Revisiting age differences in the region-specific sweat rate response during whole-body passive heating

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ABSTRACT

Aging is associated with attenuated sweat gland function, which has been suggested to occur in a peripheral-to-central manner. However, evidence supporting this hypothesis remains equivocal. We therefore revisited this hypothesis by evaluating sweat rate across the limbs and trunk in young and older men during whole-body, passive heating. A water-perfused suit was used to raise and clamp esophageal temperature at 0.6°C (low-heat strain) and 1.2°C (moderate-heat strain) above baseline in 14 young (24 [SD 5] years) and 15 older (69 [4] years) men. Sweat rate was measured at multiple sites on the trunk (chest, abdomen) and limbs (biceps, forearm, quadriceps, calf) using ventilated capsules (3.8 cm^2). Sweat rates, expressed as the average of 5 min of stable sweat rate at low- and moderate-heat strain, were compared between groups (young, older) and regions (trunk, limbs) within each level of heat strain using a linear mixed-effects model with nested intercepts (sites nested within region nested within participant). At low-heat strain, the age-related reduction in sweat rate (older-young values) was greater at the trunk (0.65 mg/cm^2/min [95% CI 0.44, 0.86]) compared to the limbs (0.42 mg/cm^2/min [0.22, 0.62]; interaction: p=0.010). At moderate-heat strain, sweat rate was lower in the older compared to young (main effect: p=0.025), albeit that reduction did not differ between regions (interaction: p=0.888). We conclude that, contrary to previous suggestions, the age-related decline in sweat rate was greater at the trunk compared to the limbs at low-heat strain, with no evidence of regional variation in that age-related decline at moderate-heat strain.

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CHAPTER I: INTRODUCTION

1.1. Introduction

Humans regulate body temperature within a narrow range (~36.5ºC-37.5ºC). During heat exposure, the body gains heat at a greater rate than it loses heat, resulting in increased body heat storage and a subsequent rise in body core temperature. This rise in body core temperature is sensed by the hypothalamus (the thermoregulatory control centre) via inputs from central and peripheral thermoreceptors, which initiates the activation of the heat loss responses (i.e., skin blood flow and sweating) (Boulant & Bignall, 1973; Hensel, 1981; Kenny & Flouris, 2014; Morrison & Nakamura, 2011). Once a perturbation in body core temperature occurs (as during heat exposure or exercise), this sympathetically mediated activation of the heat loss responses restores a balance between heat gain and heat loss, preventing a sustained rise in body core temperature under compensable conditions (i.e., achieving heat balance) (Kenny & Jay, 2013). However, under circumstances where impairments in skin blood flow and/or sweating lead to an inadequate rate of heat loss to offset any increase in heat gain for a given environmental heat load, body core temperature will continue to rise (i.e., under uncompensable environments). When the ambient air temperature is higher than skin temperature, the primary pathway to dissipate heat is via evaporative heat loss (i.e., sweating) (Kenny & Jay, 2013; Shibasaki & Crandall, 2010). Sweat rates typically range between 0.5-1.5 $L \cdot h^{-1}$ but can reach as high as 4 $L \cdot h^{-1}$ under high heat stress, such as that associated with vigorous exercise and/or exposure to extreme heat (Baker et al., 2016).

Sweat rate, and therefore evaporative heat loss, can be affected by various individual factors, including age. Older adults (aged ≥65 years) are among the most vulnerable to heat-related injuries (e.g., heatstroke, myocardial infarction) during a prolonged heat exposure (Meade et al., 2020). This vulnerability is partly due to age-

related decrements in local and whole-body heat loss (as measured during passive heat exposure) (Drinkwater et al., 1982; Inoue & Shibasaki, 1996; Kenny et al., 2017). Older adults require a higher mean body temperature to activate the heat loss responses if skin blood flow and sweating, resulting in a delay in the onset of sweating (Inoue & Shibasaki, 1996; Inoue et al., 1998). This delay causes older adults to initially store more heat (Kenny et al., 2017). Further, once sweating is initiated, older adults display a reduction in sweat gland output for a given increase in mean body temperature, which further impairs sweat rate relative to young adults (aged 18-30 years) (Inoue & Shibasaki, 1996; Sato & Sato, 1983). Taken together, an impairment in the onset of thermoeffector responses, accompanied by a reduced sweat rate, results in greater heat storage and thus increased heat strain in older individuals (Kenny et al., 2017).

The sweating response is not uniform across the body, with the torso typically displaying the highest sweat rate and the distal extremities demonstrating the lowest sweat rate during exercise in young adults (Smith & Havenith, 2011, 2012). Further, it has been suggested that the magnitude of the age-related reduction in sweat rate may differ across the body, with some regions displaying a greater age-related reduction in sweat rate than others (Drinkwater et al., 1982; Kenny et al., 2017; Stapleton et al., 2015). Indeed, an early report by Inoue et al. (1991) indicated that the magnitude of the age-related reduction in sweat rate was greater at the thigh relative to the back (Inoue et al., 1991). While limited to only two measurement sites, this initial observation suggested that age-related decrements in sweating may develop in a peripheral-to-central pattern (i.e., the age-related reduction in sweat rate first begins at the limbs and then occurs at the trunk). This hypothesis has been further supported by later work assessing the regional age-related reduction in sweat rate using lower-

limb hot water immersion (Inoue & Shibasaki, 1996) and an exercise-heat stress (Coull et al., 2021). However, these heat stress protocols elicit between-group differences in body core temperature and between-region variations in skin temperature, two important factors that can independently modulate the sweating response (Nadel, Bullard, et al., 1971; Nadel, Mitchell, et al., 1971). Not controlling for these variables makes it difficult to formulate appropriate conclusions on the magnitude of any regional variation in the age-related decline in sweating. Consequently, it becomes challenging to discern whether certain regions truly display a greater magnitude in the age-related reduction in sweat rate than others or if this is simply due to differences in core and skin temperatures. Indeed, the relative change in body core temperature at the end of the heat stress protocols mentioned above was 0.1ºC-0.4ºC higher in older than young adults (Coull et al., 2021; Inoue et al., 1991; Inoue & Shibasaki, 1996; Kenny et al., 2017). Further, mean skin temperature was consistently lower in the older adults during these heating protocols (Coull et al., 2021; Inoue et al., 1991; Inoue & Shibasaki, 1996).

