The interactive effects of age and sex on whole-body heat exchange during exercise in the heat

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Abstract

It is well established that older adults display marked impairments in the heat loss responses of sweating and skin blood flow relative to young adults which can exacerbate body heat storage by compromising whole-body heat loss (evaporative + dry heat exchange). Similarly, young women display reductions in whole-body heat loss relative to young men during exercise in dry heat. As such, it is possible that the age-related decline in whole-body heat loss will be greater among women relative to men. To examine whether the age-related decline in whole-body heat loss would be greater in women relative to men during exercise in dry heat, and whether this response would be more pronounced with a greater elevation in the level of heat stress, whole-body heat loss (evaporative ± dry heat exchange) was evaluated in 80 individuals (46 men, 34 women) aged between 18-70 years. Participants completed an incremental exercise model involving three, 30-min bouts of semi-recumbent cycling at fixed rates of metabolic heat production (150, 200, 250 W/m^2), each separated by a 15-min recovery period in hot-dry conditions (40˚C, ~15% relative humidity). Whole-body heat loss was measured using direct calorimetry whereas metabolic heat production was measured using indirect calorimetry. Whole-body heat loss declined with age (across men and women) during moderate- and vigorous-intensity exercise by 4.2 and 6.6 W/m^2 (both $P < 0.050$), respectively, however, these relationships were not modified by sex (both $P > 0.050$). Nonetheless, whole-body heat loss was lower in women relative to men during moderate- and vigorous-intensity exercise by 8.4 and 12.1 W/m^2 (both $P < 0.05$), respectively. Therefore, the results of this thesis demonstrate that the age-related decline in whole-body heat loss is not dependent on sex.

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CHAPTER I

INTRODUCTION

1.1 Introduction

Healthy humans maintain core temperature at near constant levels (~37ºC) except under the most extreme environmental conditions. To achieve this, the thermoregulatory system employs specialized heat loss effector responses to adjust the rate of dry (via increasing skin blood flow) and evaporative heat loss (via increasing sweating) to the environment to balance the rate at which heat is produced within the body (Gleeson, 1998). This balance is easily disturbed during exposure to hot environments and/or increases in metabolic heat production due to physical activity. Increases in air temperature reduce the capacity for dry heat loss such that when the environment is warmer than the skin, the body begins to gain heat, increasing the need for sweating and circulatory adjustments to achieve the rate of heat dissipation required to maintain heat balance. During exercise, the elevated metabolic rate increases the rate at which heat must be dissipated via the evaporation of sweat (the main avenue of heat loss under this condition) to prevent a dangerous rise in core temperature (Benzinger, 1969). Under circumstances where impairments in skin blood flow and sweating lead to an insufficient rate of heat loss to offset an increase in a given metabolic and/or environmental heat load, core temperature continually rises.

Numerous factors have been identified that can modulate an individual's physiological capacity to dissipate heat. This includes factors such as sex and ageing. While several studies have examined sex-related differences in thermoregulation, conclusions remain limited as to whether true physiological differences exist between sexes. A key factor which has confounded the interpretation of these findings relates to the physical differences inherent to each sex. It is well recognised that physical characteristics play an important role in the individual heat stress response (Havenith, 2001; Notley, Park, Tagami, Ohnishi, & Taylor, 2017), which is particularly relevant when thermoregulatory responses of men and women are compared during an exercise-induced heat stress since men are typically taller, heavier, and consequently have a greater body surface area amongst other differences. Despite the inherent challenges of comparing thermoregulatory responses in men and women, studies show that women exhibit an impaired sweating response compared to their opposite sex counterparts (Bittel & Henane, 1975; Dill, Yousef, & Nelson, 1973; Dubois, Ebaugh, & Hardy, 1952; Gagnon & Kenny, 2011, 2012; Hardy & Du Bois, 1940; Wyndham, Morrison, & Williams, 1965). These differences have been largely attributed to morphological differences (e.g., body mass, surface area to body mass ratio, and body adiposity) between men and women, as well as differences in aerobic fitness (Bar-Or, 1998; G. Havenith & van Middendorp, 1990; Kenney, 1985; Notley, Park, et al., 2017; Nunneley, 1978). However, Gagnon et al. (2011) showed that sex-differences in temperature regulation, particularly in whole-body evaporative heat loss, go beyond those associated with physical characteristics. This was evidenced by their observation that when exercise was performed at a fixed rate of metabolic heat production, equivalent to a moderate intensity exercise bout, women demonstrated a lower rate of whole-body evaporative heat loss which was not associated with differences in body mass and surface area. Furthermore, in a subsequent study conducted by the same group, it was found that these sex-related differences are heat load dependent such that they only occur above a certain of level heat stress (as defined by the net heat gained from exercise and/or the environment), which was found to be at the highest exercise-induced heat load (300W/m^2) (Gagnon & Kenny, 2012). This impaired whole-body evaporative heat loss response has been attributed to differences in end-organ function, namely the sweat gland function (Gagnon, Crandall, & Kenny, 2013; Madeira et al., 2010). Taken together these findings demonstrate that young women have a reduced physiological capacity to dissipate heat, a response which is worse in older women due to an age-related deterioration in heat dissipation (Larose, Wright, Sigal, et al., 2013).

Aging is associated with a decreased thermoregulatory ability and reduced tolerance during heat stress as evidenced by marked reductions in local and whole-body heat loss measured during passive (e.g., resting in hot environments) and exercise-induced heat stress (Kenny et al., 2017; Larose, Wright, Stapleton, et al., 2013; Sagawa, Shiraki, Yousef, & Miki, 1988; Stapleton et al., 2015a). This is exacerbated by reductions in physical fitness (Stapleton et al., 2015a) (indexed by cardiorespiratory fitness, VO_{2peak}) and the presence of chronic disease that generally accompany aging (Kenny, Yardley, Brown, Sigal, & Jay, 2010). These age-related impairments in whole-body heat loss have been shown to occur as early as 40 years of age, with pronounced differences occurring even during brief periods (≤15 min) of exercise (Larose, Boulay, Sigal, Wright, & Kenny, 2013). In the largest study to date (n=87), McGinn et al. (2017) reported that increasing age is a major predictor for the reduced capacity to dissipate heat in otherwise healthy men (aged 20-70 years) during exercise in a hot environment, accounting for 40% of variations in whole-body heat dissipation, and corresponding to a ~4% decrease in thermoregulatory function per decade (McGinn et al., 2017).

While the mechanisms underpinning the age-related deterioration in thermoregulatory function remain largely unresolved, studies show that the reduction in the body's physiological capacity to dissipate heat stem in part from the inability to adequately increase cutaneous blood flow (Smith, Alexander, & Kenney, 2013) and sweating (Inoue, Havenith, Kenney, Loomis, & Buskirk, 1999; Larose, Boulay, et al., 2013; Larose et al., 2014; Larose, Wright, Sigal, et al., 2013; Larose, Wright, Stapleton, et al., 2013; Smith et al., 2013). Consequently, during exposure to hot environments, the body gains more heat from the environment due to the greater air-to-skin temperature gradient (i.e., a decrease in skin blood flow is associated with a concomitant reduction in skin temperature). When paralleled by reductions in sweat production and therefore evaporative heat loss, older adults are at greater risk of a heat-related injury or death. (Larose, Boulay, et al., 2013; Larose et al., 2014; Stapleton et al., 2015a). As outlined above, studies show that these age-related impairments are also observed during an exercise-induced heat stress. Until recently, our understanding of the extent to which aging modulates the body's ability to dissipate heat remained unclear. This was largely attributed to the fact that studies comparing young and older adults during an exercise-induced heat stress assessed heat loss responses using an exercise intensity defined by a given percentage of their maximal oxygen uptake (Anderson & Kenney, 1987; Inbar, Morris, Epstein, & Gass, 2004; Wagner, Robinson, Tzankoff, & Marino, 1972). However, a key limitation with this experimental approach is the fact that, due to their greater fitness, younger adults generally have a greater absolute rate of maximal oxygen consumption relative to their older counterparts (Ilmarinen, 2001). As such, older adults would be exercising at a lower work rate for the same percentage of maximal oxygen uptake. Consequently, the exercise-induced heat load and therefore thermal drive for heat loss would be lower in the older adults relative to the young adults. To address this challenge, some studies have matched young and older adults for physical fitness (Kenney & Fowler, 1988; Tankersley, Smolander, Kenney, & Fortney, 1991) or performed exercise at a fixed rate of metabolic heat production (Kenny, Gagnon, Dorman, Hardcastle, & Jay, 2010; Larose et al., 2014; Notley, Poirier, et al., 2017; Stapleton et al., 2015a), thereby ensuring the same heat load and therefore thermal drive for heat dissipation. However, it is well known that fitness is an important modulator of the body's physiological capacity to dissipate heat (Havenith, Coenen, Kistemaker, & Kenney, 1998; Lamarche, Notley, Louie, Poirier, & Kenny, 2018; Lamarche, Notley, Poirier, & Kenny, 2018; Tankersley, Smolander, Kenney, & Fortney, 1991), with recent work showing that a greater level of aerobic fitness can modulate the age-related decline in whole-body heat loss (Stapleton et al., 2015). As discussed above, it is well known that sex is an important determinant of the body's ability to dissipate heat. However, it remains unclear if the age-related deterioration in the body's physiological capacity to dissipate heat may differ between men and women irrespective of their level of fitness (i.e., similar fitness between men and women).

1.2 Rationale and Statement of Problem

While previous research has improved our understanding of age-related reductions in thermoregulatory function across adulthood in men, similar studies examining age-related changes in whole-body heat loss in women have been restricted to between-group comparisons of young (18-30 years) and older women (50-65 years) (Drinkwater, Bedi, Loucks, Roche, & Horvath, 1982; Kenney & Anderson, 1988; Stapleton et al., 2015b). While that research confirmed that aging can also impair heat loss in older relative to young women, individuals who fall between these categories were excluded, increasing the risk of type I and type II error (Naggara et al., 2011). Further, since women were studied during exercise at lower intensities to similar studies in men (Stapleton et al., 2015a, 2015b) it remains uncertain whether the age-related decline in heat loss across adulthood in women differs to that of men. Given that whole-body heat loss is known to be reduced in young women relative to young men during moderate-to-vigorous exercise in similarly dry heat (Gagnon & Kenny, 2012), it is plausible that the age-related decline in heat loss could occur at a steeper rate to that of men. That is, a given reduction in heat loss due to age may be associated with a relatively greater decline in women who already possess compromised heat loss. This is a critical knowledge gap, especially given the rising number of older women engaging in arduous occupations and structured physical activity (Kenny, Groeller, McGinn, & Flouris, 2016) and the threat to human health posed by global climate change (Mora et al., 2017).

