. Rothman's sufficient cause model of disease (A)[195] applied to the development of common acute pathological events during extreme heat events (B and C). In this example, acute injury, heat stroke and acute kidney injury, may develop from combinations of multiple cause-components. Physiological changes associated with normal aging (e.g., increased oxidative stress and inflammation) and age-associated chronic disease (cardiovascular disease, type 2 diabetes, chronic kidney disease) act as component

causes, increasing the risk of these events. That is, aging and disease modifies the risk of acute pathophysiological events during heat events by increasing the number of cause-components and therefore the number of potential pathways to acute pathology (i.e., the number of potential combinations of cause-components). Physiological alterations associated with heat stress are indicated in black (presented relative to non-heat stress conditions) whereas age-related and disease-related alterations are denoted in red (presented relative to heat-stress condition in young adults). T_b, body temperature; ROS, reactive oxygen species, met rate, metabolic rate; Q, cardiac output; vasc inflam, vascular inflammation; AVP, arginine vasopressin; CVD, cardiovascular disease; CKD, chronic kidney disease; T2DM, type 2 diabetes mellitus.

Interestingly, the proposed links between subclinical elevations in body temperature and pathology during extreme heat events is indirectly supported by a recent analysis of ~28 million hospital admissions in adults aged ≥65 years performed by Bobb et al.[3], who unexpectedly uncovered increased sepsis-related morbidity during extreme heat events (the etiology and effects of sepsis are similar to that of the inflammatory response characterizing heat stroke discussed in 3.1 Thesis Article 1). Whether those findings are related to prolonged ‘subclinical’ hyperthermia or misdiagnosis of heat-related illness is currently unclear. Regardless, Rothman’s model provides a vantage point from which to discuss the cumulative effects of multiple physiological stressors on health during extreme heat events as well as a means through which physiological research can be readily incorporated into current health frameworks. Heat event simulations with vulnerable participants may be an effective approach for identifying plausible ‘cause-components’ of heat-related injury.

Complimenting public health research

The ultimate goal of research on the health impacts of extreme heat is to develop strategies to protect vulnerable individuals. As demonstrated in 3.3. Thesis Article 3 and 3.4 Thesis Article 4, heat simulations provide a valuable alternative for assessing the impact of heat mitigation strategies. This complementary approach is needed since epidemiological support for currently recommended strategies (e.g., electric fan use, cooling centres) is not forthcoming[87,376]. In the near-term, it will be important that extreme heat simulation studies be expanded to evaluate the effect of heat stress on the physiological systems regulating body fluid and electrolyte balance and inflammatory status[93] as well as other determinants of health such as sleep quality[412,413], particularly over multiple days of heat exposure and in individuals with common chronic health conditions. By assisting public health practitioners in the identification of efficacious cooling strategies, such work will increase precision and reduce delay in the implementation of targeted guidance to protect vulnerable persons from extreme heat.

There is also ample opportunity for research aimed at integrating current epidemiological and physiological knowledge. Much of our understanding of the effectiveness of heat mitigation strategies comes from studies evaluating the epidemiological association between certain actions and the risk of dying during a heatwave, as summarized in a monumental systematic review and meta-analysis by Bouchama et al. in 2007[6]. The use of cooling centres, for example, draws much of its support from the observed reduction in the risk of dying during a heat wave in individuals who regularly ‘visited cooled locations’. As discussed in 3.4 Thesis Article 4 it is currently unclear whether this risk reduction is due to the effect of cooling *per se*, or other associated factors (e.g., individuals who are unable to leave the home are also at increased risk). This knowledge gap was the primary impetus for directly assessing the efficacy of cooling centres in Thesis Article 4. Further, we (and other laboratories) have already begun to employ similar designs to evaluate other heat mitigation strategies such as electric fan use and skin misting.

This highlights two important points: 1) the systematic review and meta-analysis by Bouchama is now ~14 years old and should be updated with contemporary epidemiological research on prognostic factors for heat-related mortality; and 2) there is a growing wealth of studies that have assessed the physiological impacts of these heat mitigation strategies. A 'holistic' systematic review could be conducted to address these points simultaneously. In the first part of the review, the meta-analysis by Bouchama[6] would be updated. Then, in the second part, the mechanisms underpinning those associations gleaned from physiological studies could be explored with either a systematic or scoping review. Combining extant epidemiological and physiological research on heat mitigation strategies would provide an efficient means for updating current guidance as well as identifying where causal research is lacking. Such a project could even be conducted as a 'living systematic review', updated at regular intervals as new information becomes available[435]. This template could then be used to assess other similar issues, such as linking the observational and mechanistic evidence for the effects of heat stress on heart or kidney health.

Looking further into the future, physiological techniques can be more directly integrated with traditional health research. For example, physiologists working in conjunction with cellular and molecular biologists may yield novel targets for enhancing biological protection from environmental stressors[436]. The efficacy of these can in turn be evaluated in animal and pre-clinical models through to implementation on the population scale[352]. Moreover, rapid technological advances in biomonitoring mean that measurements characteristic of laboratory-based physiological research are becoming employable on an ever growing scale[437], and may therefore be utilized alongside traditional clinical risk markers[352]. This emerging subfield, coined ‘physiological epidemiology’ by Seals[352], is well suited to linking environment-related stressors and clinical outcomes at the community and population level, especially when employed in conjunction with established clinical epidemiological approaches. For example, shoe-leather epidemiological research (or ‘field-epidemiology’), which was the source of some of our earliest and most influential data on the associations between heat and health[49], may be expanded to evaluate participants in their homes or in cooling centres using advanced physiological techniques traditionally confined to laboratory settings .

4.4 Thesis conclusions

This thesis represents a considerable advance in our understanding of the physiological burden experienced by older adults during hot weather and extreme heat events. Our findings indicate that even healthy older adults experience elevated body temperatures and cardiovascular burden during extreme heat events compared to their younger counterparts. Further, we show that commonly recommended heat-health guidelines (indoor temperature limits) and mitigation strategies (cooling centres) may not provide adequate protection. More broadly, the employed extreme heat simulations provide a novel means through which we can better understand the adverse health impacts of heat stress in vulnerable groups and how best to prevent them.

CHAPTER 5 – REFERENCES

1. Watts N, Amann M, Arnell N, et al. The 2020 report of The Lancet Countdown on health and climate change: responding to converging crises. *Lancet.* 2021;397(10269):129-170.
2. Patz JA, Frumkin H, Holloway T, Vimont DJ, Haines A. Climate change: challenges and opportunities for global health. *JAMA.* 2014;312(15):1565-1580.
3. Bobb JF, Obermeyer Z, Wang Y, Dominici F. Cause-specific risk of hospital admission related to extreme heat in older adults. *JAMA.* 2014;312(24):2659-2667.
4. Suzman R, Beard JR, Boerma T, Chatterji S. Health in an ageing world--what do we know? *Lancet.* 2015;385(9967):484-486.
5. Organization WH. *World report on ageing and health.* World Health Organization; 2015.
6. Bouchama A, Dehbi M, Mohamed G, Matthies F, Shoukri M, Menne B. Prognostic factors in heat wave related deaths: a meta-analysis. *Arch Intern Med.* 2007;167(20):2170-2176.
7. Semenza JC, McCullough JE, Flanders WD, McGeehin MA, Lumpkin JR. Excess hospital admissions during the July 1995 heat wave in Chicago. *Am J Prev Med.* 1999;16(4):269-277.
8. Kenny GP, Yardley J, Brown C, Sigal RJ, Jay O. Heat stress in older individuals and patients with common chronic diseases. *CMAJ.* 2010;182(10):1053-1060.
9. Vandentorren S, Bretin P, Zeghnoun A, et al. August 2003 heat wave in France: risk factors for death of elderly people living at home. *The European Journal of Public Health.* 2006;16(6):583-591.
10. Barriopedro D, Fischer EM, Luterbacher J, Trigo RM, Garcia-Herrera R. The hot summer of 2010: redrawing the temperature record map of Europe. *Science.* 2011;332(6026):220-224.
11. Meehl GA, Tebaldi C. More intense, more frequent, and longer lasting heat waves in the 21st century. *Science.* 2004;305(5686):994-997.
12. Organization WH. Quantitative risk assessment of the effects of climate change on selected causes of death, 2030s and 2050s. 2014.
13. Flynn A, McGreevy C, Mulkerrin E. Why do older patients die in a heatwave? *Qjm.* 2005;98(3):227-229.
14. Kenney WL, Craighead DH, Alexander LM. Heat waves, aging, and human cardiovascular health. *Med Sci Sports Exerc.* 2014;46(10):1891-1899.
15. Mayrhuber EA, Duckers MLA, Wallner P, et al. Vulnerability to heatwaves and implications for public health interventions - A scoping review. *Environ Res.* 2018;166:42-54.
16. Haines A, Ebi K. The Imperative for Climate Action to Protect Health. *N Engl J Med.* 2019;380(3):263-273.
17. Vanos JK, Baldwin JW, Jay O, Ebi KL. Simplicity lacks robustness when projecting heat-health outcomes in a changing climate. *Nature Communications.* 2020;11(1):1-5.
18. Mercatelli R, Mattana S, Capozzoli L, et al. Morpho-mechanics of human collagen superstructures revealed by all-optical correlative micro-spectroscopies. *Commun Biol.* 2019;2:117.

19. Charkoudian N. Skin blood flow in adult human thermoregulation: how it works, when it does not, and why. *Mayo Clin Proc.* 2003;78(5):603-612.
20. Johnson JM, Kellogg DL, Jr. Thermoregulatory and thermal control in the human cutaneous circulation. *Front Biosci (Schol Ed).* 2010;2:825-853.
21. Johnson JM, Minson CT, Kellogg DL, Jr. Cutaneous vasodilator and vasoconstrictor mechanisms in temperature regulation. *Compr Physiol.* 2014;4(1):33-89.
22. Kenny GP, Jay O. Thermometry, calorimetry, and mean body temperature during heat stress. *Compr Physiol.* 2013;3(4):1689-1719.
23. Shibasaki M, Crandall CG. Mechanisms and controllers of eccrine sweating in humans. *Front Biosci (Schol Ed).* 2010;2:685-696.
24. Lamb DR, Gisolfi CV, Nadel ER. *Exercise, heat, and thermoregulation.* Vol 6: Brown & Benchmark Pub; 1993.
25. Shibasaki M, Okazaki K, Inoue Y. Aging and thermoregulation. *The Journal of Physical Fitness and Sports Medicine.* 2013;2(1):37-47.
26. Kenney WL. Edward F. Adolph Distinguished Lecture: Skin-deep insights into vascular aging. *J Appl Physiol (1985).* 2017;123(5):1024-1038.
27. Greaney JL, Kenney WL, Alexander LM. Sympathetic regulation during thermal stress in human aging and disease. *Auton Neurosci.* 2016;196:81-90.
28. Larose J, Boulay P, Wright-Beatty HE, Sigal RJ, Hardcastle S, Kenny GP. Age-related differences in heat loss capacity occur under both dry and humid heat stress conditions. *J Appl Physiol (1985).* 2014;117(1):69-79.
29. Larose J, Wright HE, Sigal RJ, Boulay P, Hardcastle S, Kenny GP. Do older females store more heat than younger females during exercise in the heat? *Med Sci Sports Exerc.* 2013;45(12):2265-2276.
30. Larose J, Wright HE, Stapleton J, et al. Whole body heat loss is reduced in older males during short bouts of intermittent exercise. *Am J Physiol Regul Integr Comp Physiol.* 2013;305(6):R619-629.
31. Notley SR, Poirier MP, Hardcastle SG, et al. Aging Impairs Whole-Body Heat Loss in Women under Both Dry and Humid Heat Stress. *Med Sci Sports Exerc.* 2017;49(11):2324-2332.
32. Larose J, Boulay P, Sigal RJ, Wright HE, Kenny GP. Age-related decrements in heat dissipation during physical activity occur as early as the age of 40. *PLoS One.* 2013;8(12):e83148.
33. Stapleton JM, Poirier MP, Flouris AD, et al. At what level of heat load are age-related impairments in the ability to dissipate heat evident in females? *PLoS One.* 2015;10(3):e0119079.
34. Meade RD, Notley SR, D'Souza AW, et al. Interactive effects of age and hydration state on human thermoregulatory function during exercise in hot-dry conditions. *Acta Physiol (Oxf).* 2019;226(1):e13226.
35. Meade RD, Notley SR, Kenny GP. Aging and human heat dissipation during exercise-heat stress: an update and future directions. *Current Opinion in Physiology.* 2019;10:219-225.
36. Stapleton JM, Poirier MP, Flouris AD, et al. Aging impairs heat loss, but when does it matter? *J Appl Physiol (1985).* 2015;118(3):299-309.

37. Meade RD, Kenny GP. Are All Heat Loads Created Equal? *Med Sci Sports Exerc.* 2017;49(9):1796-1804.
38. Saidj M, Menai M, Charreire H, et al. Descriptive study of sedentary behaviours in 35,444 French working adults: cross-sectional findings from the ACTI-Cites study. *BMC Public Health.* 2015;15:379.
39. Scheers T, Philippaerts R, Lefevre J. Compliance with different physical activity recommendations and its association with socio-demographic characteristics using an objective measure. *BMC Public Health.* 2013;13:136.
40. Kenny GP, Poirier MP, Metsios GS, et al. Hyperthermia and cardiovascular strain during an extreme heat exposure in young versus older adults. *Temperature (Austin).* 2017;4(1):79-88.
41. Stapleton JM, Larose J, Simpson C, Flouris AD, Sigal RJ, Kenny GP. Do older adults experience greater thermal strain during heat waves? *Appl Physiol Nutr Metab.* 2014;39(3):292-298.
42. Xu Z, FitzGerald G, Guo Y, Jalaludin B, Tong S. Impact of heatwave on mortality under different heatwave definitions: A systematic review and meta-analysis. *Environ Int.* 2016;89-90:193-203.
43. Kang SH, Oh IY, Heo J, et al. Heat, heat waves, and out-of-hospital cardiac arrest. *Int J Cardiol.* 2016;221:232-237.
44. Miescher E, Fortney SM. Responses to dehydration and rehydration during heat exposure in young and older men. *Am J Physiol.* 1989;257(5 Pt 2):R1050-1056.
45. Drinkwater BL, Bedi JF, Loucks AB, Roche S, Horvath SM. Sweating sensitivity and capacity of women in relation to age. *J Appl Physiol Respir Environ Exerc Physiol.* 1982;53(3):671-676.
46. Histrocal Climate Data. Government of Canada; 2019. http://climate.weather.gc.ca/climate_data/daily_data_e.html?StationID=49568&timeframe=2&StartYear=1840&EndYear=2019&Day=7&Year=2018&Month=7#. Accessed August 8 2019.
47. Robine JM, Cheung SL, Le Roy S, et al. Death toll exceeded 70,000 in Europe during the summer of 2003. *C R Biol.* 2008;331(2):171-178.
48. Jay O, Cramer MN, Ravanelli NM, Hodder SG. Should electric fans be used during a heat wave? *Appl Ergon.* 2015;46 Pt A:137-143.
49. Semenza JC, Rubin CH, Falter KH, et al. Heat-related deaths during the July 1995 heat wave in Chicago. *N Engl J Med.* 1996;335(2):84-90.
50. Minson CT, Wladkowski SL, Cardell AF, Pawelczyk JA, Kenney WL. Age alters the cardiovascular response to direct passive heating. *J Appl Physiol (1985).* 1998;84(4):1323-1332.
51. Low DA, Keller DM, Wingo JE, Brothers RM, Crandall CG. Sympathetic nerve activity and whole body heat stress in humans. *J Appl Physiol (1985).* 2011;111(5):1329-1334.
52. Rowell LB. Human cardiovascular adjustments to exercise and thermal stress. *Physiol Rev.* 1974;54(1):75-159.
53. Rowell LB, Brengelmann GL, Murray JA. Cardiovascular responses to sustained high skin temperature in resting man. *J Appl Physiol.* 1969;27(5):673-680.
54. Wilson TE, Brothers RM, Tollund C, et al. Effect of thermal stress on Frank-Starling relations in humans. *J Physiol.* 2009;587(Pt 13):3383-3392.