Recent studies have employed a water-perfusion suit to better control for between-group differences in body core temperature and between-region differences in skin temperature responses during whole-body heating. A water-perfusion suit, which covers most of the body surface (except for the head, hands, and feet), ensures a more homogenous skin temperature response across measurement regions (Ko et al., 2020). This whole-body heating model allows water to be perfused at a constant temperature via a high-density suit, thereby allowing tighter control over the change in body core temperature. To this end, a study by Smith, Alexander, et al. (2013) utilized a water-perfusion suit to elicit a controlled whole-body heat stress wherein young and older adults were heated to a body core temperature change of 1.0ºC from baseline

values. They assessed sweat rate at four sites (abdomen, lower back, forearm, and thigh) at a low- (0.5ºC increase in body core temperature) and moderate- (1.0ºC increase in body core temperature) heat strain in young and older adults. Unlike prior reports that have suggested a peripheral-to-central age-related decline in sweat rate (Coull et al., 2021; Inoue et al., 1991; Inoue & Shibasaki, 1996), they showed no specific pattern in the age-related reduction in sweating (i.e., no one region displayed a greater magnitude of reduction in sweating than the other). However, their findings should be interpreted with caution for two reasons. First, their report included measures of sweat rate from a single region on each of the upper and lower limbs, which may not accurately reflect sweating at the periphery due to the extensive inter- and intra-regional variations in sweat rate (Taylor & Machado-Moreira, 2013). Second, they did not assess the regional age-related reduction in sweat rate when body core temperature had stabilized at low- and moderate-heat strain (0.5ºC and 1.0ºC above baseline, respectively). A stable body core temperature is necessary to allow for the dynamic increase in thermoeffector function (i.e., sweating) to reach an output that reflects the stimulus associated with a given body temperature. Assessing regional sweat rates when changes in body core temperature vary by more than 0.1ºC may further perturb sweat rate and thus confound interpretations (Cotter & Taylor, 2005). Consequently, the heating protocol used by Smith, Alexander, et al. (2013), which did not allow for stable core temperature responses (and thus sweating) to be achieved at the target thresholds of 0.5°C and 1.0ºC, may have confounded the results of their study.

1.2. Rationale

Compared to young adults (aged 18-30 years), older adults (aged ≥65 years) have been shown to exhibit more pronounced decrements in sweat rate at the limbs

compared to the trunk (Inoue et al., 1991). This observation has led to the widespread notion that age-related decrements in sweat rate occur in a peripheral-to-central manner (Balmain et al., 2018; Kenney & Munce, 2003). However, subsequent investigations into this hypothesis have been equivocal, with some studies providing supporting evidence (Coull et al., 2021; Inoue & Shibasaki, 1996), whereas others have observed a non-region-specific pattern of reduction (Gerrett et al., 2021; Smith, Alexander, et al., 2013). Inconsistencies with previous observations may be related to differences in experimental protocols employed (i.e., different heating modalities), which have included lower-limb hot water immersion, exercise heat stress, and whole-body heating via a water-perfusion suit. Further, investigations into the regional age-related decline in sweating may have been cofounded by 1) not allowing core temperature elevations to stabilize before assessing the regional age-related decline in sweating and/or 2) between-group differences in body core and between-region variations in skin temperatures. Given these shortcomings and the potential importance of this information for understanding regional age-related changes in thermoregulatory function, it is crucial to reassess whether the regional age-related decline occurs in a peripheral-to-central pattern.

1.3. Objectives

The primary objective of my thesis was to evaluate the age-related decline in sweat rate and whether this occurs in a body region-specific manner. To achieve this objective, we evaluated local sweat rate under low- (i.e., body core temperature increase of 0.6ºC) and moderate- (i.e., body core temperature increase of 1.2ºC) heat strain induced by whole-body heating via a water-perfusion suit. Local sweat rate was assessed at the limbs (four sites: biceps, forearm, quadriceps, calf) and trunk (two

sites: chest, abdomen) in 14 young (24 [SD 5] years) and 15 older (69 [4] years) adults using the ventilated capsule technique (i.e., hygrometry).

1.4. Significance

It is well-established that aging is associated with progressive impairments in the body's capacity to sweat. However, whether a pattern in the age-related reduction in sweat rate exists (i.e., whether certain regions display a greater reduction in sweat rate than others) remains unclear. Advancing our understanding of whether a regional decline in sweat rate occurs in a specific pattern provides important insights into age-related changes to thermoregulatory function. By understanding which region demonstrates the greatest age-related reduction in sweat rate (if any), researchers can consider these differences in the design of their study. For example, suppose a researcher can only measure the age-related impairments in local sweating at one body region. In that case, they may want to consider the region that demonstrated the greatest age-related reduction in sweat rate. Ultimately, my study findings will determine whether the decrease in sudomotor function is region-dependent or whether a generalized reduction pattern occurs.

CHAPTER II: REVIEW OF LITERATURE

2.1. Human thermoregulation

Healthy humans can maintain tight control of body core temperature over a wide range of ambient conditions due to a highly effective thermoregulatory system, which is critical for maintaining optimal physiological function (Taylor, 2006). During exposure to hot ambient conditions (i.e., conditions whereby higher ambient temperatures increase the requirements for whole-body heat loss), heat balance is achieved through adjustments in the heat loss responses to balance the rate of heat gained by the body with that lost to the surrounding environment. The following human heat balance equation defines this relationship:

$M - W = (K + C + R + E_{SK}) + (C_{RES} + E_{RES}) + S$, (all units, $W \bullet m^{-2}$); where,

M = rate of metabolic heat production

W = rate of mechanical work

K = rate of conductive heat loss

C = rate of convective heat loss from the skin

R = rate of radiative heat loss from the skin

E_{SK} = rate of evaporative heat loss from the skin

C_{RES} = rate of convective heat loss from pulmonary ventilation

E_{RES} = rate of evaporative heat loss from pulmonary ventilation

S = rate of body heat storage (Parsons, 2014).

Dry heat loss is mediated by conductive, convective, and radiative heat exchange, whereas evaporative heat loss occurs through the evaporation of sweat (Kenny & Jay, 2013; Wendt et al., 2007). Dry heat exchange (K + C + R) is proportional to the temperature gradient between the surrounding environment and skin temperature. Therefore, dry heat loss occurs when skin temperature is greater than the air temperature, and dry heat gain occurs when air temperature exceeds

skin temperature (Kenny & Flouris, 2014). When air temperature exceeds skin temperature, heat is gained by the body, and the evaporation of sweat from the skin surface becomes the primary pathway to dissipate heat (Kenny & Flouris, 2014). Under these conditions, the primary role of skin blood flow is to deliver heat to the skin surface via warmed blood from the body core. The increase in whole-body heat loss and, therefore, increases in sweating and skin blood flow, in response to elevated levels of heat stress, is proportional to the amount of evaporative heat loss required to achieve heat balance (Gagnon et al., 2013). Under circumstances where impairments in skin blood flow and sweat rate limit increases in whole-body heat loss (i.e., such as occurs with aging and/or the presence of chronic disease) and heat balance cannot be achieved (i.e. uncompensable heat stress), body core temperature will continue to rise (Jay & Kenny, 2010; Kenny et al., 2010).

The regulation of body core temperature is mediated by the pre-optic anterior hypothalamus (PO/AH), which receives and integrates thermoafferent information from the central (core) and peripheral (skin) thermal receptors (Charkoudian & Stachenfeld, 2016). During heat stress, elevations in body core and skin temperature trigger the activation of the heat loss responses (i.e., skin blood flow and sweating) to offset increases in heat gain and regulate mean body temperature (Boulant & Bignall, 1973; Hensel, 1981; Kenny & Flouris, 2014; Morrison & Nakamura, 2011). During heat exposure, a change in mean body temperature (a weighted contribution of body core and skin temperature) initially occurs without activating the heat loss responses (Figure 1). However, as the rate of heat gained from the environment increases and mean body temperature begins to rise, the activation of the heat loss responses occurs, defined as the onset threshold (point A, Figure 1). After that, a sustained rise in the heat loss responses is observed. This rise is proportional to the increase in mean

body temperature and is defined as thermosensitivity (point B, Figure 1). Finally, a plateau is achieved, where despite a continued increase in mean body temperature, no further increases in the heat loss responses are observed (point C, Figure 1) (Kenny & Flouris, 2014). This phase indicates a functional limit in the body's ability to increase heat loss.