1.3 Study Objectives

The main objective of this study was to evaluate whole-body heat loss (evaporative and dry heat exchange) in men and women between 18-70 years of age to determine if the age-related decline in whole-body heat loss would be modified by sex, and whether this response was exacerbated as a function of increases in the exercise-induced heat load. To determine if age-related impairments in heat dissipation during exercise in a hot environment were greater in women as compared to men, and if this response was dependent upon the level of heat stress (as defined by the combined environmental and metabolic heat load), we measured whole-body heat loss during three 30-min successive exercise bouts performed at progressively increasing rates of metabolic heat production adjusted for body surface area [BSA; whole-body evaporative heat loss is largely influenced by BSA (Havenith, Luttikholt, & Vrijkotte, 1995)] equal to 150, 200 and 250 W/m^2, each separated by a 15-min rest in a hot environment (40°C). We used our whole-body direct calorimeter (a device that provides a very accurate measurement of the heat dissipate by the human body) to obtain a gold-standard measurement of whole-body heat loss (i.e., evaporative ± dry heat exchange).

1.4 Hypotheses

We evaluated the hypothesis that the age-related decline in whole-body heat loss will be greater in women relative to men, resulting in an increased amount of heat stored within the body which will be more pronounced with a greater elevation in the level of heat stress (as defined by the combined environmental and metabolic heat load).

1.5 Delimitations and Limitations

This study evaluated whole-body heat exchange in men and women between 18-70 years of age in a hot-dry environment. This is done to ensure full evaporation of the sweat produced in the calorimeter, allowing us to assume that 100% of the sweat produced will evaporate to help cool the body. We employed an incremental exercise model designed to evaluate group differences in whole-body heat exchange. To ensure that participants could complete the exercise protocol we recruited habitually active (i.e. performing at least 30 minutes of structured physical activity a minimum of 2 times per week) individuals whose peak aerobic capacity did not exceed the 80th percentile, according to the age- and sex-specific peak aerobic fitness guidelines created by the Canadian Society for Exercise Physiology (CSEP, 2013). Given that our sample was representative of the general population, we observed a natural, age-related decline in VO_{2peak}. As such, the findings of the current study may not be representative of responses in a sedentary or endurance trained population. Furthermore, we limited our evaluation of adults to those between 18-70 years of age. However, it is possible that the age-related decline in whole-body heat loss could be more pronounced in those adults >70 years. Lastly, we tested relatively healthy adults with no pre-existing chronic health conditions such as type 2 diabetes mellitus and hypertension as these chronic diseases have been shown to exacerbate age-related impairments in heat dissipation. Therefore, our findings are only applicable to relatively healthy men and women aged 18-70 years.

1.6 Relevance of the study

The findings of the project provide critical new information to advance our current understanding of age-related changes in thermoregulatory function in men and women during heat stress, and it will create a shift in how we understand the impact of heat on our aging population.

Existing guidelines adopted and recommended for use by government agencies worldwide (e.g., World Health Organization, Canadian Federal and Provincial Government agencies) to protect the public and workers assumes a "one size fits all" practice which we showed vastly under-protects even young healthy individuals during work in the heat (Meade, Poirier, Flouris, Hardcastle, & Kenny, 2016), increasing risk of heat-related morbidity and mortality. We can use our evidence-based data to define age- and sex-specific exposure limits to safeguard health in the boarder public and workers engaged in physical activity or work in hot environments.

CHAPTER II

Review of Literature

2.1 Human Heat Balance

In humans, the tight regulation of core temperature is critical to the maintenance of optimal physiological function, as small changes in core temperature can cause a great disruption to homeostasis within the body (Ivy, 1944). However, during physical activity (exercise elevates metabolic rate, and therefore heat production, increasing the rate at which heat must be dissipated) and/or exposure to hot ambient conditions (higher ambient temperatures increase the requirements for whole-body heat loss), core temperature can be easily subjected to change if the body is unable to balance the rate of endogenous heat production with the rate of heat loss to the environment. This concept is defined using the human heat balance equation (Gagge & Gonzalez, 1996):

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

Where all terms have units of $W \cdot m^2$ (to account for body surface area) and,
S = rate of body heat storage
M = rate of metabolic heat production
W = rate of mechanical work
C = rate of convective heat loss from the skin
R = rate of radiative heat loss from the skin
E = rate of evaporative heat loss from the skin.

As evidenced by the heat balance equation, any mismatch between the rate of metabolic heat production ($M \pm W$) and the rate of whole-body heat loss ($R + C - E$) will lead to either a positive or negative change in the rate of body heat storage (S). In a thermoneutral environment where air temperature is lower than skin temperature, heat balance is maintained primarily via dry heat exchange mechanisms ($R + C$) (Kenny & Jay, 2013). However, as air temperature increases, the temperature gradient between the skin and the environment becomes smaller, subsequently reducing the capacity for heat dissipation via dry heat exchange (Wendt, van Loon, & Lichtenbelt, 2007). When the environmental temperature exceeds skin temperature, heat is gained from the environment via dry heat exchange. The elevated level of heat stress increases the need for the heat loss responses of sweating and cutaneous blood flow to balance the increased rate of body heat storage (and therefore maintain heat balance). Similarly, during exercise when the rate of metabolic heat production increases above resting levels there is a rise in the rate of body heat storage and a subsequent elevation of core temperature. As such, the rate of heat loss to the environment must increase to prevent a dangerous elevation in core temperature. In such conditions, the evaporation of sweat from the skin surface (E) becomes the primary avenue for heat dissipation. Moreover, the increase in sweating and skin blood flow in response to elevations in metabolic and/or environmental heat load is proportional to the amount of evaporative heat loss required to achieve heat balance (Gagnon, Jay, & Kenny, 2013). However, under circumstances where the body is unable to compensate for increases in metabolic and/or environmental heat loads (as seen in older adults for example), the body will continue to store heat, causing a gradual increase in core temperature, which if left unchecked can lead to heat illness and eventually death.

To maintain thermal homeostasis, afferent information is sent from the central (i.e. hypothalamus, spinal cord) and peripheral (skin, muscle and viscera) thermoreceptors of the body to the thermoregulatory centre, the pre-optic/anterior hypothalamus (PO/AH). As core temperature rises, the PO/AH activates the heat loss responses of skin blood flow and sweating which augments whole-body heat dissipation (Figure 1) (Boulant, 1996; Hensel, 1981) and prevent dangerous elevations in core temperature under compensable heat stress conditions (Charkoudian, 2003; Johnson & Kellogg Jr, 2010; Johnson, Minson, & Kellogg Jr, 2011; Kenny & Jay, 2013; Mekjavic & Bligh, 1989; Shibasaki & Crandall, 2010). However, if the net heat load (i.e., combined environmental and metabolic heat load) exceeds the body's physiological capacity to dissipate, the body will continue to store heat causing a heat-related injury (i.e., heat exhaustion, heat stroke) or death (Kenny, Wilson, Flouris, & Fujii, 2018).

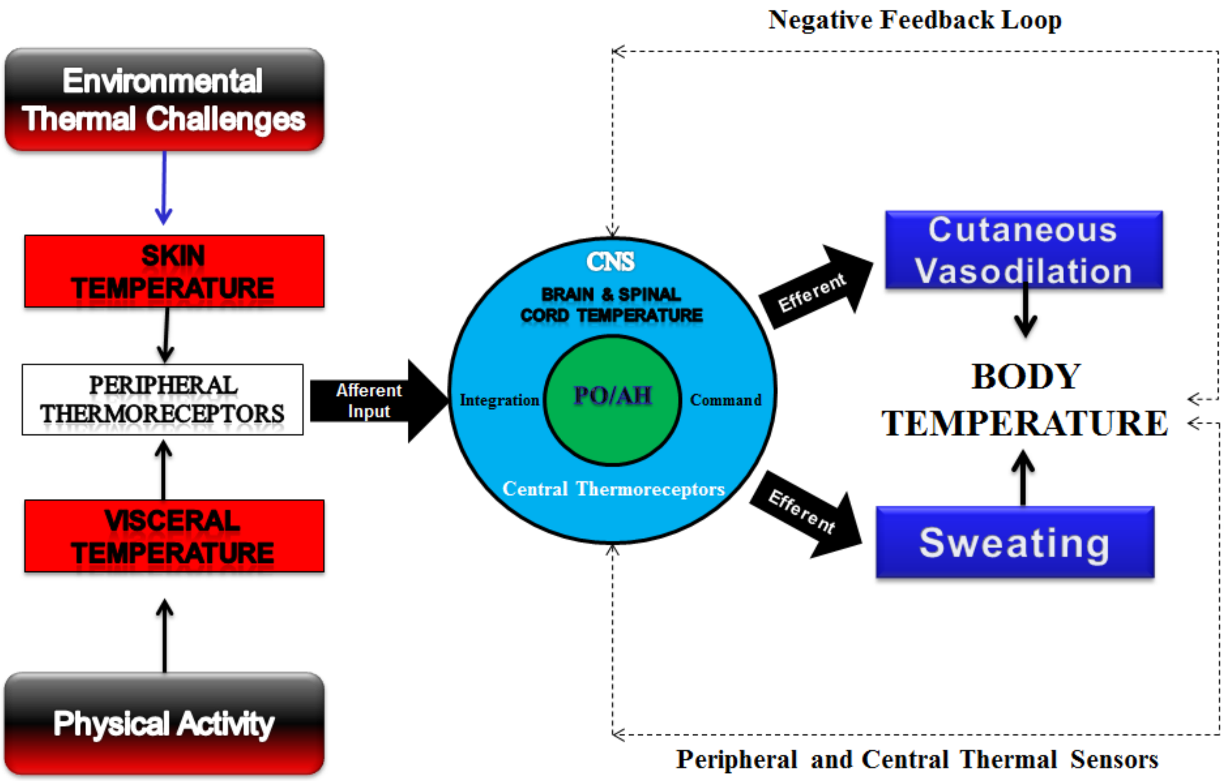

Figure 1. A schematic of the thermoeffector responses of cutaneous vasodilation and sweating under situations of increasing skin and core temperatures during heat stress (from Nagashima et al. 2000).