55. Brothers RM, Bhella PS, Shibata S, Wingo JE, Levine BD, Crandall CG. Cardiac systolic and diastolic function during whole body heat stress. *Am J Physiol Heart Circ Physiol.* 2009;296(4):H1150-1156.
56. Lucas RA, Sarma S, Schlader ZJ, Pearson J, Crandall CG. Age-related changes to cardiac systolic and diastolic function during whole-body passive hyperthermia. *Exp Physiol.* 2015;100(4):422-434.
57. Stohr EJ, Gonzalez-Alonso J, Pearson J, et al. Effects of graded heat stress on global left ventricular function and twist mechanics at rest and during exercise in healthy humans. *Exp Physiol.* 2011;96(2):114-124.
58. Bundgaard-Nielsen M, Wilson TE, Seifert T, Secher NH, Crandall CG. Effect of volume loading on the Frank-Starling relation during reductions in central blood volume in heat-stressed humans. *J Physiol.* 2010;588(Pt 17):3333-3339.
59. Crandall CG, Wilson TE, Marving J, et al. Effects of passive heating on central blood volume and ventricular dimensions in humans. *J Physiol.* 2008;586(1):293-301.
60. Rowell LB, Brengelmann GL, Blackmon JR, Twiss RD, Kusumi F. Splanchnic blood flow and metabolism in heat-stressed man. *J Appl Physiol.* 1968;24(4):475-484.
61. Chapman CL, Benati JM, Johnson BD, Vargas NT, Lema PC, Schlader ZJ. Renal and segmental artery hemodynamics during whole body passive heating and cooling recovery. *J Appl Physiol (1985).* 2019;127(4):974-983.
62. Rowell LB. Human cardiovascular adjustments to exercise and thermal stress. *Physiological reviews.* 1974;54(1):75-159.
63. Crandall CG, Wilson TE. Human cardiovascular responses to passive heat stress. *Compr Physiol.* 2015;5(1):17-43.
64. Kenney WL, Morgan AL, Farquhar WB, Brooks EM, Pierzga JM, Derr JA. Decreased active vasodilator sensitivity in aged skin. *Am J Physiol.* 1997;272(4 Pt 2):H1609-1614.
65. Lakatta EG, Levy D. Arterial and cardiac aging: major shareholders in cardiovascular disease enterprises: Part I: aging arteries: a "set up" for vascular disease. *Circulation.* 2003;107(1):139-146.
66. Mitchell GF, Parise H, Benjamin EJ, et al. Changes in arterial stiffness and wave reflection with advancing age in healthy men and women: the Framingham Heart Study. *Hypertension.* 2004;43(6):1239-1245.
67. Fleg JL, O'Connor F, Gerstenblith G, et al. Impact of age on the cardiovascular response to dynamic upright exercise in healthy men and women. *J Appl Physiol (1985).* 1995;78(3):890-900.
68. Monahan KD. Effect of aging on baroreflex function in humans. *Am J Physiol Regul Integr Comp Physiol.* 2007;293(1):R3-R12.
69. Gerritsen J, TenVoorde BJ, Dekker JM, Kostense PJ, Bouter LM, Heethaar RM. Baroreflex sensitivity in the elderly: influence of age, breathing and spectral methods. *Clin Sci (Lond).* 2000;99(5):371-381.
70. Scremin G, Kenney WL. Aging and the skin blood flow response to the unloading of baroreceptors during heat and cold stress. *J Appl Physiol (1985).* 2004;96(3):1019-1025.

71. Parsons K. *Human thermal environments: the effects of hot, moderate, and cold environments on human health, comfort, and performance.* CRC press; 2014.
72. Rowell LB, Brengelmann GL, Detry JM, Wyss C. Venomotor responses to local and remote thermal stimuli to skin in exercising man. *J Appl Physiol.* 1971;30(1):72-77.
73. Donaldson GC, Keatinge WR, Saunders RD. Cardiovascular responses to heat stress and their adverse consequences in healthy and vulnerable human populations. *Int J Hyperthermia.* 2003;19(3):225-235.
74. Vaidyanathan A, Saha S, Vicedo-Cabrera AM, et al. Assessment of extreme heat and hospitalizations to inform early warning systems. *Proc Natl Acad Sci U S A.* 2019;116(12):5420-5427.
75. Gasparrini A, Guo Y, Hashizume M, et al. Mortality risk attributable to high and low ambient temperature: a multicountry observational study. *Lancet.* 2015;386(9991):369-375.
76. Gasparrini A, Guo Y, Hashizume M, et al. Temporal variation in heat–mortality associations: a multicountry study. *Environmental health perspectives.* 2015;123(11):1200-1207.
77. Guo Y, Gasparrini A, Armstrong BG, et al. Heat Wave and Mortality: A Multicountry, Multicommunity Study. *Environ Health Perspect.* 2017;125(8):087006.
78. Spalt EW, Curl CL, Allen RW, et al. 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.* 2016;26(4):436.
79. Farrow A, Taylor H, Golding J. Time spent in the home by different family members. *Environmental Technology.* 1997;18(6):605-613.
80. White-Newsome JL, Sanchez BN, Jolliet O, et al. Climate change and health: indoor heat exposure in vulnerable populations. *Environ Res.* 2012;112:20-27.
81. Campell M, McKeown D. Update on Extreme Heat and Maximum Indoor Temperature Standard for Multi-unit Residential Buildings. Toronto Public Health; 2015.
82. Chen H, Wang J, Li Q, et al. Assessment of the effect of cold and hot temperatures on mortality in Ontario, Canada: a population-based study. *CMAJ Open.* 2016;4(1):E48-58.
83. World Health Organization. Public Health Advice: On Preventing Health Effects of Heat. Copenhagen: WHO Regional Office for Europe; 2011.
84. Berisha V, Hondula D, Roach M, et al. Assessing adaptation strategies for extreme heat: a public health evaluation of cooling centers in Maricopa County, Arizona. *Weather, climate, and society.* 2017;9(1):71-80.
85. Government of Canada. Extreme heat: heat waves. *Sun safety* 2019; https://www.canada.ca/en/health-canada/services/sun-safety/extreme-heat-heat-waves.html#b4. Accessed October 14th, 2019.
86. McGregor GR, Bessmoulin P, Ebi K, Menne B. *Heatwaves and health: guidance on warning-system development.* WMOP; 2015.
87. Widerynski S, Schramm PJ, Conlon KC, et al. Use of cooling centers to prevent heat-related illness: summary of evidence and strategies for implementation. 2017.

88. Kovats RS, Kristie LE. Heatwaves and public health in Europe. *Eur J Public Health.* 2006;16(6):592-599.
89. Sheridan SC. A survey of public perception and response to heat warnings across four North American cities: an evaluation of municipal effectiveness. *Int J Biometeorol.* 2007;52(1):3-15.
90. Kosatsky T, Dufresne J, Richard L, et al. Heat awareness and response among Montreal residents with chronic cardiac and pulmonary disease. *Canadian Journal of Public Health.* 2009;100(3):237-240.
91. Hanna EG, Tait PW. Limitations to Thermoregulation and Acclimatization Challenge Human Adaptation to Global Warming. *Int J Environ Res Public Health.* 2015;12(7):8034-8074.
92. Guo Y, Gasparrini A, Li S, et al. Quantifying excess deaths related to heatwaves under climate change scenarios: A multicountry time series modelling study. *PLoS Med.* 2018;15(7):e1002629.
93. Meade RD, Akerman AP, Notley SR, et al. Physiological factors characterizing heat-vulnerable older adults: A narrative review. *Environ Int.* 2020;144:105909.
94. Perkins SE. A review on the scientific understanding of heatwaves—their measurement, driving mechanisms, and changes at the global scale. *Atmospheric Research.* 2015;164:242-267.
95. Watts N, Amann M, Arnell N, et al. 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.* 2019;394(10211):1836-1878.
96. Székely M, Carletto L, Garami A. The pathophysiology of heat exposure. *Temperature: Multidisciplinary Biomedical Journal.* 2015;2(4):452.
97. McMichael AJ, Lindgren E. Climate change: present and future risks to health, and necessary responses. *Journal of internal medicine.* 2011;270(5):401-413.
98. Stott PA, Stone DA, Allen MR. Human contribution to the European heatwave of 2003. *Nature.* 2004;432(7017):610.
99. Mora C, Dousset B, Caldwell IR, et al. Global risk of deadly heat. *Nature climate change.* 2017;7(7):501-506.
100. Basu R, Samet JM. Relation between elevated ambient temperature and mortality: a review of the epidemiologic evidence. *Epidemiol Rev.* 2002;24(2):190-202.
101. Collins M, Knutti R, Arblaster J, et al. Long-term climate change: projections, commitments and irreversibility. *Climate Change 2013-The Physical Science Basis: Contribution of Working Group I to the Fifth Assessment Report of the Intergovernmental Panel on Climate Change*: Cambridge University Press; 2013:1029-1136.
102. Ouzeau G, Soubeyroux J-M, Schneider M, Vautard R, Planton S. Heat waves analysis over France in present and future climate: Application of a new method on the EURO-CORDEX ensemble. *Climate Services.* 2016;4:1-12.
103. UNFCCC. *Adoption of the Paris Agreement.* 2015. FCCC/CP/2015/L.9/Rev.1.
104. Tanaka K, O'Neill BC. The Paris Agreement zero-emissions goal is not always consistent with the 1.5 C and 2 C temperature targets. *Nature Climate Change.* 2018;8(4):319.
105. IPCC. *Global Warming of 1.5°C. An IPCC Special Report on the impacts of global warming of 1.5°C above pre-industrial levels and related global greenhouse gas*

emission pathways, in the context of strengthening the global response to the threat of climate change, sustainable development, and efforts to eradicate poverty. In Press2018.

106. Neufeldt H, Martinez GS, Olhoff A, Knudsen CMS, Dorkenoo KE. The Adaptation Gap Report 2018. United Nations Environment Programme (UNEP), Nairobi, Kenya. 2018.
107. Fouillet A, Rey G, Laurent F, et al. Excess mortality related to the August 2003 heat wave in France. *Int Arch Occup Environ Health.* 2006;80(1):16-24.
108. Wang Y, Nordio F, Nairn J, Zanobetti A, Schwartz JD. Accounting for adaptation and intensity in projecting heat wave-related mortality. *Environ Res.* 2018;161:464-471.
109. Harlan SL, Chowell G, Yang S, et al. Heat-related deaths in hot cities: estimates of human tolerance to high temperature thresholds. *Int J Environ Res Public Health.* 2014;11(3):3304-3326.
110. Li D, Bou-Zeid E. Synergistic interactions between urban heat islands and heat waves: The impact in cities is larger than the sum of its parts. *Journal of Applied Meteorology and Climatology.* 2013;52(9):2051-2064.
111. Oke TR. The energetic basis of the urban heat island. *Quarterly Journal of the Royal Meteorological Society.* 1982;108(455):1-24.
112. Luber G, McGeehin M. Climate change and extreme heat events. *Am J Prev Med.* 2008;35(5):429-435.
113. Taylor Jackson JC, Palacios M. Canada's Aging Population and Implications for Government Finances. 2017.
114. Statistics Canada. Canada goes urban. . 2017; http://www.statcan.gc.ca/pub/11-630-x/11-630-x2015004-eng.htm.
115. Matthies F, Bickler G, Marín NC, Hales S. *Heat-health action plans: guidance.* World Health Organization; 2008.
116. Guergova S, Dufour A. Thermal sensitivity in the elderly: a review. *Ageing Res Rev.* 2011;10(1):80-92.
117. Klinenberg E. *Heat wave: A social autopsy of disaster in Chicago.* University of Chicago Press; 2015.
118. Anderson M, Carmichael C, Murray V, Dengel A, Swainson M. Defining indoor heat thresholds for health in the UK. *Perspect Public Health.* 2013;133(3):158-164.
119. McLeod RS, Swainson M. Chronic overheating in low carbon urban developments in a temperate climate. *Renewable and Sustainable Energy Reviews.* 2017;74:201-220.
120. Gagge AP, Gonzalez RR. Mechanisms of heat exchange: biophysics and physiology. *Comprehensive physiology.* 2010:45-84.
121. Hellon RF. Central thermoreceptors and thermoregulation. *Enteroceptors*: Springer; 1972:161-186.
122. Hensel H. Thermoreceptors. *Annual review of physiology.* 1974;36(1):233-249.
123. Boulant JA. Hypothalamic mechanisms in thermoregulation. Paper presented at: Federation proceedings1981.
124. Jessen C. Interaction of body temperatures in control of thermoregulatory effector mechanisms. *Comprehensive Physiology.* 2010:127-138.