Inter-individual (e.g., sex, age, chronic disease) and intra-individual (e.g., hydration, acclimation status) factors can modulate any component of the thermoeffector response (as depicted by the red and green dashed lines in Figure 1). For example, heat acclimation, which enhances the body's physiological capacity to dissipate heat, is associated with an earlier onset threshold, enhanced thermosensitivity, and/or a higher plateau (Balmain et al., 2018). As a result, heat acclimation can improve whole-body heat dissipation (represented by the green dashed line in Figure 1) (Kenny & Flouris, 2014). Alternatively, thermoeffector function can also be impaired, such as with aging. For example, older adults exhibit a delay in the thermoeffector onset threshold, whereby a higher mean body temperature is required to activate changes in skin blood flow and sweating (red dashed line, Figure 1) (Anderson & Kenney, 1987; Inoue & Shibasaki, 1996). Further, aging is associated with reductions in thermosensitivity, resulting in a reduced rate of increase in sweating and skin blood flow for a given level of heat stress in older adults as compared to their younger counterparts (represented by the red dashed line in Figure 1) (Inoue et al., 2004).

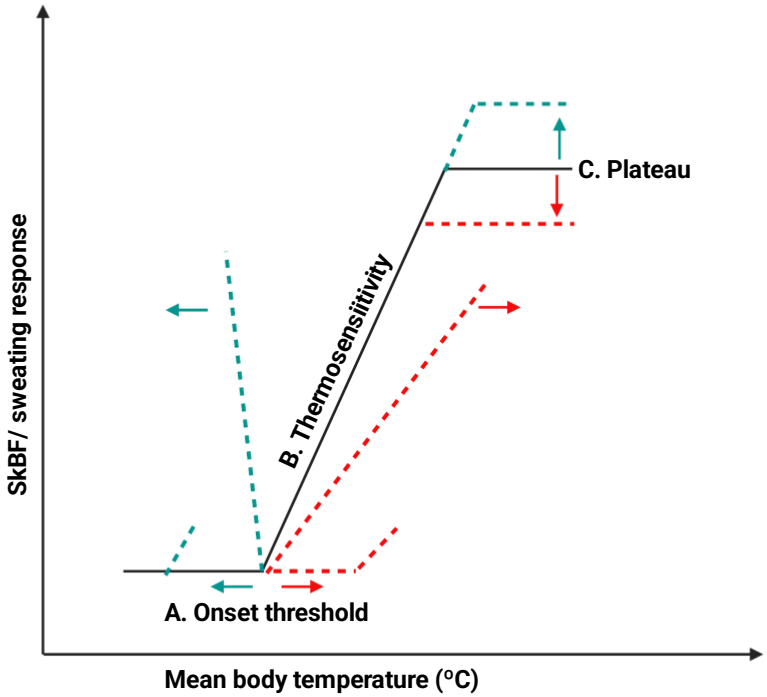

Figure II-1. Visual representation of the relationship between mean body temperature and thermoeffector responses during exercise. A) represents the onset of the thermoeffector response, B) the thermosensitivity of the heat loss responses, and C) the plateau phase in the heat loss responses. The green dashed line represents the influence of non-thermal factors that increase the rate of whole-body heat loss (e.g., heat acclimation). The red dashed line represents non-thermal factors where the thermoeffector response is delayed (e.g., aging) (Kenny & Jay, 2013)—created using BioRender.com.

2.1.1. Eccrine sweating

There are two types of sweat glands in humans that differ based on their activation method: apocrine and eccrine. The apocrine sweat glands are activated when adrenaline is increased (i.e., stress, fear, pain) (Saga, 2002). The eccrine sweat glands are stimulated via cholinergic sympathetic nerves and are responsible for thermoregulatory sweating. In addition, eccrine sweat glands secrete hypotonic (i.e., lower osmotic pressure) sweat onto the skin surface to promote the evaporation of the water content of sweat (Saga, 2002; Shibasaki et al., 2006; Wendt et al., 2007).

Evaporative heat loss (i.e., sweating) accounts for more than 80% of heat loss during exercise or environmental heat strain, compared to only 25% at rest (Cain &

McLellan, 1998; Gavin, 2003). In response to mean body temperature surpassing the onset threshold (point A, Figure 1), the PO/AH activates the eccrine sweat glands through cholinergic sympathetic nerves to increase sweat production and facilitate an increase in evaporative cooling (Shibasaki & Crandall, 2010). The sweating response varies in proportion to changes in mean body temperatures. Increased sweat rate is initially associated with an increase in the number of heat-activated sweat glands, followed by increased sweat production from the recruited glands (Kondo et al., 2001). An attenuated sweating response (i.e., such as occurs with aging) can manifest as 1) a higher mean body temperature required for the onset of sweating, 2) the lack of an appropriate increase in sweat rate for a given increase in body core temperature (i.e., thermosensitivity), and/or 3) a reduction in maximum sweat output (Shibasaki et al., 2006).

2.1.2. Measurement of local eccrine sweating

There are multiple methods employed to measure local sweat rates. The two most commonly employed techniques in current research involve gravimetry and hygrometry. Gravimetry measures collected sweat using absorbent patches, whereas hygrometry measures sweat using ventilated capsules. While both methods assess sweat production, they provide markedly different information.

The technical absorbent patch technique consists of placing custom-sized pieces of highly absorbent material onto the skin surface for a brief period (~30 seconds to 2 minutes depending on the material’s absorbency) to collect sweat as it is produced. The local sweat rate is calculated from the material's mass change over this set period. Technical absorbents allow for simultaneous measurements of sweat rate between and within body segments. Moreover, the main advantage of using the absorbent patch technique is that they allow for sampling large surface areas and are

relatively inexpensive. However, given that the patch saturation would lead to the eventual underestimation of sweat rate, this technique can only be used for single-time points. Consequently, it is not feasible to assess the time-dependent changes in sweat rate that typically occur during exposure to heat stress (Havenith et al., 2008). Further, this technique does not permit the assessment of either the onset threshold, the thermosensitivity, and/or the plateau of the sweating response.

A temperature-dependent profile is needed to assess changes in thermoeffector activity, which is only possible through the ventilated capsule technique (i.e., hygrometry). Small, custom-designed capsules (~2-5 cm^2) are adhered to the skin surface. Dry air moves through the capsule at a fixed flow rate, optimized for measuring local sweat rate. The expulsion of sweat increases the humidity (i.e., the amount of moisture in the air) in the capsule environment and measuring the changes in the humidity of the effluent air relative to inflow corresponds to the sweat rate (Brengelmann et al., 1975; Graichen et al., 1982). To ensure the sweating response being recorded is accurate, the researcher must choose an appropriate flow rate (i.e., the rate at which dry air is moved through the capsule). Selecting a flow rate that ensures complete sweat evaporation at high levels of heat strain is essential. If the flow rate is insufficient, it will be unable to facilitate complete evaporation of sweat within the capsule resulting in an artificial increase in sweating. In addition, A key limitation of the ventilated capsule technique is the relatively small surface area and, therefore, the number of sweat glands evaluated. The ventilated capsule technique only captures ~60-120 sweat glands (Gagnon et al., 2012). Considering there are over 3-4 million sweat glands, using ventilated capsules may over or underestimate the sweating response at the body region assessed. While this is a critical limitation of this technique, ventilated capsules are still reliable, as established by Kenefick et al.