2.2 Cutaneous Blood Flow

The control of cutaneous vasomotor tone, which modulates skin blood flow, is one of the central components to the regulation of core temperature (Charkoudian, 2003; Johnson et al., 2011). The cutaneous vasculature of non-glabrous (hairy) skin is primarily regulated by two populations of sympathetic nerves: a noradrenergic active vasoconstrictor system and a cholinergic active vasodilator system (Charkoudian, 2003; Kellogg Jr, 2006), whereas glaborous skin (palms, soles, and lips) is only innervated by sympathetic noradrenergic vasoconstrictor nerves (Johnson & Proppe, 1996; Stephens, Aoki, Kosiba, & Johnson, 2001) During heat stress, the initial vasodilatory response (10-20% of total cutaneous vasodilation) occurs from a withdrawal of sympathetic vasoconstrictor activity (Pergola, Kellogg, Johnson, & Kosiba, 1994; Rowell, 1974).

However, as heat stress continues the active vasodilator system, which accounts for 80-90% of the total cutaneous vasodilatory response, is engaged (Johnson & Proppe, 1996). The elevation of cutaneous blood flow during exposure to hot environments often requires an increase in cardiac output and a redistribution of blood from inactive organs such as the splanchnic and renal vascular beds to the skin (Minson, Wladkowski, Pawelczyk, & Kenney, 1999). These adjustments adequately support the demand of skin blood flow while maintaining enough oxygen to supply vital organs such as the heart (Johnson & Proppe, 1996). However, during exercise, the increased oxygen demand of the active musculature results in a reduced amount of blood available to support further elevations in skin blood flow (Rowell, 1974), and the evaporation of sweat from the skin surface becomes the main avenue of heat dissipation.

2.3 Eccrine Sweating

Humans have two subtypes of sweat glands which differ based on the method of their activation. Apocrine sweat glands, which are located in the armpits and pubic regions, are innervated by adrenergic nerves, and are therefore activated in situations wherein adrenaline is increased (i.e., stress, fear or pain) (Saga, 2002). In contrast, the eccrine sweat glands, which are stimulated via cholinergic sympathetic nerves are responsible for thermoregulatory sweating as they secrete hypotonic sweat onto the skin surface to promote evaporation of the water content of sweat (Saga, 2002; Shibasaki, Wilson, & Crandall, 2006; Wendt et al., 2007). For this proposal, we will focus solely on the role of eccrine sweat glands.

The thermoeffector response of sweating allows the body to dissipate large amounts of heat to the environment via the evaporation of sweat on the skin surface. In situations where, metabolic heat production is increased (i.e. exercise and/or environmental heat stress) evaporative heat loss becomes the major avenue for heat dissipation from the body, accounting for ≥80% of the total of heat lost to the environment. In contrast, it only accounts for ~25% of whole-body heat loss in resting conditions (Cain & McLellan, 1998; Gavin, 2003). At the onset of exercise, sweating increases independent of any changes in body temperature, indicating that the response is largely mediated by nonthermal factors such as central command (Kenny & Jay, 2013; Van Beaumont & Bullard, 1963, 1966). However, as exercise continues, the elevation of core and skin temperatures primarily drives the sweating response (Nadel, Bullard, & Stolwijk, 1971). The increased production of sweat (and therefore the evaporation of sweat) is pivotal to the regulation of core temperature. If sweat rate is insufficient to increase heat loss enough to offset the heat gained by either the environment and or exercise, core temperature will continue to rise. If left unchecked, this can lead to potentially dangerous increases that can lead to heat-related injuries or death.

2.4 Thermoregulation from a Calorimetric Perspective

At the onset of exercise, there is a rapid elevation in the rate of metabolic heat production resulting in an increased rate of body heat storage and a subsequent rise in core temperature (Kenny & Jay, 2013; Webb, 1995). The increased rate of body heat storage in the early stages of exercise is caused by a mismatch between the rapid rise of metabolic heat production, and whole-body heat loss as regulated by the activation of heat loss responses of skin blood flow and sweating (Kenny & Jay, 2013; Webb, 1995). As exercise continues, there is a gradual increase in skin blood flow and sweating causing a concomitant rise in whole-body heat loss, reducing the rate of body heat storage until heat balance (typically achieved with 30-45 minutes) and therefore steady-state core temperature is achieved (Figure 2) (Kenny & Jay, 2013). However, the magnitude of increase in the effector response is dependent upon the environmental conditions (i.e., air temperature and humidity) and the intensity of the exercise performed (Figure 3) (Kenny, Webb, Ducharme, Reardon, & Jay, 2008). When the environmental and metabolic heat load (i.e. net heat load) exceed the individual's physiological capacity to dissipate heat and therefore achieve heat balance, the body will continue to store heat, resulting in a continued rise in core temperature. Studies show that an individual's capacity to dissipate heat is defined by inter- (e.g., age, sex, chronic disease, others) and intra-individual factors (e.g., fitness, acclimation and hydration state, others). Consequently, the actual level of heat strain experienced by an individual in response to a given heat stress can vary markedly between individuals.

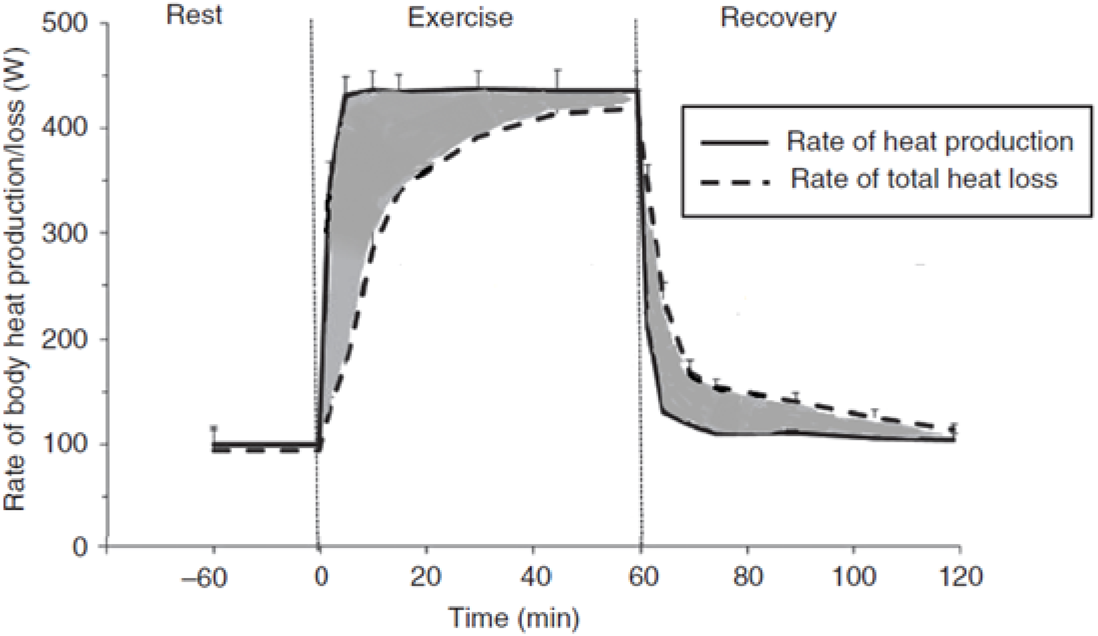

Figure 2. Whole-body calorimetric data for the rate of metabolic heat production (solid line) and the rate of total (evaporative + dry) heat loss (dashed line) and the heat stored within the body (grey shaded area) during 60 min of resting baseline, followed by 60 min of cycling performed at 70 W, followed by a 60-min recovery period (adapted from Kenny and Jay 2013).

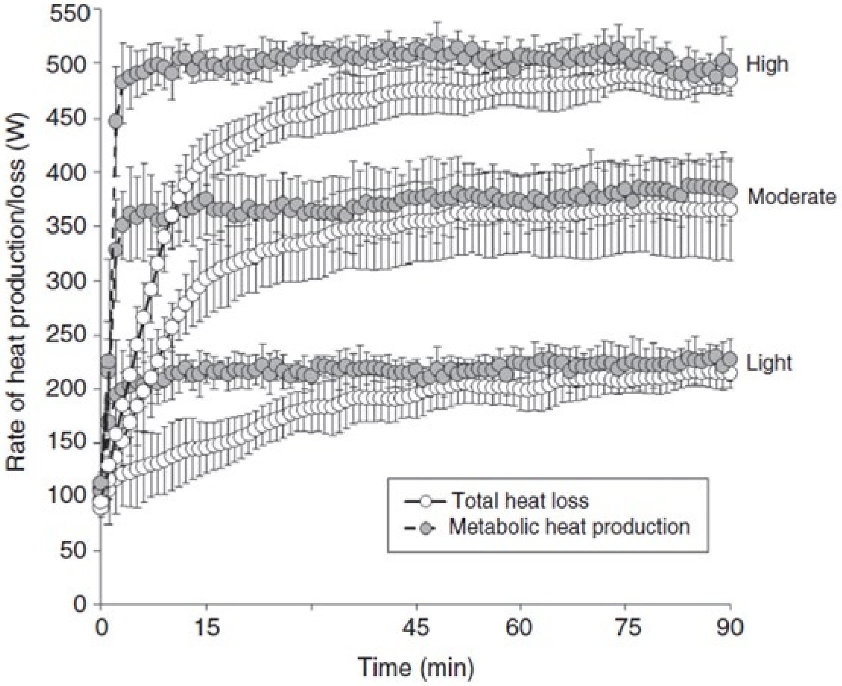

Figure 3. Calorimetric data for the rate of metabolic heat production and the rate of total (evaporative + dry) heat loss during 90 min of exercise performed at three fixed rates of metabolic heat production of 200, 350, and 500 W, equivalent to light, moderate and high intensity exercise (from Kenny and Jay 2013).