125. Taylor N, Werner J, Mekjavic IB. Concepts in physiological regulation: a thermoregulatory perspective. 2008.
126. Cain B, McLellan TM. A model of evaporation from the skin while wearing protective clothing. *Int J Biometeorol.* 1998;41(4):183-193.
127. Gavin TP. Clothing and thermoregulation during exercise. *Sports Med.* 2003;33(13):941-947.
128. Gagge A, Gonzalez R. Mechanisms of heat exchange: Biophysics and physiology. In: F.M., ed. *Expirmental Physiology*. Oxford: Oxford University Press; 1996:45-84.
129. Crandall CG, Gonzalez-Alonso J. Cardiovascular function in the heat-stressed human. *Acta Physiol (Oxf).* 2010;199(4):407-423.
130. Johnson JM, Proppe DW. Cardiovascular adjustments to heat stress. In: Fregly M, Blatteis C, eds. *Handbook of physiology - envionmental physiology*. New York: Oxford University Press; 1996:215-243.
131. Gagnon D, Jay O, Kenny GP. The evaporative requirement for heat balance determines whole-body sweat rate during exercise under conditions permitting full evaporation. *J Physiol.* 2013;591(Pt 11):2925-2935.
132. Taylor NA, Machado-Moreira CA. Regional variations in transepidermal water loss, eccrine sweat gland density, sweat secretion rates and electrolyte composition in resting and exercising humans. *Extrem Physiol Med.* 2013;2(1):4.
133. Chen X, Li N, Liu J, Zhang Z, Liu Y. Global Heat Wave Hazard Considering Humidity Effects during the 21st Century. *Int J Environ Res Public Health.* 2019;16(9).
134. Cramer MN, Jay O. Partitional calorimetry. *J Appl Physiol (1985).* 2019;126(2):267-277.
135. Kenny GP, Notley SR, Gagnon D. Direct calorimetry: a brief historical review of its use in the study of human metabolism and thermoregulation. *Eur J Appl Physiol.* 2017;117(9):1765-1785.
136. Lenhardt R, Sessler DI. Estimation of mean body temperature from mean skin and core temperature. *Anesthesiology.* 2006;105(6):1117-1121.
137. Gagnon D, Kenny GP. Does sex have an independent effect on thermoeffector responses during exercise in the heat? *J Physiol.* 2012;590(Pt 23):5963-5973.
138. Belding H, Hatch T. Index for evaluating heat stress in terms of resulting physiological strains. *Heating, piping and air conditioning.* 1955;27(8):129-136.
139. Rowell LB. Hyperthermia: a hyperadrenergic state. *Hypertension.* 1990;15(5):505-507.
140. Gagnon D, Schlader ZJ, Crandall CG. Sympathetic activity during passive heat stress in healthy aged humans. *J Physiol.* 2015;593(9):2225-2235.
141. Cui J, Wilson TE, Crandall CG. Baroreflex modulation of sympathetic nerve activity to muscle in heat-stressed humans. *Am J Physiol Regul Integr Comp Physiol.* 2002;282(1):R252-258.
142. Huang C, Barnett AG, Wang X, Tong S. Effects of extreme temperatures on years of life lost for cardiovascular deaths: a time series study in Brisbane, Australia. *Circ Cardiovasc Qual Outcomes.* 2012;5(5):609-614.

143. Vandentorren S, Bretin P, Zeghnoun A, et al. August 2003 heat wave in France: risk factors for death of elderly people living at home. *Eur J Public Health.* 2006;16(6):583-591.
144. World Health Organization. Quantitative risk assessment of the effects of climate change on selected causes of death, 2030s and 2050s. 2014.
145. Frumkin H, Hess J, Luber G. Public Health Policies and Actions. In: Levy BS, Patz JA, eds. *Climate Change and Public Health*. New York: Oxford University Press; 2015.
146. Flouris A, Schlader Z. Human behavioral thermoregulation during exercise in the heat. *Scandinavian journal of medicine & science in sports.* 2015;25:52-64.
147. Hellon RF, Lind AR. The influence of age on peripheral vasodilatation in a hot environment. *J Physiol.* 1958;141(2):262-272.
148. Hellon RF, Lind AR. Observations on the activity of sweat glands with special reference to the influence of ageing. *J Physiol.* 1956;133(1):132-144.
149. Kenney WL. Control of heat-induced cutaneous vasodilatation in relation to age. *Eur J Appl Physiol Occup Physiol.* 1988;57(1):120-125.
150. Holowatz LA, Thompson CS, Kenney WL. L-Arginine supplementation or arginase inhibition augments reflex cutaneous vasodilatation in aged human skin. *J Physiol.* 2006;574(Pt 2):573-581.
151. Meade RD, Fujii N, McGarr GW, et al. Local arginase inhibition does not modulate cutaneous vasodilation or sweating in young and older men during exercise. *J Appl Physiol (1985).* 2019;126(4):1129-1137.
152. Inoue Y, Nakao M, Araki T, Murakami H. Regional differences in the sweating responses of older and younger men. *J Appl Physiol (1985).* 1991;71(6):2453-2459.
153. Kenney WL, Fowler SR. Methylcholine-activated eccrine sweat gland density and output as a function of age. *Journal of Applied Physiology.* 1988;65(3):1082-1086.
154. Inoue Y, Shibasaki M, Ueda H, Ishizashi H. Mechanisms underlying the age-related decrement in the human sweating response. *European journal of applied physiology and occupational physiology.* 1999;79(2):121-126.
155. McGarr GW, Fujii N, Muia CM, Nishiyasu T, Kenny GP. 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.* 2019;317(1):R113-R120.
156. Kenney WL, Munce TA. Invited review: aging and human temperature regulation. *J Appl Physiol (1985).* 2003;95(6):2598-2603.
157. Dufour A, Candas V. Ageing and thermal responses during passive heat exposure: sweating and sensory aspects. *Eur J Appl Physiol.* 2007;100(1):19-26.
158. Sagawa S, Shiraki K, Yousef MK, Miki K. Sweating and cardiovascular responses of aged men to heat exposure. *J Gerontol.* 1988;43(1):M1-8.
159. Shoenfeld Y, Udassin R, Shapiro Y, Ohri A, Sohar E. Age and sex difference in response to short exposure to extreme dry heat. *J Appl Physiol Respir Environ Exerc Physiol.* 1978;44(1):1-4.
160. Celermajer DS, Sorensen KE, Spiegelhalter DJ, Georgakopoulos D, Robinson J, Deanfield JE. Aging is associated with endothelial dysfunction in healthy men

years before the age-related decline in women. *J Am Coll Cardiol.* 1994;24(2):471-476.

161. Zieman SJ, Melenovsky V, Kass DA. Mechanisms, pathophysiology, and therapy of arterial stiffness. *Arterioscler Thromb Vasc Biol.* 2005;25(5):932-943.
162. Chirinos JA, Segers P, Hughes T, Townsend R. Large-Artery Stiffness in Health and Disease: JACC State-of-the-Art Review. *J Am Coll Cardiol.* 2019;74(9):1237-1263.
163. Hashimoto J, Ito S. Pulse pressure amplification, arterial stiffness, and peripheral wave reflection determine pulsatile flow waveform of the femoral artery. *Hypertension.* 2010;56(5):926-933.
164. Schlader ZJ, Okada Y, Best SA, Fu Q, Crandall CG. Arterial stiffness during whole-body passive heat stress in healthy older adults. *Physiol Rep.* 2019;7(9):e14094.
165. Spina RJ, Turner MJ, Ehsani AA. Beta-adrenergic-mediated improvement in left ventricular function by exercise training in older men. *Am J Physiol.* 1998;274(2):H397-404.
166. Arbab-Zadeh A, Dijk E, Prasad A, et al. Effect of aging and physical activity on left ventricular compliance. *Circulation.* 2004;110(13):1799-1805.
167. Gagnon D, Romero SA, Ngo H, et al. Healthy aging does not compromise the augmentation of cardiac function during heat stress. *J Appl Physiol (1985).* 2016;121(4):885-892.
168. Schlader ZJ, Wilson TE, Crandall CG. Mechanisms of orthostatic intolerance during heat stress. *Auton Neurosci.* 2016;196:37-46.
169. Engelland RE, Hemingway HW, Tomasco OG, Olivencia-Yurvati AH, Romero SA. Neural Control of Blood Pressure is Altered Following Isolated Leg Heating in Aged Humans. *Am J Physiol Heart Circ Physiol.* 2020.
170. Morris NB, English T, Hospers L, Capon A, Jay O. The Effects of Electric Fan Use Under Differing Resting Heat Index Conditions: A Clinical Trial. *Ann Intern Med.* 2019.
171. Sawka MN, Burke LM, Eichner ER, Maughan RJ, Montain SJ, Stachenfeld NS. American College of Sports Medicine position stand. Exercise and fluid replacement. *Med Sci Sports Exerc.* 2007;39(2):377-390.
172. Sato K. The physiology, pharmacology, and biochemistry of the eccrine sweat gland. *Reviews of Physiology, Biochemistry and Pharmacology, Volume 79*: Springer; 1977:51-131.
173. Harrison MH. Effects on thermal stress and exercise on blood volume in humans. *Physiol Rev.* 1985;65(1):149-209.
174. Cheuvront SN, Kenefick RW. Dehydration: physiology, assessment, and performance effects. *Compr Physiol.* 2014;4(1):257-285.
175. Senay LC, Jr. Relationship of evaporative rates to serum [Na+], [K+], and osmolarity in acute heat stress. *J Appl Physiol.* 1968;25(2):149-152.
176. Sawka MN, Young AJ, Francesconi RP, Muza SR, Pandolf KB. Thermoregulatory and blood responses during exercise at graded hypohydration levels. *J Appl Physiol (1985).* 1985;59(5):1394-1401.
177. Sawka MN, Cheuvront SN, Kenefick RW. Hypohydration and Human Performance: Impact of Environment and Physiological Mechanisms. *Sports Med.* 2015;45 Suppl 1:S51-60.

178. Bourque CW. Central mechanisms of osmosensation and systemic osmoregulation. *Nat Rev Neurosci.* 2008;9(7):519-531.
179. Andreoli TE, Reeves WB, Bichet DG. Endocrine control of water balance. *Comprehensive Physiology.* 2010.
180. Tamma G, Goswami N, Reichmuth J, De Santo NG, Valenti G. Aquaporins, vasopressin, and aging: current perspectives. *Endocrinology.* 2015;156(3):777-788.
181. Stachenfeld NS, DiPietro L, Nadel ER, Mack GW. Mechanism of attenuated thirst in aging: role of central volume receptors. *Am J Physiol.* 1997;272(1 Pt 2):R148-157.
182. Greenleaf JE, Sargent F, 2nd. Voluntary dehydration in man. *J Appl Physiol.* 1965;20(4):719-724.
183. Phillips PA, Rolls BJ, Ledingham JG, et al. Reduced thirst after water deprivation in healthy elderly men. *N Engl J Med.* 1984;311(12):753-759.
184. Takamata A, Ito T, Yaegashi K, et al. Effect of an exercise-heat acclimation program on body fluid regulatory responses to dehydration in older men. *Am J Physiol.* 1999;277(4):R1041-1050.
185. Phillips PA, Bretherton M, Johnston CI, Gray L. Reduced osmotic thirst in healthy elderly men. *Am J Physiol.* 1991;261(1 Pt 2):R166-171.
186. Mack GW, Weseman CA, Langhans GW, Scherzer H, Gillen CM, Nadel ER. Body fluid balance in dehydrated healthy older men: thirst and renal osmoregulation. *J Appl Physiol (1985).* 1994;76(4):1615-1623.
187. Dontas AS, Marketos SG, Papanayiotou P. Mechanisms of renal tubular defects in old age. *Postgrad Med J.* 1972;48(559):295-303.
188. Yoon HE, Choi BS. The renin-angiotensin system and aging in the kidney. *Korean J Intern Med.* 2014;29(3):291-295.
189. Schoeller DA. Changes in total body water with age. *The American journal of clinical nutrition.* 1989;50(5):1176-1181.
190. Davy KP, Seals DR. Total blood volume in healthy young and older men. *J Appl Physiol (1985).* 1994;76(5):2059-2062.
191. Lowik MR, Westenbrink S, Hulshof KF, Kistemaker C, Hermus RJ. Nutrition and aging: dietary intake of "apparently healthy" elderly (Dutch Nutrition Surveillance System). *J Am Coll Nutr.* 1989;8(4):347-356.
192. Kenney WL, Chiu P. Influence of age on thirst and fluid intake. *Med Sci Sports Exerc.* 2001;33(9):1524-1532.
193. Centers for Disease Control Prevention. Percent of US adults 55 and over with chronic conditions. 2015.
194. Sturmberg JP, Picard M, Aron DC, et al. Health and Disease-Emergent States Resulting From Adaptive Social and Biological Network Interactions. *Front Med (Lausanne).* 2019;6:59.
195. Rothman KJ. Causes. *Am J Epidemiol.* 1976;104(6):587-592.
196. Lohmus M. Possible Biological Mechanisms Linking Mental Health and Heat-A Contemplative Review. *Int J Environ Res Public Health.* 2018;15(7).
197. Hermstad E, Adams B. Traumatic brain injury complicated by environmental hyperthermia. *J Emerg Trauma Shock.* 2010;3(1):66-69.

198. Lavados PM, Olavarría VV, Hoffmeister L. Ambient temperature and stroke risk: evidence supporting a short-term effect at a population level from acute environmental exposures. *Stroke.* 2018;49(1):255-261.
199. Bain AR, Nybo L, Ainslie PN. Cerebral Vascular Control and Metabolism in Heat Stress. *Compr Physiol.* 2015;5(3):1345-1380.
200. Thomas KN, van Rij AM, Lucas SJ, Cotter JD. 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.* 2017;312(3):R281-R291.
201. De Sario M, Katsouyanni K, Michelozzi P. Climate change, extreme weather events, air pollution and respiratory health in Europe. *Eur Respir J.* 2013;42(3):826-843.
202. Blachère J-C, Perreault S. *Médicaments des systèmes cardiovasculaire et rénal et canicules: rapport et recommandations.* Direction de la santé environnementale et de la toxicologie, Institut …; 2012.
203. Blachère J-C, Perreault S, Bélanger D, Gosselin P, Côté R, Kergoat M. *Médicaments du système nerveux central et canicules: rapport et recommandations.* Direction de la santé environnementale et de la toxicologie, Institut …; 2011.
204. Westaway K, Frank O, Husband A, et al. Medicines can affect thermoregulation and accentuate the risk of dehydration and heat-related illness during hot weather. *Journal of clinical pharmacy and therapeutics.* 2015;40(4):363-367.
205. Epstein Y, Yanovich R. Heatstroke. *N Engl J Med.* 2019;380(25):2449-2459.
206. Leon LR, Bouchama A. Heat stroke. *Compr Physiol.* 2015;5(2):611-647.
207. Jones TS, Liang AP, Kilbourne EM, et al. Morbidity and mortality associated with the July 1980 heat wave in St Louis and Kansas City, Mo. *Jama.* 1982;247(24):3327-3331.
208. Wang J-C, Chien W-C, Chu P, Chung C-H, Lin C-Y, Tsai S-H. The association between heat stroke and subsequent cardiovascular diseases. *PloS one.* 2019;14(2):e0211386.
209. Argaud L, Ferry T, Le QH, et al. Short- and long-term outcomes of heatstroke following the 2003 heat wave in Lyon, France. *Arch Intern Med.* 2007;167(20):2177-2183.
210. Moseley PL, Gapen C, Wallen ES, Walter ME, Peterson MW. Thermal stress induces epithelial permeability. *Am J Physiol.* 1994;267(2 Pt 1):C425-434.
211. Hall DM, Buettner GR, Oberley LW, Xu L, Matthes RD, Gisolfi CV. Mechanisms of circulatory and intestinal barrier dysfunction during whole body hyperthermia. *American Journal of Physiology-Heart and Circulatory Physiology.* 2001;280(2):H509-H521.
212. Michaud M, Balardy L, Moulis G, et al. Proinflammatory cytokines, aging, and age-related diseases. *J Am Med Dir Assoc.* 2013;14(12):877-882.
213. Liguori I, Russo G, Curcio F, et al. Oxidative stress, aging, and diseases. *Clin Interv Aging.* 2018;13:757-772.
214. Wright HE, McLellan TM, Larose J, Hardcastle SG, Boulay P, Kenny GP. Are circulating cytokine responses to exercise in the heat augmented in older men? *Appl Physiol Nutr Metab.* 2014;39(2):117-123.