(2012). Further, due to the sensitivity and precision of the ventilated capsules, they are the preferred method for evaluating the mechanisms governing the local sweating response (Taylor & Machado-Moreira, 2013).

2.1.3. Regional variations in sweating

Regional heterogeneity of the sweating response exists and has been attributed to regional variations in the number of activated sweat glands, sweat output per gland, or both factors (Kondo et al., 1998). In addition, regional variations in the size and density of sweat glands across the body exist, further contributing to this regional heterogeneity (Sato & Sato, 1983). An early report by Sato and Dobson (1970) showed that sweat gland density has the largest influence on regional sweat rate, followed by the output and number of activated glands. Regional variations in sweat gland density are partly determined by the inter-segmental growth of an individual, as the number of sweat glands is pre-determined during gestation (Taylor & Machado-Moreira, 2013). As individuals grow and their surface area increases, density declines. High sweat gland densities are found on the chest, back, and abdomen, whereas low sweat gland densities are seen on the thigh and lower leg (Taylor & Machado-Moreira, 2013).

Regional variations in sweat rate between body segments have previously been assessed in young adults. Sweat rates are typically higher on the torso and forehead, with lower sweat rates recorded on the limbs (Cotter et al., 1995; Smith & Havenith, 2011, 2012; Taylor & Machado-Moreira, 2013; Weiner, 1945). Moreover, the activation of the sweating response has been reported to differ across the body in young men, albeit these findings are inconsistent. It was first suggested a distal to proximal activation of sweating occurs (Hertzman, 1957; Park & Tamura, 1992; Rawson & Randall, 1961). However, later work by Cotter et al. (1995) reported that sweat onset at the torso preceded the head but was not significantly different from the

legs, upper torso or arms. Moreover, Smith, Kenney, et al. (2013) reported that the onset of sweating was lower on the thigh and lower back compared to the forearm in young adults during whole-body heating using a water perfusion suit.

With apparent inter-segmental differences in sweating, further research has focused on intra-segmental differences in sweating. Previous reports have indicated that variations within the torso and head regions exist in young adults during exercise (Machado-Moreira, Smith, et al., 2008; Machado-Moreira, Wilmink, et al., 2008). Specifically, the forehead displays the highest sweat rates within the head region, with the top of the head demonstrating the lowest (Machado-Moreira, Wilmink, et al., 2008). Moreover, the highest sweat rate within the torso has been observed at the lower back and the lowest at the lateral torso as assessed during whole-body passive heating (using a water perfusion suit) in young men (Machado-Moreira, Smith, et al., 2008). Later work by Smith and Havenith (2011) assessed inter-and intra-segmental differences in sweat rate across the body during exercise in young men using absorbent patches covering ~83% of total body surface area. Consistent with the findings by Machado-Moreira, Smith, et al. (2008), Smith and Havenith (2011) showed that the torso exhibited a medial to lateral decrease in sweat rate. In addition, Smith and Havenith (2011) reported a proximal to distal increase in sweat rate of the arms, such that the shoulder and bicep achieved higher sweat rates than the forearm when assessed during an exercise heat stress in young men.

2.2. Aging and thermoregulation

Older adults exhibit an impaired whole-body heat loss response during a heat stress (Meade et al., 2020). During passive exposure to extreme heat (44ºC, 30% relative humidity (RH)), older adults are unable to offset the high rate of heat gained from the environment with a corresponding elevation in heat loss needed to achieve heat

balance. As a result, they store more heat relative to their younger counterparts (Kenny et al., 2017). Further, when assessed during an exercise heat stress, these age-related impairments in whole-body heat loss are only evident at moderate to high heat loads (or rates of heat gain). Stapleton et al. (2015) evaluated age-related changes in whole-body heat loss as a function of increased exercise-induced heat loads. Young and older men cycled on a semi-recumbent bike and performed intermittent aerobic exercise (30-minute exercise bouts separated by 15-minute rest) at fixed heat production rates equal to 300, 400, and 500 W. No age-related differences in whole-body heat loss at the low intensity (i.e., 300 W) were observed, which was paralleled by similar responses to local sweat rates at the chest, upper back, and forearm. However, reductions in whole-body heat loss were observed at moderate-to-high metabolic exercise intensities (i.e., 400 and 500 W, respectively) but were not paralleled by similar differences in local sweat rates. It is possible that the lack of age-related impairments in local sweating observed was due to regional heterogeneity of sweat rates across the body (Taylor & Machado-Moreira, 2013).

2.2.1. Aging and sweating

Older adults require a higher mean body temperature during the initial phases of heat exposure to activate the heat loss responses, resulting in a delay in the onset of sweating (Inoue & Shibasaki, 1996; Inoue et al., 1998). The delay in sweating onset translates to an overall attenuation of sweat loss (and thus whole-body evaporative heat loss) in older adults in the first ~30 minutes of passive heat exposure (Inoue & Shibasaki, 1996; Kenny et al., 2017). In addition to a delayed sweat onset, older adults exhibit a lower sweat rate than their younger counterparts (Inoue et al., 2004; Sato, 1988; Shibasaki et al., 2013). These age-related decrements in sweating do not appear to be due to the number of activated sweat glands but rather are caused by a

reduction in the amount of sweat produced per gland, as demonstrated by studies employing pharmacological interventions to activate sweat glands (Inoue, Havenith, et al., 1999; Kenney & Fowler, 1988). The decline in sweat gland output with aging may reflect age-related changes in sweat glands themselves (i.e., sweat gland atrophy) or a decrease in cholinergic sensitivity (Inoue, Shibasaki, et al., 1999). Moreover, additional findings indicate regional differences in sweat gland function exist between older and young adults (Kenney & Munce, 2003). Indeed, greater age-related effects have been commonly reported for sweat gland function on the limbs when compared to sweat glands located on the trunk. In light of these findings, it has been suggested that the age-related reduction in sweat gland function may decline in a peripheral-to-central direction.

Prior research has investigated the age-related reduction in local sweat rate at different regions across the body during passive heat exposure. Drinkwater et al. (1982) assessed the sweating response between young and older adults at five sites (thigh, forearm, chest, upper back, abdomen) during a 2-hour passive heat exposure protocol whereby participants rested in a climatic chamber regulated at 40ºC. They showed that within the first 30 minutes of heat exposure, no differences in regional sweat rates between age groups occurred. However, by the end of the 2-hour heat exposure, sweating at the thigh and forearm demonstrated the greatest regional age-related differences in sweat rate. While they did not explicitly assess whether certain regions display a greater age-related reduction in sweating than others, their findings suggest the limbs demonstrate a lower sweating response than the trunk in older adults. A study by Kenny et al. (2017) recently extended upon these findings by assessing whole-body heat loss during a 3-hour exposure to extreme heat (regulated at 44ºC, 30% RH) in a direct air calorimeter. During the 3-hour exposure, Kenny et al.