2.5 Age and heat loss

Aging is a process consisting of physiological as well as physical changes which cause a progressive decline in the body's ability to sufficiently respond to internal and/or external stressors (Chodzko-Zajko & Ringel, 1987). Aging has been shown to cause a marked deterioration in the body's physiological capacity to dissipate heat, albeit findings have been inconsistent between studies (Larose, Boulay, et al., 2013; Larose et al., 2014; Larose, Wright, Stapleton, et al., 2013; Minson et al., 1999; Sagawa et al., 1988; Stapleton et al., 2015a; Tankersley et al., 1991). Specifically, some groups reported no differences in thermoeffector function and heat tolerance between young and older adults (Davies, 1979; Kenny, Gagnon, et al., 2010) whereas others showed that older adults exhibit a reduced capacity to dissipate heat relative to young adults (Anderson & Kenney, 1987; Drinkwater, Bedi, Loucks, Roche, & Horvath, 1982; Larose, Boulay, et al., 2013; Larose et al., 2014; Stapleton et al., 2015a; Wagner et al., 1972). The disparate responses can in large part be attributed to differences in the experimental paradigm employed to assess responses between young and older adults.

Many of the studies which report age-related differences in thermoregulation during exercise have compared thermoregulatory responses in young and older adults exercising at the same percentage of their maximal oxygen uptake (Anderson & Kenney, 1987; Inbar et al., 2004; Wagner et al., 1972). However, since young adults have a greater absolute rate of maximal oxygen consumption relative to their older counterparts, performing exercise at the same relative exercise intensity would result in very different heat loads and therefore thermal drive for heat dissipation. To overcome this limitation some studies have compared responses between young and older adults with similar levels of fitness (Kenney & Fowler, 1988; Tankersley et al., 1991). However, matching young and older adults for both level of physical activity and rate of maximal oxygen consumption can result in the recruitment of individuals who are exceptional in these regards, making it difficult to generalise the findings to the average aging population. Moreover, matching for fitness can lead to misguided conclusions, as it has been shown that the greater level of fitness associated with endurance training can offset age-related impairments in heat loss (Stapleton et al., 2015a; Tankersley et al., 1991). Using a model in which individuals exercise at a fixed rate of metabolic heat production ensures a similar drive for heat loss between individuals, allowing for the evaluation of the effect of age on heat dissipation independent of the influence of aerobic fitness. A study conducted by Larose et al. examined whole-body heat loss in adults aged 20-70 years (5 groups; 20 to 31, 40 to 44, 45 to 49, 50 to 55 and 56 to 70 years) during short, intermittent bouts of moderate intensity exercise (fixed rate of heat production of 400 W; level consistent with work commonly performed in various industries) in the heat. They showed for the first time that age-related impairments in heat dissipation occur in adults as young as 40 years of age (Larose, Boulay, et al., 2013). A subsequent study, by Stapleton and colleagues extended upon these findings by demonstrating that age-related changes in whole-body heat dissipation are heat load dependent. Specifically, they assessed whole-body heat loss in young (21 ± 1 year), middle-aged (48 ± 5 years), and older (65 ± 3 years) men during an incremental intermittent exercise protocol consisting of three 30-min bouts of cycling performed at increasing fixed rates of metabolic heat production of 300, 400, and 500 W, each followed by a 15-min recovery period. The authors showed that age-related impairments in heat dissipation occur at an exercise induced heat load ≥400 W in a hot-dry environment, indicating that age-related reductions in whole-body heat loss occur in a heat-load dependent manner (Stapleton et al., 2015a).

2.6 Sex-related differences in heat loss

Much like the age-related impairments in heat dissipation, many studies have found that the heat loss responses of skin blood flow and sweating differ between men and women, such that heat loss is lower in women as compared to men (Bittel & Henane, 1975; Dill et al., 1973; Gagnon & Kenny, 2011; Hardy & Du Bois, 1940; Shapiro, Pandolf, Avellini, Pimental, & Goldman, 1980; Wyndham et al., 1965). Some groups have attributed these sex-related differences to altered end-organ function (i.e. cutaneous vasculature, sweat glands) (Gagnon, Crandall, et al., 2013; Gagnon & Kenny, 2011, 2012; Madeira et al., 2010; Stephenson & Kolka, 1993) while others have found that differences between groups are due solely to differences in physical characteristics (i.e. body surface area, fitness, etc.) (Burse, 1979; Havenith & van Middendorp, 1990; Notley, Park, et al., 2017).

Body mass has been shown to influence the core temperature response to a given heat stress, such that larger individuals (e.g. men) will have less of an increase in core temperature compared to smaller (e.g. women) individuals (Gagnon, Dorman, Jay, Hardcastle, & Kenny, 2009). Since men are typically heavier than women, they usually have a greater absolute maximal rate of oxygen consumption. To account for differences in the rate of maximal oxygen consumption between men and women, experimental protocols are often designed to have both sexes exercise at the same percentage of their maximal rate of oxygen consumption. In fact, many studies which report sex-related differences in thermoregulation during exercise are based on data obtained from men and women exercising at the same percentage of their maximal rate of oxygen consumption (Ichinose-Kuwahara et al., 2010; Keatisuwan, Ohnaka, & Tochihara, 1996). However, exercise at any given percentage of the maximal oxygen consumption results in a greater metabolic heat production in men which is paralleled by a greater rate of whole-body heat loss (Gagnon, Jay, Lemire, & Kenny, 2008). Consequently, differences in heat dissipation could be attributed to differences in the thermal drive for heat loss. In this context, Gagnon et al. (2012) demonstrated that independent of morphological differences, women exhibited a reduced capacity to dissipate heat, albeit this response was heat-load dependent. In their study, 8 young men and 8 young women completed 90 minutes of cycling in a hot-dry environment (40°C, 24% relative humidity) at increasing fixed rates of metabolic heat production of 200, 250, and 300 W/m^2, with each heat load being performed sequentially for 30-min. They showed that women exhibited a reduced capacity to dissipate heat (primarily via the evaporation of sweat) compared to men during vigorous exercise in the heat equivalent to a net heat load of $\geq$300 W/m^2 (Gagnon & Kenny, 2012). They subsequently attributed the lower sweat production to differences in end organ function (i.e., activity of the sweat gland). This was evidenced by their observation that sweat production in women was lower relative men in response to the intradermal administration of incremental doses of acetylcholine and methylcholine (activators for the sweating response) (Gagnon, Crandall, et al., 2013).

2.7 Interactions between aging and sex in the control of heat loss

While a number of studies have evaluated the independent effects of age (Kenny, Gagnon, et al., 2010; Larose, Boulay, et al., 2013; Larose et al., 2014; Stapleton et al., 2015a), and sex (Drinkwater et al., 1982; Gagnon & Kenny, 2011, 2012; Stephenson & Kolka, 1993) on heat loss, only one study to date has assessed the interactive effects of age and sex on whole-body heat loss. Flouris et al. (2018) evaluated whole-body heat loss during short (15-min), repeated bouts of moderate intensity exercise in a hot-dry environment in young and older men and women. They found that the difference in whole-body heat loss between young and older adults was greater in men relative to women during moderate intensity exercise in a hot-dry environment (Flouris et al., 2018). However, it is important to note that women were exercising at a lower exercise-induced heat load relative to men, which resulted in a reduced thermal drive for heat loss. As such, it is possible that the increased requirement for heat loss in men may explain the larger difference in whole-body heat loss between young and older men. Furthermore, by dichotomizing participants into two age-groups (young and older adults), Flouris et al. (2018) were unable to provide information regarding the relationship between age and whole-body heat loss across adulthood (Altman, 1991; Altman & Royston, 2006). Thus, in the current thesis, we sought to determine whether sex would modify the age-related decline in whole-body heat loss across adulthood during exercise performed at equal, fixed rates of metabolic heat production.

CHAPTER III

Methods

3.1 Participants

The current study is in accordance with the *Declaration of Helsinki* and is approved by the University of Ottawa Health Sciences and Science Research Ethics Board. Written and informed consent was obtained from all volunteers prior to their participation in the study.

A total of 80 adults (46 men and 34 women) participated in the current study. All participants were: 1) healthy (i.e., no history of cardiovascular, metabolic or respiratory disease and not currently taking medication related to these conditions); 2) an adult between 18 and 70 years of age, 3) habitually active (i.e. performing at least 30 minutes of structured physical activity a minimum of 2 times per week), and 4) non-smoking. Testing was conducted throughout the year and each participant completed one screening session and one experimental session which were separated by at least 48 hours.

3.2 Experimental Design

Participants were instructed to refrain from alcohol, caffeine and strenuous physical activity for a minimum of 24 hours prior to arriving at the laboratory for each session. Furthermore, participants were instructed to drink 500 mL of water the night before as well as ~2 hours prior to each session to ensure adequate hydration and were also be asked to consume a small meal (no coffee or tea) approximately two hours before reporting to the laboratory on the day of the screening or experimental session.

3.2.1 Preliminary Session

During the screening session, body height, mass, density, as well as peak rate of oxygen consumption (VO_{2peak}) were determined. Body height was measured with a physician stadiometer

(Detecto, model 2391, Webb City, MO, USA), while body mass was determined using a digital high-performance weighing platform (model CBU150X Metter Toledo Inc., Mississauga, ON, Canada). Body surface area was subsequently calculated from the measurements of height and mass (Du Bois & Du Bois, 1916; Ramanathan, 1964). Body density was estimated using the hydrostatic weighing technique, and used to calculate body fat percentage (Siri, 1956). VO_{2peak} was assessed using an automated indirect calorimetry system (MCD Medgraphics Ultima Series, Sun Tech Medical, MN, USA) during a progressive incremental cycling protocol on a semi-recumbent cycle ergometer (Corival, Lode B.V., Groningen, the Netherlands). Participants performed one minute of cycling at a starting workload of 60 W. Thereafter, the workload was increased by 20 W every minute until volitional fatigue and/or the participant could no longer maintain a pedaling cadence >50 $revolutions \cdot min^{-1}$. Participants aged 60 years and older were monitored by electrocardiogram during the maximal incremental cycling protocol.