215. Ilievska J, Cicimov V, Antova E, Gjorgoski I, Hadzy-Petrushev N, Mladenov M. HEAT-INDUCED OXIDATIVE STRESS AND INFLAMMATION IN RATS IN RELATION TO AGE. *Research in Physical Education, Sport & Health.* 2016;5(2).
216. Del Vesco AP, Khatlab AS, Goes ESR, et al. Age-related oxidative stress and antioxidant capacity in heat-stressed broilers. *Animal.* 2017;11(10):1783-1790.
217. Bouchama A, Hammami MM, Haq A, Jackson J, al-Sedairy S. Evidence for endothelial cell activation/injury in heatstroke. *Crit Care Med.* 1996;24(7):1173-1178.
218. Huisse M-G, Pease S, Hurtado-Nedelec M, et al. Leukocyte activation: the link between inflammation and coagulation during heatstroke. A study of patients during the 2003 heat wave in Paris. *Critical care medicine.* 2008;36(8):2288-2295.
219. Meyer MA, Ostrowski SR, Overgaard A, et al. Hypercoagulability in response to elevated body temperature and central hypovolemia. *J Surg Res.* 2013;185(2):e93-100.
220. Previtali E, Bucciarelli P, Passamonti SM, Martinelli I. Risk factors for venous and arterial thrombosis. *Blood Transfus.* 2011;9(2):120-138.
221. Le Blanc J, Lordkipanidze M. Platelet Function in Aging. *Front Cardiovasc Med.* 2019;6:109.
222. Wilkerson WR, Sane DC. Aging and thrombosis. Paper presented at: Seminars in thrombosis and hemostasis2002.
223. Bhaskaran K, Armstrong B, Hajat S, Haines A, Wilkinson P, Smeeth L. Heat and risk of myocardial infarction: hourly level case-crossover analysis of MINAP database. *BMJ.* 2012;345:e8050.
224. Linares C, Diaz J. Impact of high temperatures on hospital admissions: comparative analysis with previous studies about mortality (Madrid). *Eur J Public Health.* 2008;18(3):317-322.
225. Davido A, Patzak A, Dart T, et al. 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. *Emergency medicine journal.* 2006;23(7):515-518.
226. Hausfater P, Doumenc B, Chopin S, et al. Elevation of cardiac troponin I during non-exertional heat-related illnesses in the context of a heatwave. *Critical care.* 2010;14(3):R99.
227. Keatinge WR, Coleshaw SR, Easton JC, Cotter F, Mattock MB, Chelliah R. 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.* 1986;81(5):795-800.
228. Roberts GT, Ghebeh H, Chishti MA, et al. Microvascular injury, thrombosis, inflammation, and apoptosis in the pathogenesis of heatstroke: a study in baboon model. *Arterioscler Thromb Vasc Biol.* 2008;28(6):1130-1136.
229. Stefanadis C, Antoniou CK, Tsiachris D, Pietri P. Coronary Atherosclerotic Vulnerable Plaque: Current Perspectives. *J Am Heart Assoc.* 2017;6(3).
230. Verheye S, De Meyer GR, Van Langenhove G, Knaapen MW, Kockx MM. In vivo temperature heterogeneity of atherosclerotic plaques is determined by plaque composition. *Circulation.* 2002;105(13):1596-1601.

231. World Health Organization. Cardiovascular Diseases. 2019; https://www.who.int/health-topics/cardiovascular-diseases. Accessed November 11, 2019.
232. Fouad FM, Slominski JM, Tarazi RC. Left ventricular diastolic function in hypertension: relation to left ventricular mass and systolic function. *J Am Coll Cardiol.* 1984;3(6):1500-1506.
233. Redfield MM, Jacobsen SJ, Burnett JC, Jr., Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. *JAMA.* 2003;289(2):194-202.
234. Feihl F, Liaudet L, Waeber B. The macrocirculation and microcirculation of hypertension. *Curr Hypertens Rep.* 2009;11(3):182-189.
235. Mattace-Raso FU, van der Cammen TJ, Hofman A, et al. Arterial stiffness and risk of coronary heart disease and stroke: the Rotterdam Study. *Circulation.* 2006;113(5):657-663.
236. Palatini P, Julius S. The role of cardiac autonomic function in hypertension and cardiovascular disease. *Curr Hypertens Rep.* 2009;11(3):199-205.
237. Shah PK, Lecis D. Inflammation in atherosclerotic cardiovascular disease. *F1000Res.* 2019;8.
238. Diaz HS, Toledo C, Andrade DC, Marcus NJ, Del Rio R. Neuroinflammation in heart failure: new insights for an old disease. *J Physiol.* 2019.
239. Gotsman I, Zwas D, Admon D, Lotan C, Keren A. Seasonal variation in hospital admission in patients with heart failure and its effect on prognosis. *Cardiology.* 2010;117(4):268-274.
240. Wroblewski H, Norgaard T, Haunso S, Kastrup J. Microvascular distensibility in two different vascular beds in idiopathic dilated cardiomyopathy. *Am J Physiol.* 1995;269(6 Pt 2):H1973-1980.
241. Green DJ, Maiorana AJ, Siong JH, et al. Impaired skin blood flow response to environmental heating in chronic heart failure. *Eur Heart J.* 2006;27(3):338-343.
242. Kubo SH, Rector TS, Bank AJ, Williams RE, Heifetz SM. Endothelium-dependent vasodilation is attenuated in patients with heart failure. *Circulation.* 1991;84(4):1589-1596.
243. Cui J, Arbab-Zadeh A, Prasad A, Durand S, Levine BD, Crandall CG. Effects of heat stress on thermoregulatory responses in congestive heart failure patients. *Circulation.* 2005;112(15):2286-2292.
244. Cui J, Sinoway LI. Cardiovascular responses to heat stress in chronic heart failure. *Curr Heart Fail Rep.* 2014;11(2):139-145.
245. Wilker EH, Yeh G, Wellenius GA, Davis RB, Phillips RS, Mittleman MA. Ambient temperature and biomarkers of heart failure: a repeated measures analysis. *Environ Health Perspect.* 2012;120(8):1083-1087.
246. Cruz DN, Giuliani A, Ronco C. Acute kidney injury in heart failure. In: Turner NN, Lameire N, Goldsmith DJ, et al., eds. *Oxford Textbook of Clinical Nephrology (4 ed.)*: Oxford University Press; 2015.
247. Mills KT, Stefanescu A, He J. The global epidemiology of hypertension. *Nat Rev Nephrol.* 2020;16(4):223-237.

248. Ticcinelli V, Stankovski T, Iatsenko D, et al. Coherence and Coupling Functions Reveal Microvascular Impairment in Treated Hypertension. *Front Physiol.* 2017;8:749.
249. Carberry PA, Shepherd AM, Johnson JM. Resting and maximal forearm skin blood flows are reduced in hypertension. *Hypertension.* 1992;20(3):349-355.
250. Smith CJ, Santhanam L, Bruning RS, Stanhewicz A, Berkowitz DE, Holowatz LA. Upregulation of inducible nitric oxide synthase contributes to attenuated cutaneous vasodilation in essential hypertensive humans. *Hypertension.* 2011;58(5):935-942.
251. Holowatz LA, Kenney WL. Up-regulation of arginase activity contributes to attenuated reflex cutaneous vasodilatation in hypertensive humans. *J Physiol.* 2007;581(Pt 2):863-872.
252. Holowatz LA, Kenney WL. Local ascorbate administration augments NO- and non-NO-dependent reflex cutaneous vasodilation in hypertensive humans. *Am J Physiol Heart Circ Physiol.* 2007;293(2):H1090-1096.
253. Kenney WL, Kamon E. Comparative physiological responses of normotensive and essentially hypertensive men to exercise in the heat. *Eur J Appl Physiol Occup Physiol.* 1984;52(2):196-201.
254. Kenney WL, Kamon E, Buskirk E. Effect of mild essential hypertension on control of forearm blood flow during exercise in the heat. *Journal of Applied Physiology.* 1984;56(4):930-935.
255. Johnson RJ, Lanaspa MA, Gabriela Sanchez-Lozada L, Rodriguez-Iturbe B. The discovery of hypertension: evolving views on the role of the kidneys, and current hot topics. *Am J Physiol Renal Physiol.* 2015;308(3):F167-178.
256. Barzilai N, Huffman DM, Muzumdar RH, Bartke A. The critical role of metabolic pathways in aging. *Diabetes.* 2012;61(6):1315-1322.
257. Slawik M, Vidal-Puig AJ. Lipotoxicity, overnutrition and energy metabolism in aging. *Ageing research reviews.* 2006;5(2):144-164.
258. Jura M, Kozak LP. Obesity and related consequences to ageing. *Age (Dordr).* 2016;38(1):23.
259. Neeland IJ, Poirier P, Despres JP. Cardiovascular and Metabolic Heterogeneity of Obesity: Clinical Challenges and Implications for Management. *Circulation.* 2018;137(13):1391-1406.
260. Ahima RS. Connecting obesity, aging and diabetes. *Nat Med.* 2009;15(9):996-997.
261. Koppe C, Sari Kovats R, Menne B, Jendritzky G, Wetterdienst D, Organization WH. *Heat-waves: risks and responses.* Copenhagen: WHO Regional Office for Europe;2004.
262. Henschel A. Obesity as an occupational hazard. *Can J Public Health.* 1967;58(11):491-493.
263. Speakman JR. Obesity and thermoregulation. *Handbook of clinical neurology.* Vol 156: Elsevier; 2018:431-443.
264. Bar-Or O, Lundegren HM, Buskirk ER. Heat tolerance of exercising obese and lean women. *J Appl Physiol.* 1969;26(4):403-409.
265. Bhowmik A, Repaka R, Mishra SC. Thermal analysis of the increasing subcutaneous fat thickness within the human skin—a numerical study. *Numerical Heat Transfer, Part A: Applications.* 2015;67(3):313-329.

266. Dervis S, Coombs GB, Chaseling GK, Filingeri D, Smoljanic J, Jay O. A comparison of thermoregulatory responses to exercise between mass-matched groups with large differences in body fat. *J Appl Physiol (1985).* 2016;120(6):615-623.
267. Notley SR, Lamarche DT, Meade RD, Flouris AD, Kenny GP. Revisiting the influence of individual factors on heat exchange during exercise in dry heat using direct calorimetry. *Exp Physiol.* 2019;104(7):1038-1050.
268. Skrapari I, Tentolouris N, Perrea D, Bakoyiannis C, Papazafiropoulou A, Katsilambros N. Baroreflex sensitivity in obesity: relationship with cardiac autonomic nervous system activity. *Obesity (Silver Spring).* 2007;15(7):1685-1693.
269. Lee JF, Harrison ML, Christmas KM, Kim K, Hurr C, Brothers RM. Elevated resting heart rate and reduced orthostatic tolerance in obese humans. *Clin Auton Res.* 2014;24(1):39-46.
270. Vasan RS. Cardiac function and obesity. *Heart.* 2003;89(10):1127-1129.
271. Rosinger AY, Lawman HG, Akinbami LJ, Ogden CL. The role of obesity in the relation between total water intake and urine osmolality in US adults, 2009–2012. *The American journal of clinical nutrition.* 2016;104(6):1554-1561.
272. Stookey J, Barclay D, Arieff A, Popkin B. The altered fluid distribution in obesity may reflect plasma hypertonicity. *European journal of clinical nutrition.* 2007;61(2):190.
273. Stevens LA, Viswanathan G, Weiner DE. CKD and ESRD in the elderly: current prevalence, future projections, and clinical significance. *Advances in chronic kidney disease.* 2010;17(4):293.
274. Climie RE, van Sloten TT, Bruno R-M, et al. Macrovasculature and microvasculature at the crossroads between type 2 diabetes mellitus and hypertension. *Hypertension.* 2019;73(6):1138-1149.
275. Kenny GP, Sigal RJ, McGinn R. Body temperature regulation in diabetes. *Temperature (Austin).* 2016;3(1):119-145.
276. World Health Organization. *Global report on diabetes: executive summary.* World Health Organization;2016.
277. Beer S, Feihl F, Ruiz J, et al. Comparison of skin microvascular reactivity with hemostatic markers of endothelial dysfunction and damage in type 2 diabetes. *Vasc Health Risk Manag.* 2008;4(6):1449-1458.
278. Williams SB, Cusco JA, Roddy MA, Johnstone MT, Creager MA. Impaired nitric oxide-mediated vasodilation in patients with non-insulin-dependent diabetes mellitus. *J Am Coll Cardiol.* 1996;27(3):567-574.
279. Wick DE, Roberts SK, Basu A, et al. Delayed threshold for active cutaneous vasodilation in patients with Type 2 diabetes mellitus. *J Appl Physiol (1985).* 2006;100(2):637-641.
280. Sokolnicki LA, Strom NA, Roberts SK, Kingsley-Berg SA, Basu A, Charkoudian N. Skin blood flow and nitric oxide during body heating in type 2 diabetes mellitus. *J Appl Physiol (1985).* 2009;106(2):566-570.
281. Petrofsky JS, Lee S, Patterson C, Cole M, Stewart B. Sweat production during global heating and during isometric exercise in people with diabetes. *Med Sci Monit.* 2005;11(11):CR515-521.