(2017) assessed local sweat rates at four sites (thigh, upper back, forearm, chest) using the ventilated capsule technique. By the end of the 3-hour passive heat exposure, the magnitude of the difference in sweat rate from the start of the trial was not different at the forearm, upper back, and chest. Further, even though the sweat rate at the thigh was already reduced in the older adults at the beginning of the protocol compared to the other sites, the magnitude of difference increased by the end of the 3-hour exposure. Taken together, these studies indicate that older adults display lower sweat rates at the limbs than their younger counterparts. Moreover, these studies further support the long-standing hypothesis that the greatest age-related decline in sweating occurs at the periphery in response to heat stress (Inoue et al., 1991; Kenney & Munce, 2003). However, while these aforementioned studies assessed the age-related reduction in local sweat rate at various sites on the body, they have not directly compared between sites, *per se*, to elucidate whether a specific pattern in the age-related reduction in sweating occurs.

An early report by Inoue et al. (1991) directly assessed the regional age-related reduction in sweating at two sites (back and thigh) during a 60-minute lower-limb hot water immersion protocol. Ten older (64 ± SD 1 years) and nine young (22 ± 1 years) habitually active men immersed their lower legs in 40ºC water for 60 minutes while resting in a climatic chamber regulated at 35ºC and 45% RH. Consistent with previous studies assessing age-related reductions in sweat rate, the older adults demonstrated an attenuated sweating response at both the thigh and back when taken as an average over the entire heating protocol. Interestingly, they noted a greater magnitude in the age-related reduction in sweating at the thigh by 186 g/m^2/h (0.31 mg/cm^2/min) than at the limbs (80 g/m^2/h or 0.13 mg/cm^2/min) when performed in the winter months. This early report was the first to suggest that the magnitude of the age-related

reduction in sweating does not occur uniformly but instead may follow a peripheral-to-central (i.e., limbs-to-trunk) reduction pattern. However, Inoue and colleagues only assessed sweat rate at one site on the limbs (thigh) and one site on the trunk (back), which may not accurately reflect sweat rate at peripheral and central regions.

A subsequent study by Inoue and Shibasaki (1996) assessed the regional age-related reduction in sweating in ten older (68 ± 1 years) and ten young (23 ± 0 years) habitually active adults throughout February. They used the same lower-limb hot water immersion protocol as mentioned above. Building off the two measurement sites assessed by Inoue et al. (1991), Inoue and Shibasaki (1996) measured sweat rate at five sites (forehead, back, thigh, forearm, and chest) using the ventilated capsule technique. Regardless of the site, within the first 30 minutes of heat exposure, and when the change in core temperature achieved an elevated level of 0.3ºC for the older and 0.2ºC for the younger adults above baseline levels, the older participants demonstrated an attenuated sweating response than the young. However, by the end of the 60-minute heat exposure, and when the change in core temperature from baseline was 0.9ºC and 0.5ºC for the older and young adults, respectively, the only sites showing an attenuated sweating response were the thigh and back. Consistent with the findings by Inoue et al. (1991), they observed that the age-related decrement in sweating was markedly greater at the thigh (i.e., 37% reduction in sweat rate relative to the young) than at the back (i.e., 12% reduction in sweat rate relative to the young). However, in both studies, while the absolute core temperature was the same in both groups at baseline, the relative change in body core temperature at the end of the 60-minute exposure was 0.3-0.4ºC higher in older relative to young adults (Inoue et al., 1991; Inoue & Shibasaki, 1996). Notably, both studies only reported the mean skin temperature (lower in older adults) and did not report the regional skin temperature

response at measurement sites. The lower limbs likely had a higher skin temperature than the torso and upper body, given the upper body was exposed to warm air, which has 20-fold lower thermal conductivity than the hot water bath. Consequently, this heating modality creates an unequal thermal stimulus across measurement sites and age groups, which may have influenced the sweating response in young and older adults differently. Not accounting for these differences in thermal stimuli between groups and regions represents a critical limitation in the prior work in this area (Nadel, Bullard, et al., 1971; Nadel, Mitchell, et al., 1971).

In recent work, Coull et al. (2021) supported the notion of a peripheral-to-central age-related decline in sweat rate when assessed during an exercise heat stress. Fourteen older (68 ± 5 years) and fourteen young (24 ± 2 years) physically active adults walked on a treadmill at a fixed workload (200 W•m^2) in the heat (32ºC, 50% RH) for 25 minutes. Sweat production was measured using absorbent patches that covered ~83% of the total body surface area. Due to the absorbent patches, Coull et al. (2021) could only assess the regional age-related decline in sweat rate during the last 5 min of the exercise protocol. Consistent with the findings by Inoue et al. (1991) and Inoue and Shibasaki (1996), they indicated that the greatest age-related reduction in sweat rate occurred at the lower limbs (80.40 g/m^2/h or 0.13 mg/cm^2/min) and the smallest at the trunk (12.0 g/m^2/h or 0.02 mg/cm^2/min). Moreover, the large surface area covered via the absorbent patches could assess intra-regional age-related decrements in sweating. For example, they showed that sweating at the calf was reduced by ~52% more than the thigh in older adults. However, Coull et al. (2021) had similar limitations to the previous studies using lower-limb hot water immersion. First, older adults had a lower resting body core temperature (~37.1ºC) compared to the young (~37.4ºC) but a higher relative change in core temperature by the end of

exercise (0.5ºC in the older versus 0.2ºC in the younger). Recent evidence suggests that thermoeffector activation is more closely coupled with the relative change in core temperature, rather than a threshold absolute core temperature (Taylor et al., 2019). Therefore, it would be more important to ensure an equal relative change in core temperature to examine any age-related reductions in sweat rate. Second, exercise is subject to regional variations in skin temperature. Indeed, Coull et al. (2021) assessed skin temperature responses via whole-body infrared thermal imaging. They indicated that the limbs and lower torso displayed a higher skin temperature response during exercise than the upper body in both age groups. During exercise, high lower-body skin temperatures due to heat production from active muscle tissue can result in regional variations in sweating, particularly given the large muscle mass in the thigh (Kenny & Flouris, 2014; Todd et al., 2014). Additionally, exercise stimulates sweating both thermally and non-thermally (Van Beaumont & Bullard, 1963), a factor that may contribute to further discrepancies in the evaluation of age-related, regional differences in sweating.

While the studies mentioned above support the notion that age-related reductions in sweat rate occur in a peripheral-to-central manner, other investigators have reported a non-region-specific pattern of reduction (i.e., no one region displays a greater age-related reduction in sweat rate than the other). For example, a recent study by Gerrett et al. (2021) performed a lower limb hot water immersion protocol in middle-aged (50-54 years) and older adults (80-84 years) between October and May. They observed no specific pattern in the regional age-related decline in sweat rate when assessed at the forearm, chest, and thigh when body core temperature was raised +0.8ºC above baseline. This finding contrasts previous observations using a similar heat stress protocol (Inoue et al., 1991; Inoue & Shibasaki, 1996). The disparity

between studies may be due to including middle-aged adults as the ‘younger’ comparator group. Since the influence of age on some sudomotor functions has been reported to occur by the 5th decade (Larose et al., 2013), any noticeable effect of age may have already taken place in the age cohorts that were compared (i.e., 50-54 versus 80-84).