3.2.2 Experimental Session

Upon arrival to the laboratory for the experimental session, participants provided a urine sample for the measurement of urine specific gravity (an index of hydration status) and voided the remainder of their bladder prior to a baseline measurement of semi-nude (i.e. shorts and sports bra for women, shorts only for men) body mass. Thereafter, resting arterial blood pressure and heart rate were recorded. Participants then entered the calorimeter, regulated at an ambient temperature of 40°C and a relative humidity ~15%, for a 15-minute instrumentation period, and followed by a 15-min baseline period in an upright seated position. Thereafter, participants completed three, 30-min exercise bouts performed at progressively greater fixed rates of metabolic heat production equal to 150, 200, and 250 W/m^2, each followed by a 15-min rest period. These heat loads were equivalent to low (~35 %$VO_{2\ peak}$), moderate (~45 %$VO_{2\ peak}$) and vigorous (~60% $VO_{2\ peak}$) intensity exercise and were chosen to ensure that individuals of all ages can complete the protocol. Upon completion of the experimental protocol, participants exited the calorimeter and completed a final post-trial measurement of semi-nude body mass.

3.3 Measurements

3.3.1 Direct Calorimetry

The experimental session took place in the Snellen whole-body direct air calorimeter, which is a very accurate method of measuring the rates of whole-body evaporative and dry heat loss, as well as the change in body heat content. The calorimeter inflow to outflow values of humidity and temperature were collected at 8 second intervals throughout the experimental trials via dew point hygrometers (RH Systems model 373H, Albuquerque, NM, USA), and RTD high precision thermistors (Black Stack model 1560, Hart Electronics, UT, USA), respectively. The air mass flow through the calorimeter was measured using differential thermometry over a known heat source placed in the effluent air stream. Differential thermometry over the heater was measured using a third high precision thermistor placed down-stream from the heater. Air mass flow rate (kg_{air}/min) was continuously measured during each trial. The real time data for humidity, temperature and air mass flow was displayed and recorded on a personal computer with LabVIEW software (Version 7.0, National Instruments, TX, USA). Evaporative heat loss was calculated every minute using the following equation:

$$\text{Evaporative heat loss} = \frac{(\text{Massflow x (Humidity}_{\text{out}} - \text{Humidity}_{\text{in}}) \text{ x } 2426)}{60}$$

Where: Mass flow is the rate of flow of air mass (kg_{air}•s^{-1}); ($Humidity_{out}$ – $Humidity_{in}$) is the calorimeter inflow-outflow difference in absolute humidity (g water • kg air^{-1}); and 2426 is the latent heat of vaporization of sweat (J • g $sweat^{-1}$) at 30°C (Wenger, 1972).

Dry heat loss from radiation, convection and conduction was calculated from the calorimetry data every minute using the following equation:

$$\text{Dry heat loss} = \frac{(\text{Massflow x (Temperature}_{out} - \text{temperature}_{in}\text{) x 1005)}}{60}$$

Where: Mass flow is the rate of flow of air mass (kg air•s^{-1}); ($Temperature_{out}$ –$Temperature_{in}$) is the calorimeter inflow-outflow difference in air temperature (ºC), and 1005 is the specific heat of air (J• (kg air • °C)$^{-1}$).

3.3.2 Indirect Calorimetry

Indirect calorimetry was used for the continuous measurement of metabolic energy expenditure (Nishi, 1981). Expired gas samples were drawn from the 6 L fluted mixing box located within the calorimeter and were analyzed for the concentrations of oxygen (O_2) and carbon dioxide (CO_2) using electrochemical gas analyzers (AMETEK model S-3A/1 and CD 3A, Applied Electrochemistry, Pittsburgh, PA, USA). Expired air was then recycled into the calorimeter to account for respiratory dry and evaporative heat loss. Throughout the experimental condition, participants wore a face mask (Model 7600 V2, Hans-Rudolph, Kansas City, MO, USA), which was attached to a 2-way T-shape non-rebreathing valve (Model 2700, Hans Rudolph). Oxygen uptake and respiratory exchange ratio will be obtained as 30-second averages which was used to calculate metabolic rate, while metabolic heat production was calculated as the difference between metabolic rate and external work. Furthermore, indirect calorimetry was used in conjunction with direct calorimetry to calculate the rate of body heat storage (ΔH_b) throughout the experimental session using the following equation.

$$\Delta H_b(\mathrm{kJ}) = \int_{t=0}^{t_i} [(M\text{-}W)\text{-}(H_{dry} + H_{evap} + H_{resp})]d$$

Where: M-W is the rate of metabolic heat production, H_{dry} is the rate of dry heat loss via radiation, convection and conduction, H_{evap} is the rate of evaporative heat loss from the skin, and H_{resp} is the rate of heat loss from respiration.

3.3.3 Cardiovascular responses

Systolic and diastolic arterial blood pressures was measured at the brachial artery via manual auscultation prior to and following the experimental session. Heart Rate was monitored continuously throughout the experimental sessions using a Polar coded transmitter, Polar M400, and Polar FlowSync software (Polar Electro Oy, Kempele, Finland). Percent heart rate reserve (%HRR) was then calculated using the following equation:

$$\%HRR = \left(\frac{HR_t - HR_{rest}}{HR_{max} - HR_{rest}}\right) \times 100\%$$

Where: HR_t is the heart rate at a given minute during the experimental protocol, HR_{rest} is the resting heart rate measured after seated rest for ~15 min in a thermoneutral condition, and HR_{max} is the maximal heart rate attained during the peak aerobic capacity test.

3.3.4 Urine specific gravity

To evaluate hydration state, participants provided a urine sample upon arrival to the laboratory for the measurement of urine specific gravity (an index of hydration) using a handheld total solids refractometer (Model TS400, Reichter Inc., Depew, NY, USA). Euhydration was defined as a urine specific gravity < 1.025 (Kenefick & Cheuvront, 2012).

3.4 Data Analysis

Minute averages were calculated for metabolic heat production, whole-body heat loss, evaporative and dry heat loss, the change in mean body temperature, as well as percent heart rate reserve. Statistical analyses were performed using an average of the final 5-min of each exercise period. The change in body heat content as measured using calorimetry (ΔH_b) was expressed as the change in mean body temperature per hour (ΔT_b) during light-, moderate- and vigorous-intensity exercise using the following equation:

$$\Delta T_b = \frac{\Delta H_b \times 60 \times 60}{b_m \times C_p}$$

Where: ΔH_b is the change in body heat content derived from calorimetry (in kJ/s), b_m is total body mass (in kg), and C_p is the average specific heat capacity of the tissues of the body (in $kJ \cdot kg^{-1} \cdot {}^{\circ}C^{-1}$).

3.5 Statistical Analysis

To evaluate whether the relationship between age and whole-body heat exchange is modified by sex, we conducted dichotomous moderator linear-regression analyses within each exercise period (light-, moderate- and vigorous-intensity exercise). The first step in this analysis was to assess the relationship between the dependent variable (e.g. whole-body heat loss) and age across all participants (both men and women). In instances where a significant relationship was observed, we included an interaction term (age x sex) to identify whether the relationship between age and the dependent variable differed between the sexes. If the interaction term was statistically significant, the regression slopes were analyzed (and presented) separately. However, if no interaction effect was observed (i.e., sex did not explain a significantly greater amount of the total variance in a given dependent variable) only the regression equation describing the relationship between the main effects of age and sex for a dependent variable was presented. This process is like that of an ANOVA wherein an evaluation of the simple main effects is conducted when an interaction is observed, and when there is no significant interaction, the procedure is to evaluate the main effects. Tests of the regression assumptions (i.e., multicollinearity, homoscedasticity, normality, outliers, leverage points, influential points, and linearity) were completed for all dependent variables. An *a priori* power analysis was conducted to determine the minimal sample size required to detect a significant change in the coefficient of determination (r^2) for whole-body heat loss with the addition of the interaction term. It was found that for a large effect size (Cohen's $f^2 = 0.35$) with at least 80% statistical power, forty-two participants were required to detect a significant change in the r^2 for whole-body heat loss in the interaction model. The level of significance for all analyses was set to $P < 0.050$.

CHAPTER IV

Results

4.1. Participant characteristics

Participant characteristics are presented in Table 1. By design, men and women were heterogenous in terms of physical characteristics but had a similar VO_{2peak}. As such, women were on average, shorter and lighter, and had a greater percent body fat relative to men (Table 1). Additionally, as per the pre-trial instructions, all participants arrived at the laboratory adequeately hydrated, as confirmed by pre-trial measures of urine specific gravity [mean (SD); 1.012 (0.007)].

Table 1. Physical characteristics.

	Men	Women
Height (m)	1.8 (0.7)*	1.6 (0.5)
Body mass (kg)	82.9 (8.6)*	63.0 (7.7)
Surface area (m^2)	2.0 (0.1)*	1.7 (0.1)
Body fat (%)	20.6 (7.8)*	24.1 (6.4)
Peak oxygen consumption ($ml \cdot kg^{-1} \cdot min^{-1}$)	39.1 (6.4)	36.1 (6.9)

Data presented are mean (standard deviation). * indicates a significant difference between men and women ($P < 0.050$).

4.2. Whole-body direct calorimetry

4.2.1. Evaporative heat loss

During light-intensity exercise, no statistically significant relationship between age and evaporative heat loss was observed ($P = 0.073$). Therefore, no further analyses were performed for evaporative heat loss during light-intensity exercise. In contrast, a significant decline in evaporative heat loss of 4.1 and 6.6 W/m^2 per decade was observed across all participants during moderate- ($P = 0.001$) and vigorous-intensity exercise ($P < 0.001$), respectively (Figure 4). As such, the interaction term was added to identify whether sex modified the age-related decline in evaporative heat loss. Interestingly, the age-related decline in evaporative heat loss was found to be similar between men and women during moderate- ($P = 0.188$) and vigorous-intensity exercise

($P = 0.393$) in a hot-dry environment, only explaining an additional 1.9 and 0.7% of the total variance in evaporative heat loss. However, irrespective of age, evaporative heat loss was lower in women relative to men by 10 and 15 W/m^2 during moderate- ($P = 0.010$) and vigorous-intensity exercise ($P < 0.001$), respectively.