282. Rand S, Petrofsky JS, Zimmerman G. Diabetes: sweat response and heart rate variability during electrical stimulation in controls and people with diabetes. *JOURNAL OF APPLIED RELIABILITY.* 2008;8(1):48.
283. Fealey RD, Low PA, Thomas JE. Thermoregulatory sweating abnormalities in diabetes mellitus. *Mayo Clin Proc.* 1989;64(6):617-628.
284. Luo KR, Chao CC, Hsieh PC, Lue JH, Hsieh ST. Effect of glycemic control on sudomotor denervation in type 2 diabetes. *Diabetes Care.* 2012;35(3):612-616.
285. Kenny GP, Stapleton JM, Yardley JE, Boulay P, Sigal RJ. Older adults with type 2 diabetes store more heat during exercise. *Med Sci Sports Exerc.* 2013;45(10):1906-1914.
286. Notley SR, Poirier MP, Sigal RJ, et al. Exercise Heat Stress in Patients With and Without Type 2 Diabetes. *JAMA.* 2019;322(14):1409-1411.
287. Poirier MP, Notley SR, Boulay P, et al. Type 2 diabetes does not exacerbate body heat storage in older adults during brief, extreme passive heat exposure. *Temperature (Austin).* 2020;7(3):263-269.
288. Atkinson MA, Eisenbarth GS, Michels AW. Type 1 diabetes. *Lancet.* 2014;383(9911):69-82.
289. Tancredi M, Rosengren A, Svensson A-M, et al. Excess mortality among persons with type 2 diabetes. *New England Journal of Medicine.* 2015;373(18):1720-1732.
290. Petrofsky JS, Focil N, Prowse M, et al. Autonomic stress and balance—the impact of age and diabetes. *Diabetes Technology & Therapeutics.* 2010;12(6):475-481.
291. Low PA, Walsh JC, Huang CY, McLeod JG. The sympathetic nervous system in diabetic neuropathy. A clinical and pathological study. *Brain.* 1975;98(3):341-356.
292. Pikkujämsä SM, Huikuri HV, Airaksinen KJ, et al. Heart rate variability and baroreflex sensitivity in hypertensive subjects with and without metabolic features of insulin resistance syndrome. *American journal of hypertension.* 1998;11(5):523-531.
293. Petrofsky J, Lee S, Macnider M, Navarro E. Autonomic, endothelial function and the analysis of gait in patients with type 1 and type 2 diabetes. *Acta diabetologica.* 2005;42(1):7-15.
294. Liamis G, Liberopoulos E, Barkas F, Elisaf M. Diabetes mellitus and electrolyte disorders. *World J Clin Cases.* 2014;2(10):488-496.
295. Molitch ME, DeFronzo RA, Franz MJ, Keane WF. Nephropathy in diabetes. *Diabetes care.* 2004;27:S79.
296. Satirapoj B. Nephropathy in diabetes. *Diabetes*: Springer; 2013:107-122.
297. de Lorenzo A, Liano F. High temperatures and nephrology: The climate change problem. *Nefrologia.* 2017;37(5):492-500.
298. Ó Flatharta T, Flynn A, Mulkerrin EC. Heat-related chronic kidney disease mortality in the young and old: differing mechanisms, potentially similar solutions? *BMJ Evid Based Med.* 2019;24(2):45-47.
299. Lim Y-H, So R, Lee C, et al. Ambient temperature and hospital admissions for acute kidney injury: A time-series analysis. *Science of The Total Environment.* 2018;616:1134-1138.
300. McTavish RK, Richard L, McArthur E, et al. Association between high environmental heat and risk of acute kidney injury among older adults in a northern

climate: a matched case-control study. *American Journal of Kidney Diseases.* 2018;71(2):200-208.

301. Semenza JC. Acute renal failure during heat waves. *Am J Prev Med.* 1999;17(1):97.
302. Conti S, Masocco M, Meli P, et al. General and specific mortality among the elderly during the 2003 heat wave in Genoa (Italy). *Environmental research.* 2007;103(2):267-274.
303. Lunyera J, Mohottige D, Von Isenburg M, Jeuland M, Patel UD, Stanifer JW. CKD of uncertain etiology: a systematic review. *Clinical Journal of the American Society of Nephrology.* 2016;11(3):379-385.
304. Schlader ZJ, Hostler D, Parker MD, et al. The Potential for Renal Injury Elicited by Physical Work in the Heat. *Nutrients.* 2019;11(9).
305. Weiner M, Epstein F. Signs and symptoms of electrolyte disorders. *The Yale journal of biology and medicine.* 1970;43(2):76.
306. Perazella M. Hyperkalemia in the elderly: a group at high risk. *Connecticut medicine.* 1996;60(4):195-198.
307. Inoue Y, Havenith G, Kenney WL, Loomis JL, Buskirk ER. Exercise- and methylcholine-induced sweating responses in older and younger men: effect of heat acclimation and aerobic fitness. *Int J Biometeorol.* 1999;42(4):210-216.
308. Giordano M, Ciarambino T, Adinolf L. Severe hyponatremia in the elderly: the seasonalvariability in the emergency department. *Italian Journal of Emergency Medicine.* 2018;1:1-14.
309. Giordano M, Ciarambino T, Castellino P, et al. Seasonal variations of hyponatremia in the emergency department: age-related changes. *The American journal of emergency medicine.* 2017;35(5):749-752.
310. Moore K, Thompson C, Trainer P. Disorders of water balance. *Clin Med (Lond).* 2003;3(1):28-33.
311. Arieff AI. Hyponatremia, convulsions, respiratory arrest, and permanent brain damage after elective surgery in healthy women. *New England Journal of Medicine.* 1986;314(24):1529-1535.
312. Wald R, Jaber BL, Price LL, Upadhyay A, Madias NE. Impact of hospital-associated hyponatremia on selected outcomes. *Arch Intern Med.* 2010;170(3):294-302.
313. Leshem M. Salt appetite is not increased in summer heat. *Appetite.* 2017;108:28-31.
314. Hendi K, Leshem M. Salt appetite in the elderly. *Br J Nutr.* 2014;112(10):1621-1627.
315. Giordano M, Ciarambino T, Castellino P, et al. Diseases associated with electrolyte imbalance in the ED: age-related differences. *The American journal of emergency medicine.* 2016;34(10):1923-1926.
316. Lindner G, Pfortmüller CA, Leichtle AB, Fiedler GM, Exadaktylos AK. Age-related variety in electrolyte levels and prevalence of dysnatremias and dyskalemias in patients presenting to the emergency department. *Gerontology.* 2014;60(5):420-423.

317. Kellum JA, Lameire N, Aspelin P, et al. Kidney disease: improving global outcomes (KDIGO) acute kidney injury work group. KDIGO clinical practice guideline for acute kidney injury. *Kidney international supplements.* 2012;2(1):1-138.
318. Basile DP, Anderson MD, Sutton TA. Pathophysiology of acute kidney injury. *Compr Physiol.* 2012;2(2):1303-1353.
319. Thadhani R, Pascual M, Bonventre JV. Acute renal failure. *N Engl J Med.* 1996;334(22):1448-1460.
320. Pascual J, Liaño F, Ortuno J. The elderly patient with acute renal failure. *Journal of the American Society of Nephrology.* 1995;6(2):144-153.
321. Doyle JF, Forni LG. Acute kidney injury: short-term and long-term effects. *Crit Care.* 2016;20(1):188.
322. Hollenberg NK, Adams DF, Solomon HS, Rashid A, Abrams HL, Merrill JP. Senescence and the renal vasculature in normal man. *Circ Res.* 1974;34(3):309-316.
323. Smith JH, Robinson S, Pearcy M. Renal responses to exercise, heat and dehydration. *J Appl Physiol.* 1952;4(8):659-665.
324. Stocker SD, Hunwick KJ, Toney GM. Hypothalamic paraventricular nucleus differentially supports lumbar and renal sympathetic outflow in water-deprived rats. *The Journal of physiology.* 2005;563(1):249-263.
325. Bie P. Osmoreceptors, vasopressin, and control of renal water excretion. *Physiological Reviews.* 1980;60(4):961-1048.
326. Di Nicolantonio R, Mendelsohn F. Plasma renin and angiotensin in dehydrated and rehydrated rats. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology.* 1986;250(5):R898-R901.
327. Weinstein JR, Anderson S. The aging kidney: physiological changes. *Adv Chronic Kidney Dis.* 2010;17(4):302-307.
328. Chen YF, Li PL, Zou AP. Oxidative stress enhances the production and actions of adenosine in the kidney. *Am J Physiol Regul Integr Comp Physiol.* 2001;281(6):R1808-1816.
329. Tank JE, Vora JP, Houghton DC, Anderson S. Altered renal vascular responses in the aging rat kidney. *Am J Physiol.* 1994;266(6 Pt 2):F942-948.
330. Zou AP, Li N, Cowley AW, Jr. Production and actions of superoxide in the renal medulla. *Hypertension.* 2001;37(2 Pt 2):547-553.
331. Baylis C. Sexual dimorphism in the aging kidney: differences in the nitric oxide system. *Nat Rev Nephrol.* 2009;5(7):384-396.
332. Nath KA, Norby SM. Reactive oxygen species and acute renal failure. *Am J Med.* 2000;109(8):665-678.
333. Cirillo P, Gersch MS, Mu W, et al. Ketohexokinase-dependent metabolism of fructose induces proinflammatory mediators in proximal tubular cells. *J Am Soc Nephrol.* 2009;20(3):545-553.
334. Roncal-Jimenez CA, Ishimoto T, Lanaspa MA, et al. Aging-associated renal disease in mice is fructokinase dependent. *American Journal of Physiology-Renal Physiology.* 2016;311(4):F722-F730.
335. Lanaspa MA, Ishimoto T, Cicerchi C, et al. Endogenous fructose production and fructokinase activation mediate renal injury in diabetic nephropathy. *J Am Soc Nephrol.* 2014;25(11):2526-2538.

336. Sato Y, Roncal-Jimenez CA, Andres-Hernando A, et al. Increase of core temperature affected the progression of kidney injury by repeated heat stress exposure. *Am J Physiol Renal Physiol.* 2019;317(5):F1111-F1121.
337. Schmitt R, Coca S, Kanbay M, Tinetti ME, Cantley LG, Parikh CR. Recovery of kidney function after acute kidney injury in the elderly: a systematic review and meta-analysis. *Am J Kidney Dis.* 2008;52(2):262-271.
338. Levey AS, Coresh J. Chronic kidney disease. *Lancet.* 2012;379(9811):165-180.
339. Vlassara H, Torreggiani M, Post JB, Zheng F, Uribarri J, Striker GE. Role of oxidants/inflammation in declining renal function in chronic kidney disease and normal aging. *Kidney Int Suppl.* 2009(114):S3-11.
340. Ishani A, Xue JL, Himmelfarb J, et al. Acute kidney injury increases risk of ESRD among elderly. *Journal of the American Society of Nephrology.* 2009;20(1):223-228.
341. Stevens LA, Li S, Tamura MK, et al. 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). *American Journal of Kidney Diseases.* 2011;57(3):S9-S16.
342. Zhang QL, Rothenbacher D. Prevalence of chronic kidney disease in population-based studies: systematic review. *BMC Public Health.* 2008;8:117.
343. Abuelo JG. Normotensive ischemic acute renal failure. *N Engl J Med.* 2007;357(8):797-805.
344. Mahaldar AR. Acid base and fluid electrolyte disturbances in chronic kidney disease. *Clinical Queries: Nephrology.* 2012;1(4):295-299.
345. Musso C, Liakopoulos V, De Miguel R, Imperiali N, Algranati L. Transtubular potassium concentration gradient: comparison between healthy old people and chronic renal failure patients. *Int Urol Nephrol.* 2006;38(2):387-390.
346. Frassetto L, Sebastian A. Age and systemic acid-base equilibrium: analysis of published data. *J Gerontol A Biol Sci Med Sci.* 1996;51(1):B91-99.
347. Huang MJ, Wei RB, Wang Y, et al. Blood coagulation system in patients with chronic kidney disease: a prospective observational study. *BMJ Open.* 2017;7(5):e014294.
348. Darlington A, Ferreiro JL, Ueno M, et al. Haemostatic profiles assessed by thromboelastography in patients with end-stage renal disease. *Thromb Haemost.* 2011;106(1):67-74.
349. Vaziri ND, Gonzales EC, Wang J, Said S. Blood coagulation, fibrinolytic, and inhibitory proteins in end-stage renal disease: effect of hemodialysis. *Am J Kidney Dis.* 1994;23(6):828-835.
350. Billman GE. Homeostasis: The Underappreciated and Far Too Often Ignored Central Organizing Principle of Physiology. *Frontiers in Physiology.* 2020;11:200.
351. Joyner MJ. Physiology: alone at the bottom, alone at the top. *J Physiol.* 2011;589(Pt 5):1005.
352. Seals DR. Translational physiology: from molecules to public health. *J Physiol.* 2013;591(14):3457-3469.
353. Bircher J. Towards a dynamic definition of health and disease. *Medicine, Health Care and Philosophy.* 2005;8(3):335-341.

354. Kenefick RW, Cheuvront SN. Hydration for recreational sport and physical activity. *Nutr Rev.* 2012;70 Suppl 2:S137-142.
355. Tremblay MS, Warburton DE, Janssen I, et al. New Canadian physical activity guidelines. *Appl Physiol Nutr Metab.* 2011;36(1):36-46; 47-58.
356. Du Bois D. A formula to estimate the approximate surface area if height and weight be known. *Nutrition.* 1989;5:303-313.
357. Siri WE. The gross composition of the body. *Advances in biological and medical physics.* Vol 4: Elsevier; 1956:239-280.
358. Gizdulich P, Imholz B, van den Meiracker A, Parati G, Wesseling K. Finapres tracking of systolic pressure and baroreflex sensitivity improved by waveform filtering. *Journal of hypertension.* 1996;14(2):243-250.
359. Penaz J. Photoelectric measurement of blood pressure, volume and flow in the finger'In: Digest of the 10th International Conference on Medical and Biological Engineering. *Dresden.* 1973;104.
360. Snellen JW, Chang KS, Smith W. Technical description and performance characteristics of a human whole-body calorimeter. *Med Biol Eng Comput.* 1983;21(1):9-20.
361. ISO I. 9886: 2004. *Ergonomics–evaluation of thermal strain by physiological measurements. Geneva: International Standards Organization.* 2004.
362. Kitamura K, Jorgensen CR, Gobel FL, Taylor HL, Wang Y. Hemodynamic correlates of myocardial oxygen consumption during upright exercise. *J Appl Physiol.* 1972;32(4):516-522.
363. White WB. Heart rate and the rate-pressure product as determinants of cardiovascular risk in patients with hypertension. *American journal of hypertension.* 1999;12(S2):50S-55SS.
364. Dill DB, Costill DL. Calculation of percentage changes in volumes of blood, plasma, and red cells in dehydration. *J Appl Physiol.* 1974;37(2):247-248.
365. Du Bois D, Du Bois EF. Clinical calorimetry: tenth paper a formula to estimate the approximate surface area if height and weight be known. *Archives of Internal Medicine.* 1916;17(6_2):863-871.
366. Rowell LB, Brengelmann GL, Blackmon JR, Murray JA. Redistribution of blood flow during sustained high skin temperature in resting man. *J Appl Physiol.* 1970;28(4):415-420.
367. Rowell LB, Detry JR, Profant GR, Wyss C. Splanchnic vasoconstriction in hyperthermic man--role of falling blood pressure. *J Appl Physiol.* 1971;31(6):864-869.
368. Gravel H, Chaseling GK, Barry H, Debray A, Gagnon D. Cardiovascular control during heat stress in older adults: time for an update. *Am J Physiol Heart Circ Physiol.* 2020.
369. Millyard A, Layden JD, Pyne DB, Edwards AM, Bloxham SR. Impairments to Thermoregulation in the Elderly During Heat Exposure Events. *Gerontol Geriatr Med.* 2020;6:2333721420932432.
370. Morris NB, Gruss F, Lempert S, et al. A Preliminary Study of the Effect of Dousing and Foot Immersion on Cardiovascular and Thermal Responses to Extreme Heat. *JAMA.* 2019;322(14):1411-1413.