A study by Smith, Alexander, et al. (2013) examined the regional age-related decline in sweat rate at two sites on the limbs (thigh, forearm) and two sites on the trunk (abdomen, lower back). In their study, nine young (23 ± 3 years) and eight older (64 ± 7 years) habitually active adults were passively heated with a water-perfusion suit to a predefined elevation in body core temperature of 0.5ºC (low-heat strain) and 1.0ºC (moderate-heat strain) above baseline values. Consistent with prior studies, Smith, Alexander, et al. (2013) showed that sweat rate was attenuated in the older adults relative to their younger counterparts at all measurement sites and throughout the entire ramp heating protocol. However, in contrast with the studies that observed a greater age-related reduction in sweating at the limbs (Coull et al., 2021; Inoue et al., 1991; Inoue & Shibasaki, 1996), they indicated that the magnitude of the age-related decline in sweating did not differ between regions. Specifically, at low-heat strain, the magnitude of reduction at the trunk was approximately 0.5 mg/cm^2/min compared to the limbs (~0.2 mg/cm^2/min). Further, at moderate-heat strain, the magnitude of reduction at the trunk was approximately 0.4 mg/cm^2/min compared to the limbs (~0.1 mg/cm^2/min). While Smith, Alexander, et al. (2013) used a water-perfusion suit to better control for between-group differences in body core and between region variations in skin temperature, a key limitation of their study was that they did not assess sweat rate at low- or moderate-heat strain when body core temperature was stable. A stable body core temperature is necessary to ensure a

stable thermoeffector drive. Thus, the protocol used by Smith, Alexander, et al. (2013), which by design did not allow for a stable body core temperature to be achieved, may have influenced the sweating response differently between regions and age groups. Additionally, this report, along with others (Gerrett et al., 2021; Inoue & Shibasaki, 1996; Inoue et al., 1991), included measures of sweat rate from a single region on the upper and lower limbs. With clear inter- and intra-segmental differences in sweating observed in young and older adults (Coull et al., 2021; Smith & Havenith, 2011; Taylor & Machado-Moreira, 2013), assessing sweating at multiple sites across body segments is necessary to ensure sweat rates are not heavily influenced by one site.

Despite our growing understanding of age-related reductions in the sweating response, it remains unclear if the magnitude of reduction occurs differently across body segments. Therefore, my thesis aimed to evaluate the possible regional age-related decline in sweat rate during passive heat stress eliciting controlled elevations in body core and skin temperatures between older and young adults. To ensure regional sweat rates were not overly influenced by one site, sweat rate was measured at four sites on the limbs and two sites on the trunk in young and older adults. Further, sweat rate was assessed at two levels of heat strain (0.6°C and 1.2°C above baseline) when body core temperature had stabilized (i.e., body core temperature did not vary by >0.1ºC and sweat rate did not fluctuate by >0.05 mg/cm^2/min). With this approach, I provided a more robust test of a peripheral-to-central decline in the age-related reduction in sweat rate while also determining whether these effects are consistent across two increasing levels of hyperthermia.

CHAPTER III: THESIS ARTICLE

Revisiting regional variation in the age-related reduction in sweat rate during passive heat stress

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Revisiting regional variation in the age-related reduction in sweat rate during passive heat stress

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All authors conceived and designed of the work, revised the manuscript, approved the final version of the manuscript, and agree to be accountable for all aspects of the work. M.D.S., S.R.N., A.P.A., R.D.M., and M.M.R. performed data collection and analysis. M.D.S., S.R.N., and R.D.M., performed statistical analysis. M.D.S and S.R.N drafted the manuscript. M.D.S. prepared figures. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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ABSTRACT

Aging is associated with attenuated sweat gland function, which has been suggested to occur in a peripheral-to-central manner. However, evidence supporting this hypothesis remains equivocal. We therefore revisited this hypothesis by evaluating sweat rate across the limbs and trunk in young and older men during whole-body, passive heating. A water-perfused suit was used to raise and clamp esophageal temperature at 0.6°C (low-heat strain) and 1.2°C (moderate-heat strain) above baseline in 14 young (24 [SD 5] years) and 15 older (69 [4] years) men. Sweat rate was measured at multiple sites on the trunk (chest, abdomen) and limbs (biceps, forearm, quadriceps, calf) using ventilated capsules (3.8 cm^2). Sweat rates, expressed as the average of 5 min of stable sweating at low- and moderate-heat strain, were compared between groups (young, older) and regions (trunk, limbs) within each level of heat strain using a linear mixed-effects model with nested intercepts (sites nested within region nested within participant). At low-heat strain, the age-related reduction in sweat rate (older-young values) was greater at the trunk (0.65 mg/cm^2/min [95% CI 0.44, 0.86]) compared to the limbs (0.42 mg/cm^2/min [0.22, 0.62]; interaction: p=0.010). At moderate-heat strain, sweat rate was lower in older compared to young (main effect: p=0.025), albeit that reduction did not differ between regions (interaction: p=0.888). We conclude that, contrary to previous suggestions, the age-related decline in sweat rate was greater at the trunk compared to the limbs at low-heat strain, with no evidence of regional variation in that age-related decline at moderate-heat strain.

Key words: aging, heat, sweat, thermoregulation

INTRODUCTION

Older adults (aged ≥65 years) are among the most vulnerable to the adverse health effects of heat exposure (Meade et al., 2020), due at least in part to age-related decrements in sudomotor function (Inoue & Shibasaki, 1996; Shibasaki et al., 2013). These include a delay in the onset of sweating and a reduction in sweat gland output, which reduces sweat rate relative to young adults (aged 18-30 years) at a given increase in mean body temperature (Inoue & Shibasaki, 1996; Sato & Sato, 1983). Interestingly, some investigations have reported that the magnitude of this reduction is greater at the limbs compared to the trunk (Coull et al., 2021; Inoue et al., 1991; Inoue & Shibasaki, 1996; Kenney & Munce, 2003), leading to the suggestion that age-related decrements in sweat rate may develop in a peripheral-to-central manner (Inoue et al., 1991; Kenney & Munce, 2003). However, subsequent investigations of this hypothesis are equivocal, with some providing supporting evidence, whereas others have observed a non-region-specific pattern of reduction (Gerrett et al., 2021; Smith, Alexander, et al., 2013).

Inconsistencies with previous observations may relate to differences in the experimental protocols employed, which have included walking on a treadmill in the heat (Coull et al., 2021) or lower-limb water immersion (Gerrett et al., 2021; Inoue et al., 1991; Inoue & Shibasaki, 1996). The former resulted in higher skin temperatures at the trunk and lower limbs compared to the upper limbs in older adults (Coull et al., 2021), an observation likely due to the increased heat production from the active musculature in the lower limbs (Kenny & Flouris, 2014; Todd et al., 2014). This makes it difficult to discern the true magnitude of any regional variation in the age-related decline in sweating, and whether regional variations in that decline reflect a peripheral-to-central pattern or simply reflect segmental differences in skin temperature, which

can independently modulate sweat rate (Nadel, Bullard, et al., 1971). While those investigators employing lower-limb hot-water immersion did not report regional skin temperature (Gerrett et al., 2021; Inoue et al., 1991; Inoue & Shibasaki, 1996), it is likely that a similar regional difference occurred given the upper body was exposed to warm air, which has markedly lower thermal conductivity. Further, since both models elicited a single step change in body core temperature of ≤0.8°C, it remains uncertain as to whether regional variations in the age-related reduction in sweating (if any) occur at higher levels of heat strain.