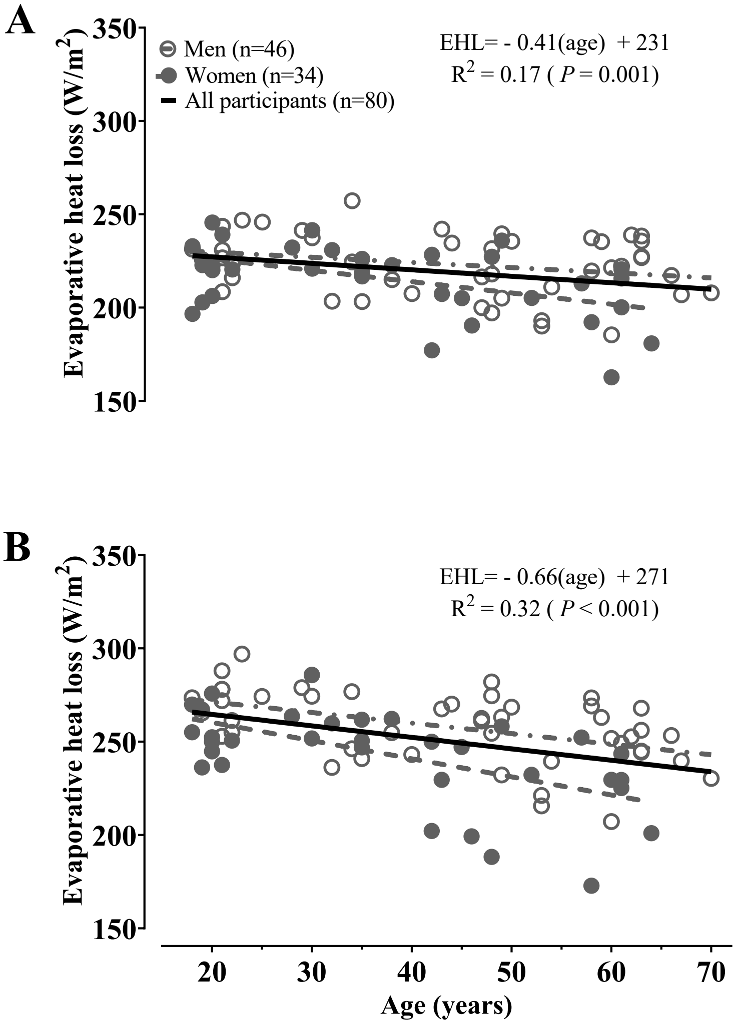

Figure 4. Whole-body evaporative heat loss (W/m^2) during the moderate- (A; 200 W/m^2), and vigorous-intensity exercise (B; 250 W/m^2) bouts in 80 (46 men, 34 women) adults. The grey, dashed-and-dotted regression line and the grey, dashed regression line represent the relationship between age and whole-body evaporative heat loss (EHL) in men and women, respectively. The solid black line represents relationship between age and whole-body evaporative heat loss when pooled across both sexes (i.e., main effect of age). The equation of the regression line, coefficient of determination and *p*-value on each panel represent the main effect of age for the respective exercise bout.

4.2.2. Dry heat exchange

No statistically significant linear relationship was observed between dry heat exchange and age during light- ($P = 0.384$), moderate- ($P = 0.932$), or vigorous-intensity exercise ($P = 0.627$) in a hot-dry environment. As such, no further analyses were performed for the dependent variable of dry heat exchange.

4.2.3. Whole-body heat loss

Whole-body heat loss and age were not significantly related during light-intensity exercise ($P = 0.062$). Therefore, no further analyses were performed for whole-body heat loss during light-intensity exercise. However, during moderate- ($P = 0.001$) and vigorous-intensity exercise ($P < 0.001$), a statistically significant negative linear relationship was observed between whole-body heat loss and age, with a decline in whole-body heat loss of 4.2 and 6.6 W/m^2 per decade (Figure 5). Thus, further analyses were conducted to assess whether the age-related decline on whole-body heat loss was modified by sex during these exercise bouts. Sex was found to have no significant effect on the relationship between age and whole-body heat loss during moderate- ($P = 0.327$) or vigorous-intensity exercise ($P = 0.521$) in a hot-dry environment, only explaining an additional 0.1, and 0.04% of the total variance in the two respective exercise periods. Nonetheless, when pooled across age, the rate of whole-body heat loss was 8.4 and 12.1 W/m^2 lower in women relative to men during moderate- ($P = 0.04$) and vigorous-intensity exercise ($P = 0.002$), respectively (Table 2).

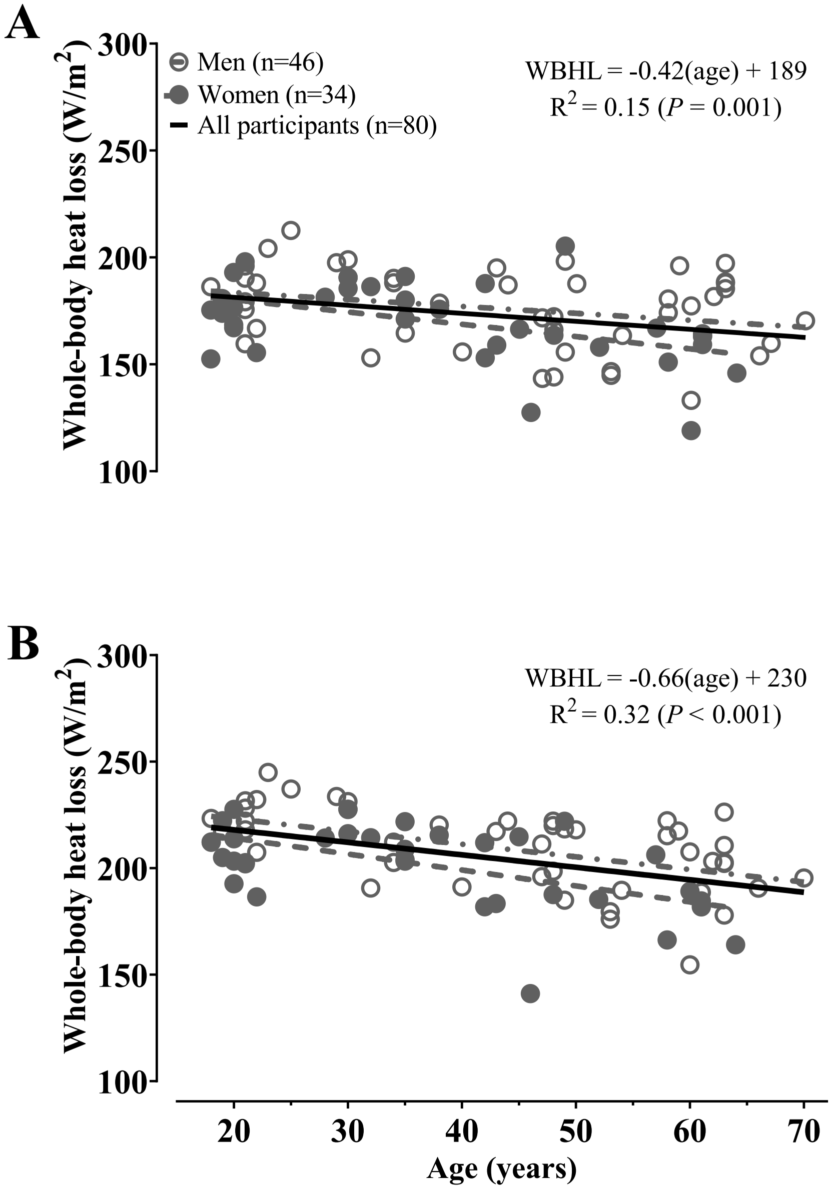

Figure 5. Whole-body heat loss (W/m^2) during the moderate- (A; 200 W/m^2), and vigorous-intensity exercise (B; 250 W/m^2) bouts in 80 (46 men, 34 women) adults. The grey dashed-and-dotted regression line and the grey dashed regression line represent the relationship between age and whole-body heat loss in men and women, respectively. The solid black line represents relationship between age and whole-body heat loss when pooled across both sexes (i.e., main effect of age). The equation of the regression line, coefficient of determination and *p*-value on each panel represent the main effect of age for the respective exercise bout.

4.2.4. Change in mean body temperature.

Much like the rate of whole-body heat loss, no statistically significant relationship between age and the change in mean body temperature was observed during light-intensity exercise (*P* = 0.106), but during moderate- (*P* = 0.005) and vigorous-intensity exercise (*P* < 0.001), the change in mean body temperature was found to increase by 0.09 and 0.15 ˚C/hour each decade, respectively (Figure 6). Since there was no significant linear relationship between age and the change in mean body temperature during light-intensity exercise, no further analyses were conducted for this exercise bout. However, we sought to determine whether sex modified the relationship between age and the change in mean body temperature during moderate- and vigorous-intensity exercise. The increase in mean body temperature with age was found to be similar between men and women during moderate- (*P* = 0.533) and vigorous- (*P* = 0.884) intensity exercise, explaining less than 0.1% of the total variance in the change in mean body temperature during both exercise bouts. Furthermore, when pooled across age, women experienced a greater change in mean body temperature relative to men by 0.18 and 0.24˚C/hour during moderate- (*P* = 0.027) and vigorous-intensity exercise (*P* < 0.001) in dry heat, respectively.