371. Gosmanova EO, Mikkelsen MK, Molnar MZ, et al. Association of Systolic Blood Pressure Variability With Mortality, Coronary Heart Disease, Stroke, and Renal Disease. *J Am Coll Cardiol.* 2016;68(13):1375-1386.
372. Mitchinson MJ. The hypotensive stroke. *Lancet.* 1980;1(8162):244-246.
373. Franciosi S, Perry FKG, Roston TM, Armstrong KR, Claydon VE, Sanatani S. The role of the autonomic nervous system in arrhythmias and sudden cardiac death. *Auton Neurosci.* 2017;205:1-11.
374. Notley SR, Meade RD, D'Souza AW, McGarr GW, Kenny GP. Cumulative effects of successive workdays in the heat on thermoregulatory function in the aging worker. *Temperature (Austin).* 2018;5(4):293-295.
375. Notley SR, Meade RD, D'Souza AW, Friesen BJ, Kenny GP. Heat Loss Is Impaired in Older Men on the Day after Prolonged Work in the Heat. *Med Sci Sports Exerc.* 2018;50(9):1859-1867.
376. Gupta S, Carmichael C, Simpson C, et al. Electric fans for reducing adverse health impacts in heatwaves. *Cochrane Database of Systematic Reviews.* 2012(7).
377. Morris NB, English T, Hospers L, Capon A, Jay O. The effects of electric fan use under differing resting heat index conditions: a clinical trial. *Annals of Internal Medicine.* 2019;171(9):675-677.
378. Reardon FD, Leppik KE, Wegmann R, Webb P, Ducharme MB, Kenny GP. The Snellen human calorimeter revisited, re-engineered and upgraded: design and performance characteristics. *Med Biol Eng Comput.* 2006;44(8):721-728.
379. Shibasaki M, Wilson TE, Bundgaard-Nielsen M, Seifert T, Secher NH, Crandall CG. Modelflow underestimates cardiac output in heat-stressed individuals. *Am J Physiol Regul Integr Comp Physiol.* 2011;300(2):R486-491.
380. Control CfD, Prevention. Heat illness and deaths--New York City, 2000-2011. *MMWR. Morbidity and mortality weekly report.* 2013;62(31):617.
381. Kenny GP, Flouris AD, Yagouti A, Notley SR. Towards establishing evidence-based guidelines on maximum indoor temperatures during hot weather in temperate continental climates. *Temperature (Austin).* 2019;6(1):11-36.
382. Smargiassi A, Fournier M, Griot C, Baudouin Y, Kosatsky T. Prediction of the indoor temperatures of an urban area with an in-time regression mapping approach. *J Expo Sci Environ Epidemiol.* 2008;18(3):282-288.
383. Wright A, Young A, Natarajan S. Dwelling temperatures and comfort during the August 2003 heat wave. *Building Services Engineering Research and Technology.* 2005;26(4):285-300.
384. Kim YM, Kim S, Cheong HK, Ahn B, Choi K. Effects of heat wave on body temperature and blood pressure in the poor and elderly. *Environ Health Toxicol.* 2012;27:e2012013.
385. Basu R, Samet JM. An exposure assessment study of ambient heat exposure in an elderly population in Baltimore, Maryland. *Environ Health Perspect.* 2002;110(12):1219-1224.
386. Hondula DM, Kuras ER, Betzel S, et al. Novel metrics for relating personal heat exposure to social risk factors and outdoor ambient temperature. *Environment International.*146:106271.
387. Clarke JF. Some effects of the urban structure on heat mortality. *Environmental research.* 1972;5(1):93-104.

388. Hondula DM, Davis RE, Leisten MJ, Saha MV, Veazey LM, Wegner CR. Fine-scale spatial variability of heat-related mortality in Philadelphia County, USA, from 1983-2008: a case-series analysis. *Environ Health.* 2012;11:16.

389. Achebak H, Devolder D, Ballester J. Trends in temperature-related age-specific and sex-specific mortality from cardiovascular diseases in Spain: a national time-series analysis. *Lancet Planet Health.* 2019;3(7):e297-e306.

390. Fu SH, Gasparrini A, Rodriguez PS, Jha P. Mortality attributable to hot and cold ambient temperatures in India: a nationally representative case-crossover study. *PLoS Med.* 2018;15(7):e1002619.

391. Son JY, Lee JT, Anderson GB, Bell ML. Vulnerability to temperature-related mortality in Seoul, Korea. *Environ Res Lett.* 2011;6(3).

392. Bunker A, Wildenhain J, Vandenbergh A, et al. Effects of Air Temperature on Climate-Sensitive Mortality and Morbidity Outcomes in the Elderly; a Systematic Review and Meta-analysis of Epidemiological Evidence. *EBioMedicine.* 2016;6:258-268.

393. Carrillo AE, Flouris AD, Herry CL, et al. Heart rate variability during high heat stress: a comparison between young and older adults with and without Type 2 diabetes. *Am J Physiol Regul Integr Comp Physiol.* 2016;311(4):R669-R675.

394. Lucas RA, Cotter JD, Morrison S, Ainslie PN. The effects of ageing and passive heating on cardiorespiratory and cerebrovascular responses to orthostatic stress in humans. *Exp Physiol.* 2008;93(10):1104-1117.

395. Ewing DJ, Martyn CN, Young RJ, Clarke BF. The value of cardiovascular autonomic function tests: 10 years experience in diabetes. *Diabetes Care.* 1985;8(5):491-498.

396. Spallone V, Bellavere F, Scionti L, et al. Recommendations for the use of cardiovascular tests in diagnosing diabetic autonomic neuropathy. *Nutrition, Metabolism and Cardiovascular Diseases.* 2011;21(1):69-78.

397. Stranieri A, Abawajy J, Kelarev A, Huda S, Chowdhury M, Jelinek HF. An approach for Ewing test selection to support the clinical assessment of cardiac autonomic neuropathy. *Artif Intell Med.* 2013;58(3):185-193.

398. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart Rate Variability. *Circulation.* 1996;93(5):1043-1065.

399. Camm A, Malik M, Bigger J, et al. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *Circulation.* 1996;93(5):1043-1065.

400. Toichi M, Sugiura T, Murai T, Sengoku A. A new method of assessing cardiac autonomic function and its comparison with spectral analysis and coefficient of variation of R-R interval. *J Auton Nerv Syst.* 1997;62(1-2):79-84.

401. Bravi A. CIMVA Core Description manual. 2013.

402. Consolazio C, Johnson R, Pecora L. Physiological variability in young men. *Physiological measurements of metabolic functions in man.* 1963:453-480.

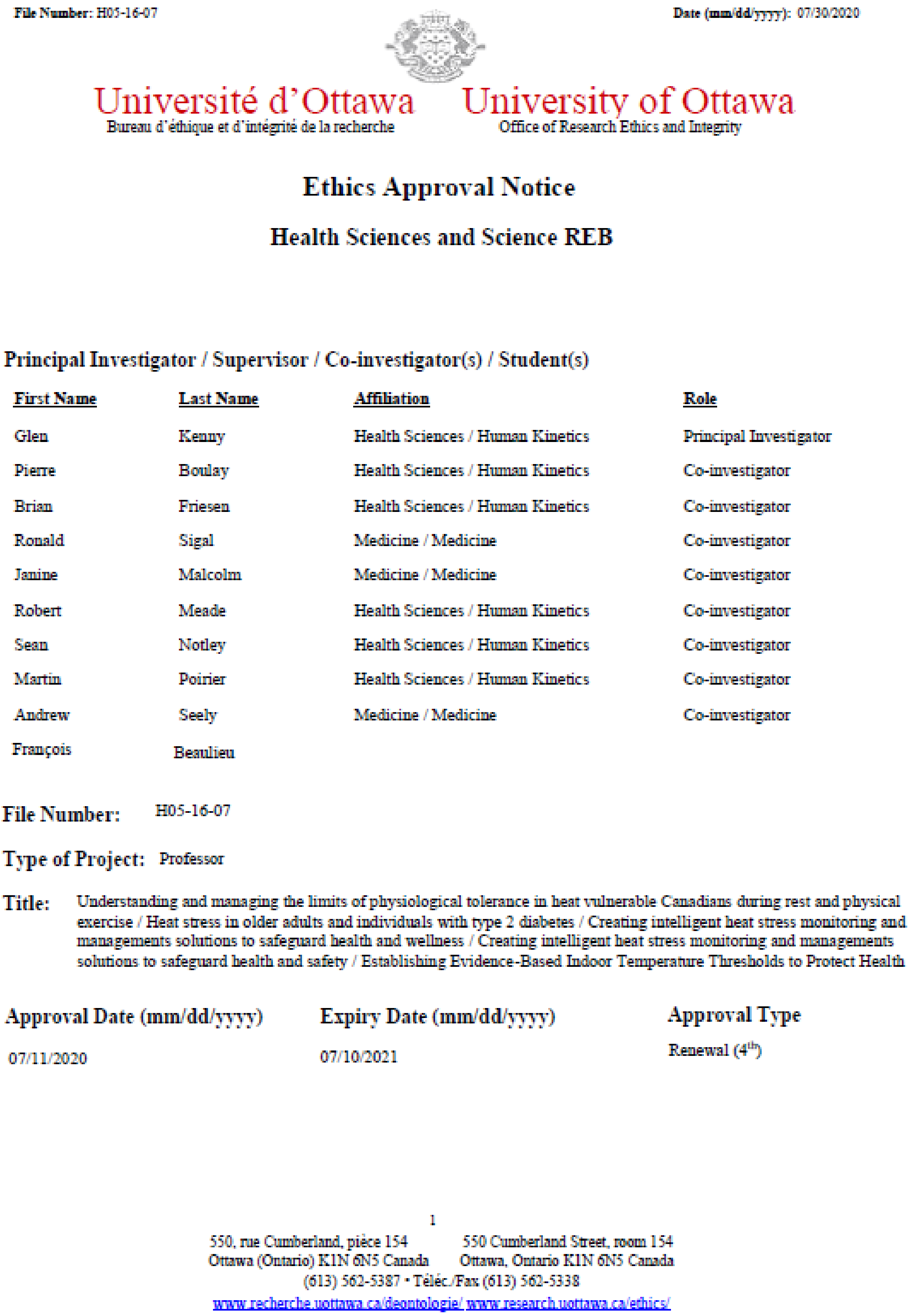
403. Pinheiro J, Bates D, DebRoy S, et al. Package ‘nlme’. *Linear and nonlinear mixed effects models, version.* 2017;3(1).

404. Lenth R, Singmann H, Love J, Buerkner P, Herve M. Emmeans: Estimated marginal means, aka least-squares means. *R package version.* 2018;1(1):3.
405. Benarroch EE. The arterial baroreflex: functional organization and involvement in neurologic disease. *Neurology.* 2008;71(21):1733-1738.
406. Crandall CG. Carotid baroreflex responsiveness in heat-stressed humans. *Am J Physiol Heart Circ Physiol.* 2000;279(4):H1955-1962.
407. Crandall CG, Zhang R, Levine BD. Effects of whole body heating on dynamic baroreflex regulation of heart rate in humans. *Am J Physiol Heart Circ Physiol.* 2000;279(5):H2486-2492.
408. Yamazaki F, Sone R. Thermal stress modulates arterial pressure variability and arterial baroreflex response of heart rate during head-up tilt in humans. *Eur J Appl Physiol.* 2001;84(4):350-357.
409. Reardon M, Malik M. Changes in heart rate variability with age. *Pacing Clin Electrophysiol.* 1996;19(11 Pt 2):1863-1866.
410. Jandackova VK, Scholes S, Britton A, Steptoe A. Are Changes in Heart Rate Variability in Middle-Aged and Older People Normative or Caused by Pathological Conditions? Findings From a Large Population-Based Longitudinal Cohort Study. *J Am Heart Assoc.* 2016;5(2).
411. Morgan C, Foster J, Poston A, Sharpe T. Overheating in Scotland: contributing factors in occupied homes. *Building Research & Information.* 2017;45(1-2):143-156.
412. Ohnaka T, Tochihara Y, Kanda K. Body movements of the elderly during sleep and thermal conditions in bedrooms in summer. *Applied Human Science.* 1995;14(2):89-93.
413. van Loenhout JA, le Grand A, Duijm F, et al. The effect of high indoor temperatures on self-perceived health of elderly persons. *Environ Res.* 2016;146:27-34.
414. Sivertsen B, Pallesen S, Glozier N, et al. Midlife insomnia and subsequent mortality: the Hordaland health study. *BMC public health.* 2014;14(1):1-10.
415. Hajat S, O'Connor M, Kosatsky T. Health effects of hot weather: from awareness of risk factors to effective health protection. *Lancet.* 2010;375(9717):856-863.
416. Government of Ontario. A Guide to the Long-Term Care Homes Act, 2007 and Regulation 79/10. 2007; http://health.gov.on.ca/en/public/programs/ltc/docs/ltcha_guide_phase1.pdf. Accessed January 16, 2021.
417. Sampson NR, Gronlund CJ, Buxton MA, et al. Staying cool in a changing climate: Reaching vulnerable populations during heat events. *Glob Environ Change.* 2013;23(2):475-484.
418. Lakens D. Equivalence Tests: A Practical Primer for t Tests, Correlations, and Meta-Analyses. *Soc Psychol Personal Sci.* 2017;8(4):355-362.
419. Bongers CC, Hopman MT, Eijsvogels TM. Cooling interventions for athletes: an overview of effectiveness, physiological mechanisms, and practical considerations. *Temperature.* 2017;4(1):60-78.
420. Booth JD, Wilsmore BR, MacDonald AD, Zeyl A, Storlien LH, Taylor NA. Intramuscular temperatures during exercise in the heat following pre-cooling and pre-heating. *Journal of Thermal Biology.* 2004;29(7-8):709-715.