To our knowledge, the only study employing a different approach was Smith, Alexander, et al. (2013), who utilized a water-perfused suit covering most of the body surface to raise body core temperature 0.5°C and 1.0°C above resting levels. This model ensures a more homogenous skin temperature response across measurement regions, while also allowing sweat rate to be assessed at two body core temperatures that were matched between young and older adults. However, this report, along with others (Gerrett et al., 2021; Inoue, 1996; Inoue et al., 1991), included measures of sweat rate from a single region on the upper (forearm) and lower (quadriceps) limbs, and two sites on the trunk (abdomen and lower back) which may not accurately reflect sweat rate at the periphery due to the extensive inter- and intra-regional variation in sweat rate (Taylor & Machado-Moreira, 2013).

The purpose of the present study was therefore to evaluate sweat rate during passive heat stress eliciting controlled elevations in body core and skin temperatures between young and older adults, as an exploratory extension of our recent work on regional variation in the reliability of sweat rate measured using the ventilated capsule technique (Rutherford et al., 2021). To ensure regional sweat rates were not overly influenced by one site, sweat rate was measured at four sites on the limbs and two

sites on the trunk in young and older adults at two levels of heat strain (0.6° and 1.2°C above baseline). With this unique approach, we were able to provide a more robust test of a peripheral-to-central decline in the age-related reduction in sweat rate, while also determining whether these effects are consistent across two separate levels of heat strain.

METHODS

Ethical approval

The experiment was approved by the University of Ottawa Health Sciences and Science Research Ethics Board (H-05-16-17) and agrees with the latest revision of the *Declaration of Helsinki*, except for registration in a data base. All participants provided written informed consent prior to participating. All experiments took place at the Human and Environmental Physiology Research Unit located at the University of Ottawa.

Participants

Fifteen older (mean (SD); 69 (4) years) and fourteen young men (24 (5) years) participated (Table 1). Only participants who were healthy (free of any cardiovascular, respiratory, autonomic or metabolic conditions), non-smokers, and not taking prescription medication were eligible to participate in the current study. Further, all participants were habitually active (i.e., performed ≥30 min of structured physical activity at least twice per week) as determined by a standardized questionnaire (Baecke et al., 1982). Data from the young men have been reported as part of a larger project assessing the reliability of microvascular, sudomotor, and cardiovascular autonomic function (Akerman et al., 2021; Gemae et al., 2021; Rutherford et al., 2021). Given the exploratory nature of the study, no a priori power analysis was performed.

Experimental design

Participants completed one screening session and one experimental trial in a temperature-controlled laboratory (~25°C). The experimental trial for the young group was the first of three sessions reported in our previous work (Akerman et al., 2021; Gemae et al., 2021; Rutherford et al., 2021). The first trial for the young group was chosen as it provided the most naïve assessment between both age groups. The experimental sessions for the older adults were performed during the northern hemisphere fall and winter months (September-February) whereas the young group completed the experimental session during the southern hemisphere summer and fall months (June-November). Prior to each session, participants were instructed to abstain from heavy exercise and alcohol for ≥24 hours, caffeine for at least four hours, and food consumption for ≥2 hours.

Screening session

Standing height, body mass, body surface area, and body fat percentage, as well as peak oxygen consumption were determined during the preliminary visit. Body surface area was derived from measures of standing height (model 2391, Detecto, Webb City, MO, USA) and body mass (IND560, Mettler Toledo Inc., Mississauga, ON, Canada) (DuBois & DuBois, 1915). Hydrostatic weighing was used to estimate body fat percentage (Siri, 1956). The only exceptions were three older adults who had their body fat percentage estimated with bioelectrical impedance (BF-679W, TANITA Corporation, Tokyo, Japan). Peak oxygen consumption was measured (MCD Medgraphics Ultima Series, MGC Diagnostics, MN, USA) during incremental cycle exercise to volitional exhaustion (CSEP, 1986).

Experimental trial

After confirming euhydration (urine specific gravity of ≤1.025) (Kenefick & Cheuvront, 2012), participants were instrumented in the supine position before donning a high-

density water perfusion suit (Med-Eng, Ottawa, Canada) covering the entire body except for the feet, head, and hands, which was perfused with water regulated to 34°C (DC30-K20 Digitcal Control Bath, Thermo Scientific Haake, Germany). Participants then reassumed a supine position for ~30 min before baseline data were collected for 10 min (no-heat strain [**NHS**]). Water bath temperature was then increased to 49.5°C and participants were covered up to the neck with a plastic sheet, fleece blanket, and two natural runner mats to increase esophageal temperature by 0.6°C (low-heat strain [**LHS**]) and 1.2°C (moderate-heat strain [**MHS**]) above baseline. At each level of heat strain, water bath temperature was reduced to 43°C when esophageal temperature was 0.1°C below the target temperature to elicit a plateau. Once esophageal temperature and sweat rate had stabilized, data were collected for 10 min before increasing water temperature to 49.5°C to the next level of heat strain.

Measurements

Esophageal temperature was measured using a thermocouple probe inserted ~40 cm past the nares (Mon-a-therm general purpose temperature probe; Mallinckrodt Medical, St Louis, MO, USA) and recorded at 15-s intervals (HP Agilent data-acquisition module, model 2497A or Powerlab, ADInstruments, Colorado Springs, CO). Skin temperature was measured at 1-min intervals using digital thermometers (iButton DS1921H-F5#, Maxim Integrated Products, San Jose, CA, USA) affixed to the chest, abdomen, biceps, forearm, quadriceps, and calf (~1 cm adjacent to each ventilated capsule) using tape (Transpore; 3M, St. Paul, MN, USA). Mean skin temperature was approximated from a weighted average of four sites (biceps: 30%, chest: 30%, quadriceps: 20%, calf: 20%) (22). Mean body temperature was estimated as the weighted average of esophageal (80%) and mean skin temperature (20%) (23).

Local sweat rate was measured at six sites (chest, abdomen, biceps, forearm, quadriceps, calf) using 3.8 cm^2 plastic ventilated capsules affixed to the skin using adhesive rings and topical skin glue (Collodion HV; Mavidon Medical Products, Lake Worth, FL, USA), and covered by custom-made perforated plastic dome-shaped shields (~37 cm^2) to minimize temperature and pressure artefacts (Frei et al., 2019). A landmarking guide was used to standardize capsule placement (Figure 1A). Dry, compressed air was passed through each capsule at a rate of 0.75 L/min (Omega FMA-A2307, Omega Engineering, Stamford, CT, USA). The absolute humidity of effluent air from each sweat capsule was measured with capacitance hygrometers (model HMT333, Vaisala, Helsinki, Finland), which were calibrated according per manufacturer's specifications with standard salt solutions (LiCl, 11% relative humidity; NaCl, 75% relative humidity) prior to experimentation (HMK15 Humidity Calibrator, Vaisala, Helsinki, Finland). Local sweat rate was calculated every 5 s using the differences in the absolute humidity of effluent and influent air multiplied by the flow rate and normalized to the encapsulated skin surface area (mg/cm^2/min).