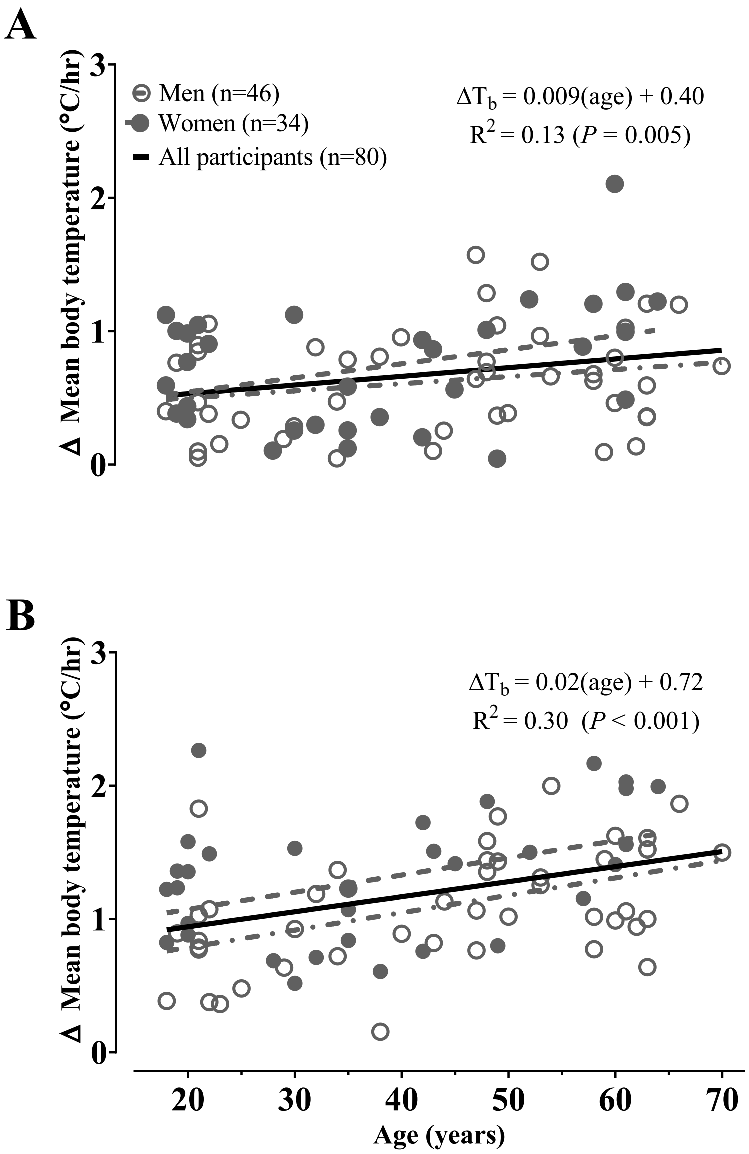

Figure 6. Change in mean body temperature (T_b) calculated from heat storage as assessed by direct calorimetry during the moderate- (A; 200 W/m^2), and vigorous-intensity exercise (B; 250 W/m^2) bouts in 80 (46 men, 34 women) adults. The dashed and dotted regression line and the dashed regression line represent the relationship between age and the change in mean body temperature ($\Delta T_{b,cal}$) in men and women, respectively. Whereas the solid black line represents the relationship between age and the change in mean body temeperature when pooled across both sexes (i.e., main effect of age). The equation of the regression line, coefficient of determination and *p*-value on each panel represent the main effect of age for the respective exercise bout.

4.2.5. Heart rate reserve

In contrast to whole-body heat exchange, heart rate reserve was found to increase with age during light- ($P = 0.001$), moderate- ($P < 0.001$), and vigorous-intensity exercise ($P < 0.001$) in dry heat by 2.2%, 4.2%, and 6.7% per decade, respectively. However, the significant positive relationships between heart rate reserve and age observed during all three exercise bouts were not significantly modified by sex (light; $P = 0.529$, moderate; $P = 0.153$, or vigorous; $P = 0.444$) (Figure 7), as the interaction term only explained an additional 0.04, 0.2 and 0.05% of the total variance in the relationship between age and heart rate reserve. Regardless, heart rate reserve was found to be significantly lower in men relative to women during light- (6%; P <0.001), moderate- (8%; P <0.001) and vigorous-intensity exercise (9%; P <0.001) in a hot-dry environment, irrespective of age (Table 2).

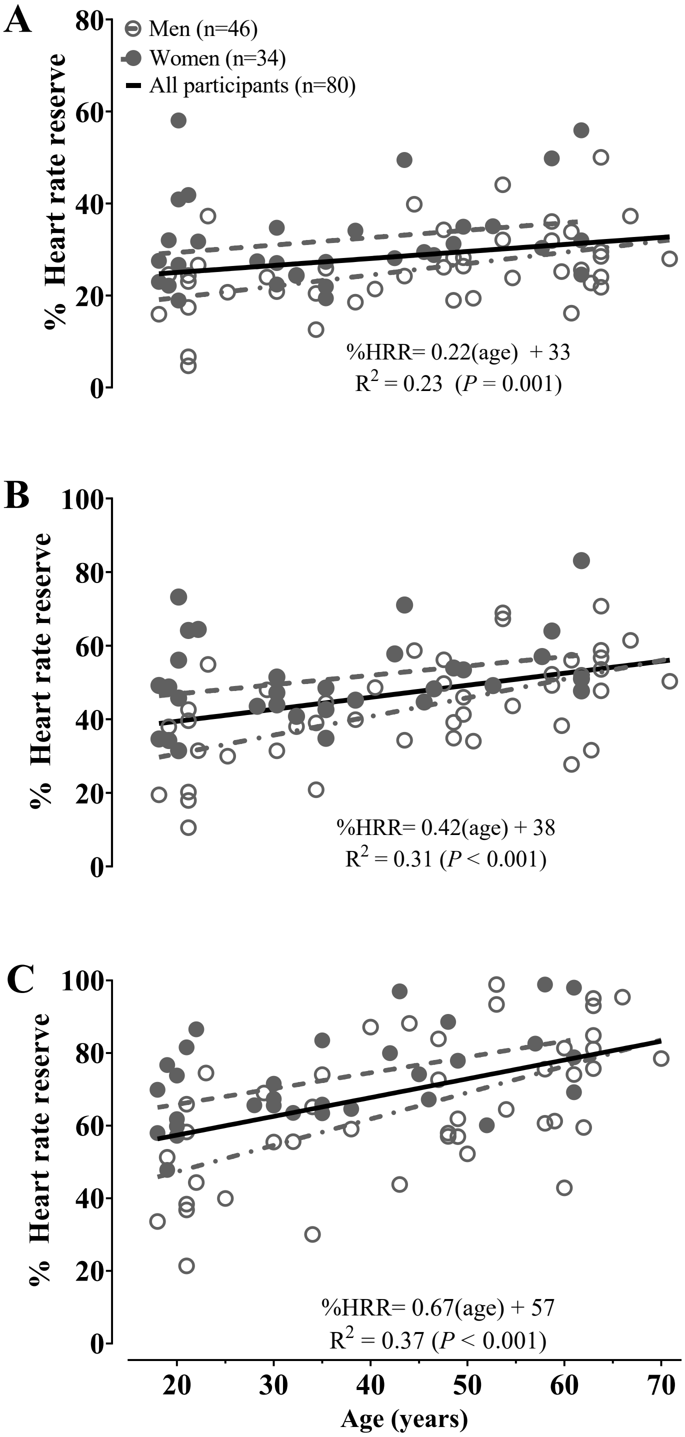

Figure 7. Heart rate reserve (%) during the low- (A; 150 W/m^2), moderate- (B; 200 W/m^2), and vigorous-(C; 250 W/m^2) intensity exercise bouts in 80 (46 men, 34 women) adults. The dashed and dotted regression line and the dashed regression line represent the relationship between age and the change in percent heart rate reserve in men and women, respectively. Whereas the solid black line represents the relationship between age and percent heart rate reserve when pooled

across both sexes (i.e., main effect of age). The equation of the regression line, coefficient of determination and *p*-value on each panel represent the main effect of age for the respective exercise bout.

Table 2. Evaporative heat loss, whole-body heat loss, change in mean body temperature and heart rate reserve responses during the incremental exercise protocol.

	Men (n=46)		Women (n=34)		All Participants (n=80)	
Variable	Mean (SD)	Range (min-max)	Mean (SD)	Range (min-max)	Mean (SD)	Range (min-max)
Light-intensity						
Evaporative heat loss (W/m^2)	173 (15)	137-197	173 (16)	128-207	173 (15)	128-207
Whole-body heat loss (W/m^2)	128 (18)	93-159	127 (15)	80-152	128 (17)	80-159
Change in mean body temperature (˚C/hr)	0.58 (0.34)	0.01-1.00	0.68 (0.43)	0.04-1.76	0.59 (0.43)	0.01-1.76
Heart rate reserve (%)	26 (9)*	5-50	32 (10)	19-58	28 (10)	5-58
Moderate-intensity						
Evaporative heat loss (W/m^2)	223 (18)*	185-257	215 (19)	163-246	219 (18)	163-257
Whole-body heat loss (W/m^2)	176 (19)*	133-213	169 (18)	119-205	173 (19)	119-213
Change in mean body temperature (˚C/hr)	0.63 (0.39)*	0.05-1.57	0.77 (0.51)	0.04-1.29	0.69 (0.45)	0.05-1.57
Heart rate reserve (%)	43 (14)*	11-71	51 (12)	31-83	46 (14)	11-83
Vigorous-intensity						
Evaporative heat loss (W/m^2)	257 (20)*	207-297	246 (22)	199-286	253 (21)	199-297
Whole-body heat loss (W/m^2)	209 (19)*	155-245	199 (21)	141-228	206 (20)	141-245
Change in mean body temperature (˚C/hr)	1.06 (0.41)*	0.15-1.86	1.35 (0.58)	0.52-2.03	1.18 (0.51)	0.15-2.03
Heart rate reserve (%)	64 (19)*	21-95	73 (13)	48-98	69 (18)	21-98

Data presented are mean (standard deviation). All data represents an average of the final 5-min of each exercise period. * indicates a significant difference between men and women ($P < 0.050$).

CHAPTER V

Discussion

This thesis sought to determine whether the age-related decline in whole-body heat loss (across adulthood) would be modified by sex, such that the rate of decline in whole-body heat loss with age would be greater in women relative to men. Contrary to our hypothesis, we found that sex does not influence the reductions in whole-body heat dissipation associated with aging during light, moderate or vigorous-intensity exercise in a hot-dry environment. However, during moderate and vigorous-intensity exercise, whole-body heat loss was found to decrease by 3 and 5% per decade, respectively, when pooled across sex. This reduction in heat dissipation translated to an 8 and 16% greater change in mean body temperature per decade in both men and women during moderate and vigorous-intensity exercise respectively. Furthermore, our findings indicate that when pooled across age, whole-body heat loss is greater in men relative to women by 4 and 5% during moderate- and vigorous-intensity exercise respectively. Subsequently, the change in mean body temperature was found to be 23% lower in men relative to women during moderate intensity exercise, and 22% lower in men during vigorous-intensity exercise performed in a hot-dry environment.