421. Zimmermann M, Landers G, Wallman K, Kent G. Precooling With Crushed Ice: As Effective as Heat Acclimation at Improving Cycling Time-Trial Performance in the Heat. *Int J Sports Physiol Perform.* 2018;13(2):228-234.
422. Palecki MA, Changnon SA, Kunkel KE. The nature and impacts of the July 1999 heat wave in the midwestern United States: learning from the lessons of 1995. *Bulletin of the American Meteorological Society.* 2001;82(7):1353-1368.
423. Bassil KL, Cole DC. Effectiveness of public health interventions in reducing morbidity and mortality during heat episodes: a structured review. *Int J Environ Res Public Health.* 2010;7(3):991-1001.
424. McGlothlin AE, Lewis RJ. Minimal clinically important difference: defining what really matters to patients. *JAMA.* 2014;312(13):1342-1343.
425. Heng HH. Heterogeneity-mediated cellular adaptation and its trade-off: searching for the general principles of diseases. *J Eval Clin Pract.* 2017;23(1):233-237.
426. Goh KI, Cusick ME, Valle D, Childs B, Vidal M, Barabasi AL. The human disease network. *Proc Natl Acad Sci U S A.* 2007;104(21):8685-8690.
427. Glaser R, Kiecolt-Glaser JK. Stress-induced immune dysfunction: implications for health. *Nat Rev Immunol.* 2005;5(3):243-251.
428. Wallace DC. A mitochondrial bioenergetic etiology of disease. *J Clin Invest.* 2013;123(4):1405-1412.
429. Versari D, Daghini E, Virdis A, Ghiadoni L, Taddei S. Endothelial dysfunction as a target for prevention of cardiovascular disease. *Diabetes care.* 2009;32(suppl 2):S314-S321.
430. Furman D, Campisi J, Verdin E, et al. Chronic inflammation in the etiology of disease across the life span. *Nat Med.* 2019;25(12):1822-1832.
431. Bernard C. *Introduction à l'étude de la médecine expérimentale.* Ch. Delagrave; 1898.
432. Beaudoin M, Gosselin P. An effective public health program to reduce urban heat islands in Quebec, Canada. *Rev Panam Salud Publica.* 2016;40(3):160-166.
433. Downey L, Van Willigen M. Environmental stressors: the mental health impacts of living near industrial activity. *Journal of Health and Social Behavior.* 2005;46(3):289-305.
434. Davidson P, Anderton DL. Demographics of dumping. II: A national environmental equity survey and the distribution of hazardous materials handlers. *Demography.* 2000;37(4):461-466.
435. Macdonald H, Loder E, Abbasi K. Living systematic reviews at The BMJ. *BMJ.* 2020;370:m2925.
436. Penke B, Bogar F, Crul T, Santha M, Toth ME, Vigh L. Heat Shock Proteins and Autophagy Pathways in Neuroprotection: from Molecular Bases to Pharmacological Interventions. *Int J Mol Sci.* 2018;19(1).
437. Nose H, Morikawa M, Yamazaki T, et al. Beyond epidemiology: field studies and the physiology laboratory as the whole world. *J Physiol.* 2009;587(Pt 23):5569-5575.

APPEDICES

APPENDIX A – Ethics approval



File Number: H05-16-07 **Date (mm/dd/yyyy):** 07/30/2020

Université d'Ottawa
Bureau d'éthique et d'intégrité de la recherche

University of Ottawa
Office of Research Ethics and Integrity

Ethics Approval Notice

Health Sciences and Science REB

Principal Investigator / Supervisor / Co-investigator(s) / Student(s)

First Name	Last Name	Affiliation	Role
Glen	Kenny	Health Sciences / Human Kinetics	Principal Investigator
Pierre	Boulay	Health Sciences / Human Kinetics	Co-investigator
Brian	Friesen	Health Sciences / Human Kinetics	Co-investigator
Ronald	Sigal	Medicine / Medicine	Co-investigator
Janine	Malcolm	Medicine / Medicine	Co-investigator
Robert	Meade	Health Sciences / Human Kinetics	Co-investigator
Sean	Notley	Health Sciences / Human Kinetics	Co-investigator
Martin	Poirier	Health Sciences / Human Kinetics	Co-investigator
Andrew	Seely	Medicine / Medicine	Co-investigator
François	Beaulieu		

File Number: H05-16-07

Type of Project: Professor

Title: Understanding and managing the limits of physiological tolerance in heat vulnerable Canadians during rest and physical exercise / Heat stress in older adults and individuals with type 2 diabetes / Creating intelligent heat stress monitoring and managements solutions to safeguard health and wellness / Creating intelligent heat stress monitoring and managements solutions to safeguard health and safety / Establishing Evidence-Based Indoor Temperature Thresholds to Protect Health

Approval Date (mm/dd/yyyy)	Expiry Date (mm/dd/yyyy)	Approval Type
07/11/2020	07/10/2021	Renewal (4th)

1

550, rue Cumberland, pièce 154 550 Cumberland Street, room 154
Ottawa (Ontario) K1N 6N5 Canada Ottawa, Ontario K1N 6N5 Canada
(613) 562-5387 • Téléc./Fax (613) 562-5338
www.recherche.uottawa.ca/deontologie/ www.research.uottawa.ca/ethics/

APPENDIX B – Final published version of Thesis Article 1

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

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 thermoeffector 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

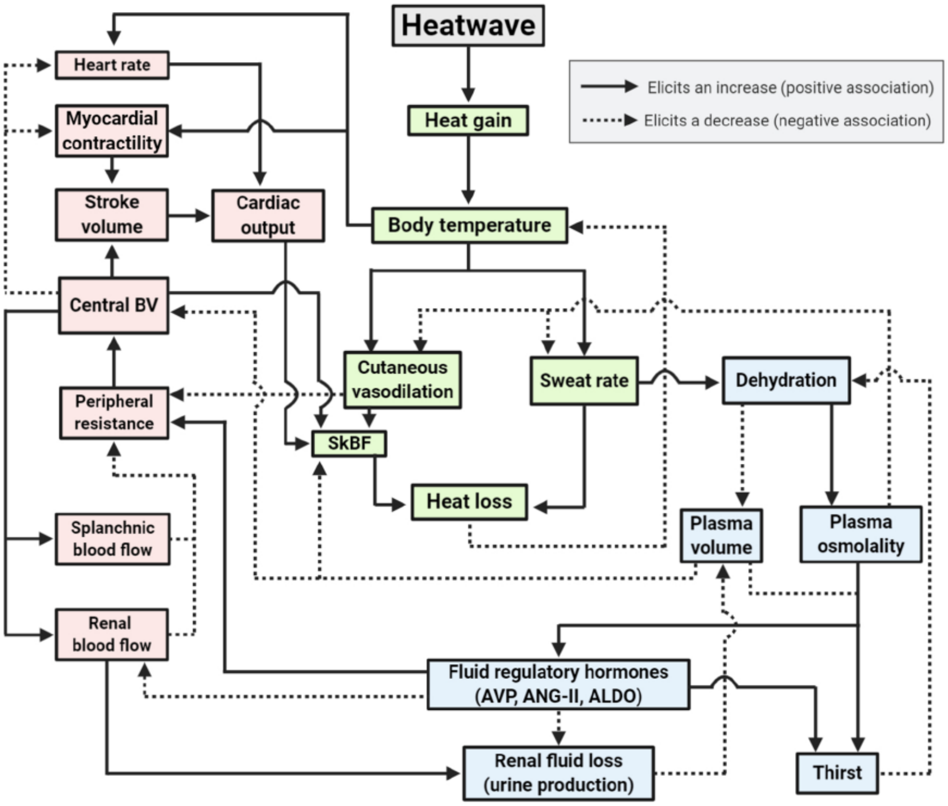


Fig. 1. A schematic summary of the integrated physiological responses tasked with maintaining homeostasis during extreme heat exposure. The green, red and blue boxes denote the thermoregulatory, cardiovascular and fluid regulatory systems, respectively. These broad classifications reflect the discussion 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.)

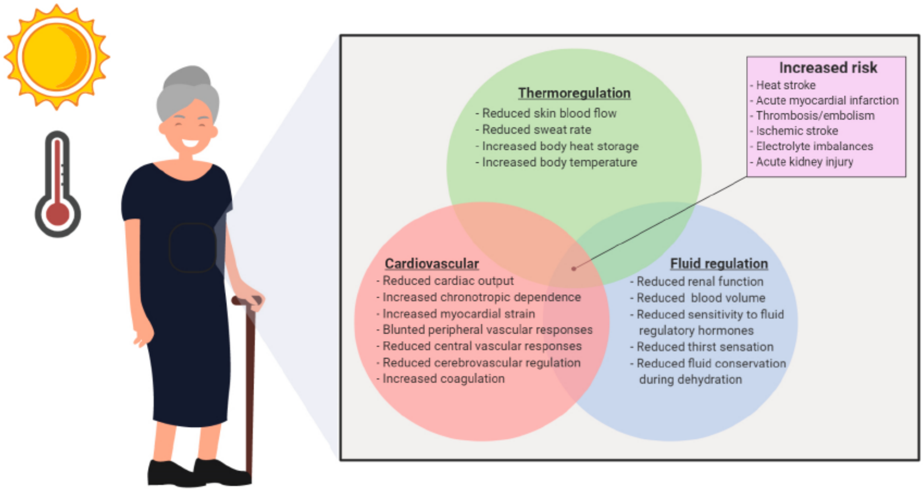


Fig. 2. A Venn diagram summarizing the age-related impairments in the integrated physiological responses to heat stress thought to contribute to the increased risk of acute adverse health events in older relative to young adults during heatwaves (see main text for details).

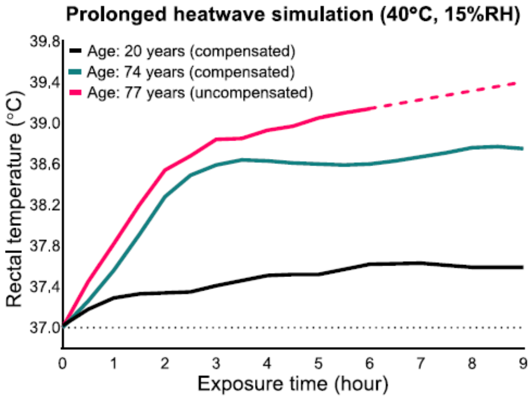


Fig. 3. Unpublished data from our laboratory showing rectal temperature in one young and two older women over a 9-h heatwave simulation (40°C, ~15% relative humidity; heat index: 38°C). These conditions were chosen to simulate the heat index experienced during recent heatwaves in North America in 2018 (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	21 (3) 65 (5)	36.5°C, 20% RH Heat index: 35°C	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.
	12 adults 12 adults	21 (3) 65 (5)	36.5°C, 60% RH Heat index: 50°C	120 min	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

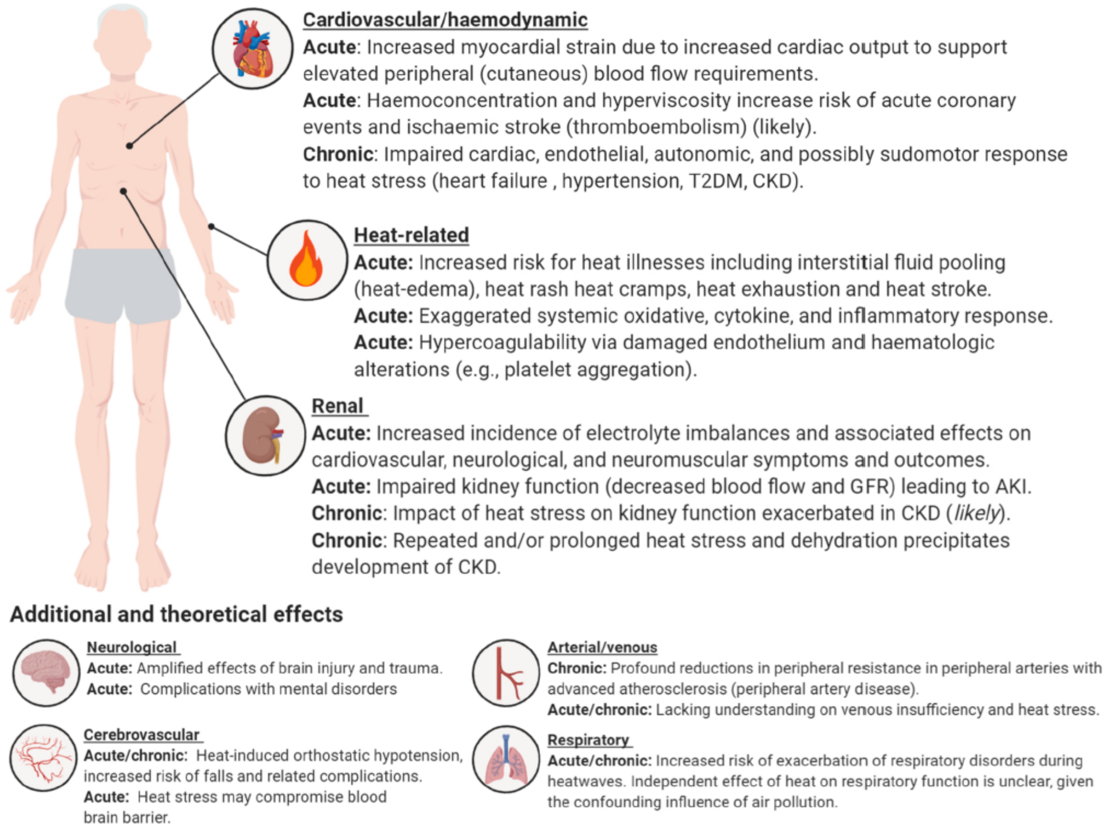
Heat illness is a blanket term used to describe multiple pathophysiological conditions related directly to elevated body temperature. These exist on a continuum describing the extent of dysregulation, ranging from heat edema, heat-cramps and heat rash, to heat exhaustion and heat stroke (Székely et al., 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



Cardiovascular/haemodynamic

Acute: Increased myocardial strain due to increased cardiac output to support elevated peripheral (cutaneous) blood flow requirements.

Acute: Haemoconcentration and hyperviscosity increase risk of acute coronary events and ischaemic stroke (thromboembolism) (likely).

Chronic: Impaired cardiac, endothelial, autonomic, and possibly sudomotor response to heat stress (heart failure , hypertension, T2DM, CKD).

Heat-related

Acute: Increased risk for heat illnesses including interstitial fluid pooling (heat-edema), heat rash heat cramps, heat exhaustion and heat stroke.

Acute: Exaggerated systemic oxidative, cytokine, and inflammatory response.

Acute: Hypercoagulability via damaged endothelium and haematologic alterations (e.g., platelet aggregation).

Renal

Acute: Increased incidence of electrolyte imbalances and associated effects on cardiovascular, neurological, and neuromuscular symptoms and outcomes.

Acute: Impaired kidney function (decreased blood flow and GFR) leading to AKI.

Chronic: Impact of heat stress on kidney function exacerbated in CKD (*likely*).

Chronic: Repeated and/or prolonged heat stress and dehydration precipitates development of CKD.

Additional and theoretical effects

Neurological

Acute: Amplified effects of brain injury and trauma.

Acute: Complications with mental disorders

Cerebrovascular

Acute/chronic: Heat-induced orthostatic hypotension, increased risk of falls and related complications.

Acute: Heat stress may compromise blood brain barrier.

Arterial/venous

Chronic: Profound reductions in peripheral resistance in peripheral arteries with advanced atherosclerosis (peripheral artery disease).

Acute/chronic: Lacking understanding on venous insufficiency and heat stress.

Respiratory

Acute/chronic: Increased risk of exacerbation of respiratory disorders during heatwaves. Independent effect of heat on respiratory function is unclear, given the confounding influence of air pollution.

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).

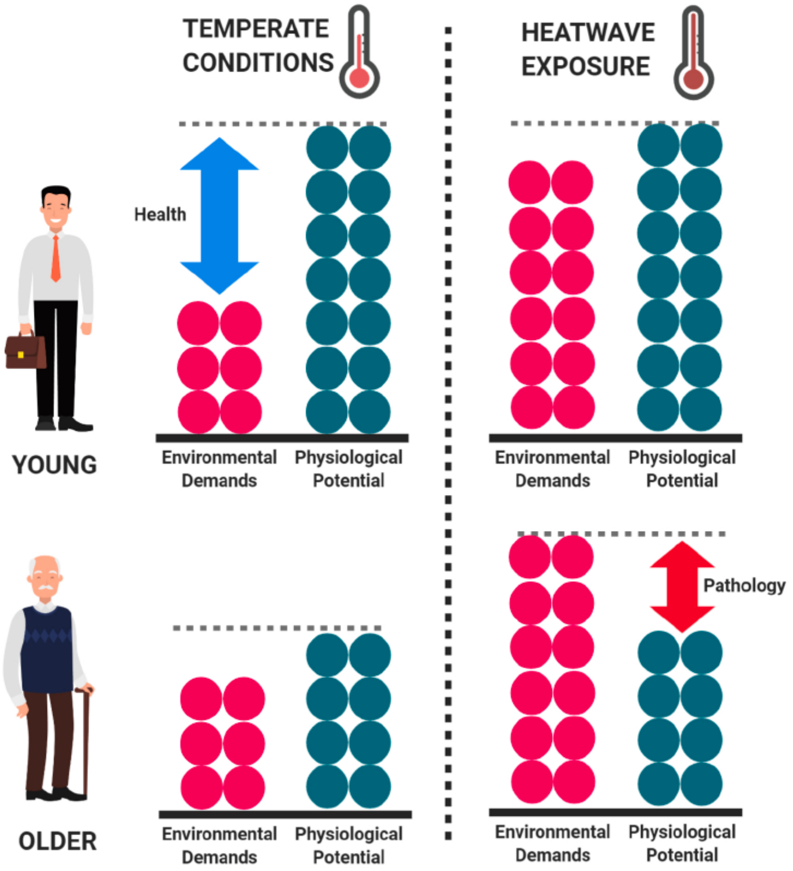


Fig. 5. Bircher's model of health (Bircher, 2005) applied to heatwaves. In this example health is seen as a *balance* between physiological potential (complex and adaptive interactions between physiological systems) and environmental demands (determined by the number and magnitude of environmental stressors). 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.

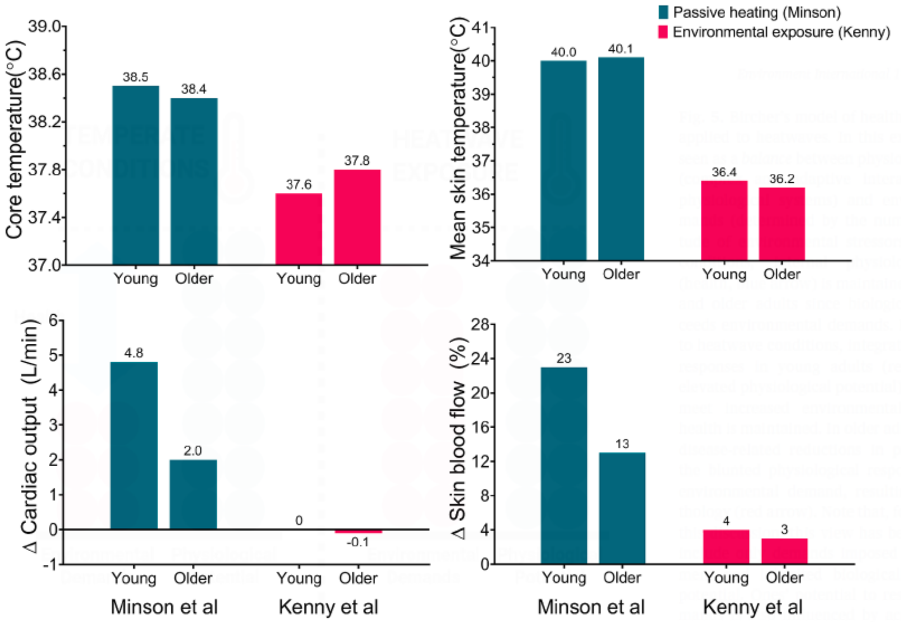


Fig. 6. Differences in thermal and cardiovascular responses during whole-body passive heating and environmental exposure. Data presented are changes in core and mean skin temperatures, cardiac output and forearm blood flow forearm blood flows in studies by Kenny et al. (2017) and Minson et al. (1998). 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 ed˘eds: 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 ed˘eds: 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., Cornwall 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.

APPENDIX C – Scientific papers published during the tenure of the thesis

1. Notley SR, **Meade RD** and Kenny GP. Ingestion time does not influence the validity of gastrointestinal temperature sensors during exercise-heat stress. *Temperature*. 2021;8(1):12-20. doi: 10.1080/23328940.2020.1801119

2. McCormick JJ, King KE, Cote MD, **Meade RD**, Akerman AP and Kenny GP. Impaired autophagy following ex vivo heating at physiologically relevant temperatures in peripheral blood mononuclear cells from older adults. *J Therm Biol*. 2021;95:102790. doi: 10.1016/j.jtherbio.2020.102790.

3. Akerman AP, **Meade RD**, Notley SR, Rutherford MM and Kenny GP. Myths and Methodologies: Reliability of non-invasive estimates of cardiac autonomic modulation during whole-body passive heating. *Exp Physiol*. 2020. doi: 10.1113/EP089069. Online ahead of print.

4. Rutherford MM, Akerman AP, Notley SR, **Meade RD**, Schmidt MD and Kenny GP. Myths and Methodologies: Regional variation in the reliability of sweat rate measured via the ventilated capsule technique during passive heating. Submitted to *Exp Physiol*. 2020. doi: 10.1113/EP089074. Online ahead of print.

5. Gemae MR, Akerman AP, McGarr GW, Schmidt MD, **Meade RD**, Notley SR, Rutherford MM and Kenny GP. Myths and Methodologies: Reliability of Forearm Cutaneous Vasodilatation Measured Using Laser-Doppler Flowmetry During Whole-body Passive Heating. *Exp Physiol*. 2020. doi: 10.1113/EP089073. Online ahead of print.

6. **Meade RD,** Notley SR, Rutherford MM, Boulay P, Sigal RJ and Kenny GP Aging attenuates the effect of extracellular hyperosmolality on whole-body heat exchange during exercise-heat stress. *J Physiol.* 2020;598(22):5133-5148. doi: 10.1113/JP280132.

7. **Meade RD**, Akerman AP, Notley SR, McGinn R, Poirier P, Gosselin P and Kenny GP. Physiological factors characterizing heat-vulnerable older adults: A narrative review. *Environ Int.* 2020;144:105909. doi: 10.1016/j.envint.2020.105909.

8. Notley SR, **Meade RD**, D'Souza AW, Rutherford MM, Kim JH and Kenny GP. Heat exchange in young and older men during constant- and variable-intensity work. *Med Sci Sports Exerc.* 2020;52(12):2628-2636. doi: 10.1249/MSS.0000000000002410.

9. Notley SR, D'Souza AW, Meade RD, Richards B and Kenny GP. Heat exchange in men and women during constant- and variable-intensity work of the same average intensity. *Eur J Appl Physiol*. 2020 Dec;120(12):2665-2675. doi: 10.1007/s00421-020-04486-3.

10. Macartney MJ, Notley SR, **Meade RD**, Herry CL and Kenny GP. Heart rate variability on the day following prolonged work in the heat. *J Occup Environ Hyg*. 2020;17(9):383-389. doi: 10.1080/15459624.2020.1779932.

11. Notley SR, **Meade RD**, Akerman AP, Poirier MP, Boulay P, Flouris AD, Sigal R and Kenny GP. Evidence for age-related differences in heat acclimatization responsiveness. *Exp Physiol*. 2020. Online ahead of print. doi: 10.1113/EP088728.

12. Notley SR, Akerman AP, **Meade RD**, McGarr GW and Kenny GP. Exercise thermoregulation in prepubertal children: is our understanding still in its infancy? *Med Sci Sports Exerc*. 2020. Online ahead of print. doi: 10.1249/MSS.0000000000002391.

13. Macartney MJ, **Meade RD**, Notley SR, Herry CL, Seely AJE and Kenny GP. Fluid loss during exercise-heat stress reduces cardiac vagal autonomic modulation. *Med Sci Sports Exerc.* 2020;52(2):362-369. doi: 10.1249/MSS.0000000000002136.

14. D'Souza AW, Notley SR, **Meade RD** and Kenny GP. Intermittent pneumatic compression does not enhance whole-body heat loss in elderly adults during dry heat exposure*. Appl Physiol Nutr Metab*. 2019;44(12):1383-1386 doi: 10.1139/apnm-2019-0364.

15. **Meade RD**, Notley SR and Kenny GP. Aging and human heat dissipation during exercise in the heat: an update and future directions. *Curr Opin Physiol*. 2019; 10:219-225. DOI: 10.1016/j.cophys.2019.07.003.

16. Fujii N, Hatam K, McGarr GW, **Meade RD**, Boulay P, Nishiyasu T and Kenny GP. Exogenous activation of protease-activated receptor 2 attenuates cutaneous vasodilatation and sweating in older men exercising in the heat. *Skin Pharmacol Physiol*. 2019;32(5):235-24. 10.1016/j.cophys.2019.07.003.

17. Notley SR, Lamarche DR, **Meade RD**, Flouris AD and Kenny GP. Revisiting the influence of individual factors on whole-body heat exchange during exercise in dry heat using direct calorimetry. *Exp Physiol*. 2019;104(7):1038-1050. DOI: 10.1113/EP087666.

18. Notley SR, **Meade RD,** D'Souza AW, McGarr GW and Kenny GP. Cumulative effects of successive workdays in the heat on thermoregulatory function in the aging worker. *Temperature*. 2018;5(4):293-295. DOI: 10.1080/23328940.2018.1512830.

19. **Meade RD,** Notley SR, D'Souza AD, Dervis S, Boulay P, Sigal RJ and Kenny GP. Interactive effects of age and hydration state on human thermoregulatory function during exercise in hot-dry conditions. *Acta Physiol.* 2019;226(1):e13226*. DOI: 10.1111/apha.13226.*

20. Fujii N, Danquah, MO, **Meade RD,** Nishyasu T and Kenny GP. The effect of exogenous protease-activated receptor 2 activation on cutaneous vasodilatation and sweating in young males during rest and exercise in the heat. *Temperature*. 2018;5(3):257-266. DOI: 10.1080/23328940.2018.1506563.

21. Fujii N, Pastore OL, McGarr GW, **Meade RD,** McNeely BD, Nishiyasu T, Sigal RJ and Kenny GP. Cyclooxygenase-1 and -2 modulate sweating but not cutaneous vasodilation during exercise in the heat in young men. *Physiol Rep*. 2018;6(17):e13844. DOI: 10.14814/phy2.13844.

22. Notley SR, **Meade RD**, D'Souza AW, Friesen BJ and Kenny GP. Heat loss is impaired in older men on the day after prolonged work in the heat. *Med Sci Sports Exerc.* 2018;50(9):1859-1867. DOI: 10.1249/MSS.0000000000001643.

23. **Meade RD**, Crandall CG, Gagnon D and Kenny GP. Greater fluid loss does not fully explain the divergent hemodynamic balance mediating post-exercise hypotension in endurance-trained males. *J Appl Physiol*. 2018;124(5):1264-1273. DOI: 10.1152/japplphysiol.00988.2017.

24. Fujii N, **Meade RD,** Louie JC, Akbari P, Boulay P, Sigal RJ and Kenny GP. Effect of P2 receptor blockade on cutaneous vasodilatation during rest and exercise in the heat in young and older healthy adults. *Appl Physiol Nutr Metab*. 2018;43(3):312-315. DOI: 10.1113/EP086746.

25. Fujii N, **Meade RD**, McNeely BD, Nishiyasu T, Sigal RJ and Kenny GP. Type 2 diabetes specifically attenuates purinergic skin vasodilatation without affecting muscarinic and nicotinic skin vasodilatation and sweating. *Exp Physiol*. 2018;103(2):212-221. DOI: 10.1113/EP086694.

26. Notley SR, **Meade RD**, Friesen BJ, D'Souza AW and Kenny GP. Does a prolonged work day in the heat impair heat loss on the next day in young men? *Med Sci Sports Exerc*. 2018;50(2):318-326. DOI: 10.1249/MSS.0000000000001444.

27. **Meade RD** and Kenny GP. Are all heat loads created equal? *Med Sci Sports Exerc*. 2017;49(9):1796-1804. DOI: 10.1249/MSS.0000000000001309