5.1. The interactive effects of sex and age on whole-body heat loss

Although it is well known that the influence of age (Stapleton et al., 2015a, 2015b) and sex (Gagnon & Kenny, 2012) on whole-body heat loss are proportional to the exercise-induced heat load, the only study assessing the interaction between these two variables employed an exercise model wherein participants completed a repeated, moderate-intensity exercise-induced heat load (Flouris et al., 2018). Therefore, to evaluate the heat load (if any) at which point sex would modify the age-related decline in whole-body heat loss, we employed an incremental heat load model consisting of low-, moderate- and vigorous-intensity exercise. This approach allowed us to perform the first evaluation to determine if sex would modify the age-related changes in whole-body heat loss, and the threshold wherein this effect would be observed. To date, only one study has evaluated the influence of age and sex on whole-body heat loss during exercise in a hot environment, reporting that the age-related decline in whole-body heat loss was greater in men relative to women (Flouris et al., 2018). In contrast to that work, we found the rate of decline in heat loss associated with aging to be similar between men and women. These disparate results may be attributed to differences in the rate of metabolic heat production employed during exercise. In the study by Flouris et al. (2018), men and women were exercising at different rates of metabolic heat production which resulted in an unequal thermal drive for heat dissipation between men and women. In contrast, all participants in the current study completed exercise at an equal, fixed rate of metabolic heat production, ensuring an equal stimulus for heat loss between all participants and allowing for a comparison of the independent influence of sex and age on whole-body heat loss. Therefore, to the best of our knowledge, this is the first study uniquely designed to provide a direct comparison of the interactive effects of sex and age on whole-body heat loss.

Our analysis revealed that the factors of age and sex only explained a small (but statistically significant) proportion of the inter-individual variation in whole-body heat loss during moderate- (16%) and vigorous-intensity exercise (32%), resulting in 68-84% of the variation in whole-body heat loss being unexplained. This indicates that despite being examined in a relatively large sample, other factors beyond those considered in the current study could contribute to the observed inter-individual variation. For example, recent work has shown that in eumenorrheic women, whole-body heat loss is not influenced by menstrual cycle phase (Notley, Dervis, Poirier, & Kenny, 2019), however there is evidence which indicates that the use of oral contraceptive pills impairs the sweating response during exercise in a hot environment relative to eumenorrheic women (Lei et al., 2019). Therefore, it is possible that oral contraceptive use may explain a greater amount of the inter-individual variance observed in the current study. Another factor which may explain a greater proportion of the individual variance in our data is the use of hormone replacement therapy. Older women undergoing hormone replacement therapy have been found to experience a downward shift in the core temperature thresholds for sweating (Brooks et al., 1997; Tankersley, Nicholas, Deaver, Mikita, & Kenney, 1992) and skin blood flow (Brooks-Asplund, Cannon, & Kenney, 2000; Brooks-Asplund & Kenney, 1998), and an increased sweating rate (Tankersley et al., 1992). These outcomes call attention to important gaps in the current understanding of how other inter-individual factors (e.g. sex hormones, chronic disease, heat acclimation, others) might aid in explaining the individual variation in thermoregulatory function. While the purpose of the current study was not to evaluate the variance explained in whole-body heat loss by several inter-individual factors, this remains an important area of future research as identifying key factors that influence heat dissipation may help to protect individuals who are at a greater risk of heat-related illness.

5.2. The influence of age on whole-body heat loss across sex

While many studies have assessed the influence of age on thermoregulation during exercise-induced heat stress (Larose, Boulay, et al., 2013; Larose et al., 2014; Notley, Poirier, et al., 2017; Stapleton et al., 2015a; Tankersley et al., 1991), to the best of our knowledge only one study to date has evaluated the decline in heat loss associated with aging across adulthood (McGinn et al., 2017). McGinn et al. (2017) found that whole-body heat loss declined by ~4% per decade from the age of 20 during a repeated, short duration (15 minutes) exercise at a fixed rate of metabolic heat production of 400 W (~200 W/m^2). However, given that the magnitude of the age-related impairment in whole-body heat loss is proportional to the exercise-induced heat load, the current study extended on the findings of McGinn et al. (2017) by evaluating the age-related decline in heat loss across adulthood during light- (150 W/m^2), moderate- (200 W/m^2) and vigorous (250 W/m^2) intensity exercise. While no linear relationship was observed between whole-body heat loss and age during light-intensity exercise, we found that the age-related decline in heat loss per decade was slightly greater during vigorous-intensity exercise relative to the moderate-intensity exercise bout. This outcome indicates that during vigorous-intensity exercise, both men and women experience a greater age-related reduction in heat loss per decade.

5.3. Sex-related differences in whole-body heat loss across age

Sex-related differences in thermoregulatory function during exercise-induced heat stress have been studied for many years, finding that heat loss is typically impaired in women compared to men (Bittel & Henane, 1975; Dill et al., 1973; Gagnon & Kenny, 2011; Hardy & Du Bois, 1940; Shapiro et al., 1980; Wyndham et al., 1965). However, only recently has it been reported that these sex-related differences in whole-body heat loss begin to occur beyond a certain threshold requirement for heat loss (i.e. exercise-induced heat load) (Gagnon & Kenny, 2012). Importantly, these findings were limited to young adults only, whereas in the current study, we provide the first comparison of sex-related differences in whole-body heat loss across adulthood. In line with the idea that sex-related differences in whole-body heat loss only occur beyond a threshold requirement for heat loss, we found that irrespective of age, heat dissipation is impaired (primarily due to a reduction in whole-body evaporative heat loss) in women relative to men (i.e. main effect of sex) during moderate and vigorous-intensity exercise, only. These novel findings indicate that the sex-related differences may be due to inherent biological differences between men and women, independent of age. In young adults, sex-related differences in whole-body heat loss during exercise in a hot-dry environment were found to be primarily driven by an impaired rate of whole-body evaporative heat loss in young women, specifically due to a reduced sweat gland output (Gagnon & Kenny, 2012). The same group later built on these findings, reporting that women exhibited a lower maximal sweating response relative to men when administered incremental intradermal doses of acetylcholine and methylcholine (sweating agonists) (Gagnon, Crandall, et al., 2013). This observation provided novel information that sex-related differences in heat dissipation among young adults are due to peripherally mediated changes in the sweat gland, and that they may be attributed to differences in the size of the sweat glands between men and women. While we cannot be certain that the mechanisms which influence the sweat gland are the same in older and young women, nor that the sweat gland size is different between men and women across adulthood, future work is required to address these important questions to further our understanding of sex-related differences in heat dissipation.

5.4. Perspectives

The outcomes from the current study have important implications for the design of physical activity and occupational guidelines. Currently, the heat stress guidelines adopted and recommended for use by international (e.g., World Health Organization) and national (i.e. Canadian Federal and Provincial governments) agencies to protect the public and workers do not account for inter-individual factors such as sex and age which can markedly influence the body's physiological capacity to dissipate heat. Our observations of an age-related decline in whole-body heat loss in both men and women (Figure 5), with an impaired ability to dissipate heat in women relative to men across adulthood (Table 2) clearly indicates that revisions to these guidelines are imperative. Given that we have a rapidly aging population and workforce, and that women represent an increasingly greater proportion of these populations (Kenny et al., 2016), the need for age- and sex-specific heat stress guidelines is of the utmost importance.

5.5. Considerations

To evaluate the influence of sex on the age-related changes in whole-body heat loss as a function of the exercise-induced heat load, we used an incremental model which has been used to assess differences in the body's physiological capacity to dissipate heat as a function of a number of factors such as: fitness, menstrual cycle, heat acclimation, age, sex, others (Gagnon & Kenny, 2012; Lamarche, Notley, Louie, Poirier, & Kenny, 2018; Lamarche, Notley, Poirier, et al., 2018; Notley et al., 2019; Stapleton et al., 2015a). This experimental protocol consisted of three, 30-min bouts of exercise at increasing fixed rates of metabolic heat production of 150 (light), 200 (moderate), and 250 W/m^2 (vigorous), each followed by a 15-min rest period. Given that previous work has shown that there is a greater activation of whole-body heat loss following an initial exercise and rest cycle (Larose, Wright, Sigal, et al., 2013; Larose, Wright, Stapleton, et al., 2013), we cannot discount the possibility that separating this incremental exercise model into three bouts of exercise performed on separate days, and perhaps of longer duration, may have revealed sex-related differences in the age-related decline in whole-body heat loss. Therefore, future work is required to assess how the influence of sex on the age-related decline in whole-body heat loss is altered by a preceding exercise and recovery cycle during moderate- and vigorous-intensity exercise in a hot-dry environment.

Since aerobic fitness declines naturally with age (Becklake, Frank, Dagenais, Ostiguy, & Guzman, 1965; Fleg & Lakatta, 1988; Grimby, Nilsson, & Saltin, 1966), and is known to independently influence heat loss (Lamarche, Notley, Louie, et al., 2018; Lamarche, Notley, Poirier, et al., 2018), it has been suggested that the decline in heat loss associated with age is due to age-related reductions in aerobic fitness rather than aging itself (Tankersley et al., 1991). However, recent work from our laboratory has shown that short-term aerobic exercise training, which elicited a ~10% increase in VO_{2peak}, was found not to influence whole-body heat loss during exercise in the heat in young men (Stapleton, Gagnon, & Kenny, 2010). Therefore, while we observed a natural decline in aerobic fitness with aging (~6.5% decline in VO_{2peak} per decade), as we studied a representative (habitually active) population, we believe our finding of a reduction in whole-body heat dissipation across adulthood is ascribed to aging per se, as opposed to age-related reductions in aerobic fitness. Nonetheless, further studies are required to delineate the independent influence of aerobic fitness on the age-related decline in whole-body heat loss in men and women, across adulthood.

CHAPTER VI

CONCLUSION

6.1. Conclusion

The current thesis sought to evaluate whether sex would modify the age-related decline in whole-body heat loss. We demonstrated, for the first time, that the rate of decline in whole-body heat loss associated with aging is similar between men and women during exercise in dry heat. However, consistent with previous literature, we observed that the separate effects of age and sex occurred in a heat load dependent manner. As such, whole-body heat loss was observed to decline with age among men and women during the moderate and vigorous-intensity exercise periods only. Similarly, women demonstrated an impaired whole-body heat loss response (primarily via a reduced rate of evaporative heat loss) during moderate and vigorous-intensity exercise, but not the light intensity exercise period. These impairments in whole-body heat loss translated to a greater change in mean body temperature with increasing age (across sex), as well as in women (across age) during the moderate- and vigorous-intensity exercise periods.

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CHAPTER VII

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