The following equation was used to calculate local sweat rate (in mg/cm^2/min):

$$\text{Sweat rate (mg/cm}^2\text{/min)} = \frac{\text{Absolute humidity x flow rate}}{\text{Surface area}}$$

Where flow rate is the rate of air flow through the capsules in L/min, surface area was the area of skin covered by the sweat capsule in cm^2 and the absolute humidity of effluent air, in g/m^3 was determined by:

$$\text{Absolute humidity} = 2.17 \times \frac{\text{Saturated water vapor pressure x Relative humidity}}{\text{Air temperature + 273.15}}$$

Where the saturated water vapor pressure is the partial pressure of water vapor in fully saturated air in kPa, relative humidity is the % saturation of effluent air leaving the capsules with water, air temperature is the temperature of effluent air in °C, and 273.15 is the conversion from °C to °K.

Data were recorded with LabVIEW software (version 7.0; National Instruments, TX, USA). Sweat rates at each site were normalized to the individual NHS values to account for baseline variation.

Data analysis

The onset threshold of sweating, thermosensitivity, local sweat rates, esophageal, mean skin, and mean body temperatures were expressed as minute averages, with an average of the final 5 min of each 10 min data collection period being used for the statistical analysis (Figure 1B). The onset threshold for the activation of sweating was determined as the mean body temperature (derived at 1 min intervals) at which a sustained increase in sweat rate of >0.05 mg/cm^2/min occurred (Patterson et al., 2004). The thermosensitivity (slope) of the relationship between sweat rate and mean body temperature after the onset was determined using linear regression.

Statistical analysis

Physical characteristics and heating time within each stage were compared between-groups using unpaired, two-tailed *t*-tests. Body temperature data were compared using a linear mixed-effects model with the fixed factors of group (young, older) and heating stage (NHS, LHS, MHS). Random effects (random intercept or intercept and slope) and variance/covariance structures were determined using Akaike's information criterion. When a significant interaction was detected, *post-hoc* comparisons were carried out using Bonferroni-adjusted unpaired (group) and paired (stage), two-tailed

t-tests. Sweating onset, thermosensitivity, and local sweat rate within LHS and MHS were compared using linear mixed effects models with the fixed factors of group (young, older) and region (trunk, limbs) and a nested random intercept (site within region within participant), with a significant interaction indicating a difference in the magnitude of the age-related decrement between the trunk and limbs. Local skin temperature at each site was included as a covariate to account for any between-group and between-region variations in skin temperature. As a secondary component, we explored whether differences in the age-related change in sweating exist between- and within-body segments at these six sites under two levels of heat strain (LHS, MHS). To achieve this, a mixed-effects model with the fixed effects of group and site (six levels: chest, abdomen, biceps, forearm, quadriceps, calf) and the same nested intercept as mentioned above was used.

Test assumptions of normality, linearity and homoscedasticity were confirmed by inspecting quantile-comparison, scatter and residual plots. *Alpha* was set at 0.050, with data being reported as mean (SD) unless stated otherwise as mean [95% CI]. P-values for the exploratory comparisons of sweat rate between sites were corrected using the Bonferroni procedure. All analyses were performed using R (Version 1.3.959) (Lenth et al., 2018; Pinheiro et al., 2017; Team, 2018).

RESULTS

Compared to the young, the older group were shorter, possessed a higher body fat percentage, and had a lower peak oxygen consumption (all $p \leq 0.029$; Table 1). Body mass and surface area did not differ between groups (both $p \geq 0.083$; Table 1). Heating time was not different between the young and older adults at LHS (50 (5) and 52 (6) min, respectively; $p=0.287$) and at MHS (84 (11) and 85 (9) min, respectively; $p=0.657$).

Body temperature data are presented in Table 2. Esophageal temperature increased with heating stage across groups (main effect: $p<0.001$) and was higher in young compared to older adults across stages due to a higher resting body core temperature (main effect: $p=0.001$). The change in esophageal temperature increased with heating stage (main effect: $p<0.001$), but it did not differ between groups (main effect: $p=0.142$). Mean skin temperature and mean body temperature differed as a function of group and heating stage (interaction: all $p<0.001$), such that they were higher in young compared to older adults at all stages (both $p\leq0.001$). Trunk skin temperature (interaction: $p=0.001$) was lower in the older adults at NHS and MHS (both $p\leq0.023$) but was not different between groups at LHS ($p=0.312$). Limb skin temperature increased with heating stage (main effect: both $p<0.001$) and was higher in the young compared to older adults (main effect: both $p<0.001$).

The onset and thermosensitivity of the sweating response are presented in Figure 2. The onset of sweating was 0.3°C [0.1, 0.4] higher in the older compared to young (main effect: $p=0.004$), but it did not differ between regions (main effect: $p=0.626$). Further, the age-related delay in the onset threshold for sweating was not region-dependent (interaction: $p=0.349$). The thermosensitivity of the sweating response was 0.44 mg/cm^2/min /°C [0.25, 0.63] higher at the trunk compared to the limbs (main effect: $p=0.001$) but did not differ between groups (main effect: $p=0.711$). Further, the region-related difference in thermosensitivity was not influenced by age (interaction: $p=0.595$).

The individual and the averaged sweat rates at LHS and MHS are presented in Figure 3. A group-by-region interaction for sweat rate at LHS was observed ($p<0.010$), indicating that sweat rate was reduced in older compared to young adults to a greater extent at the trunk by 0.65 mg/cm^2/min [0.44, 0.86] compared to the limbs (0.42

mg/cm^2/min [0.22, 0.62]). At MHS, sweat rate did not differ as a function of group and region (interaction: p=0.888) but it was reduced by 0.34 mg/cm^2/min [0.13, 0.54] in older compared to young adults across regions (main effect: p=0.025), and lower by 0.17 mg/cm^2/min [0.06, 0.27] at the limbs relative to the trunk across groups (main effect: p=0.001).

The individual site analysis at LHS and MHS are presented in Figure 4. At LHS, a group-by-site interaction for sweat rate was observed (p<0.001). When comparing between body segments, a greater age-related reduction in sweat rate at the chest and abdomen compared to the biceps and quadriceps (all p≤0.017) was observed. When comparing within body segments, the age-related change in sweat rate was lower at the biceps (0.21 mg/cm^2/min [0.06, 0.36], p=0.004) and quadriceps (0.19 mg/cm^2/min [0.0.4, 0.33], p=0.011) compared to the forearm and calf, respectively. At MHS, sweat rate did not differ as a function of group and site (group-by-site interaction: p=0.089), however, the age-related change in sweat rate was still lower at the quadriceps (0.29 mg/cm^2/min [0.0.11, 0.48], p=0.003) compared to the calf.

DISCUSSION

In this report, we revaluated the hypothesis that age-related decrements in sweat rate may be more pronounced at the limbs compared to the trunk. This was achieved by measuring sweat rate at six sites across the trunk and limbs in young and older adults during whole-body passive heat stress to increase and clamp esophageal temperature by 0.6°C (low-heat strain) and 1.2°C (moderate-heat strain) above baseline. Contrary to previous suggestions, sweat rate was attenuated in older relative to young men to a greater extent at the trunk compared to the limbs at low-heat strain, with no evidence of regional variation in that age-related reduction during moderate-heat strain. These outcomes therefore advance our knowledge by indicating that aging may compromise

sweat rate to a greater extent at central compared to peripheral regions during low-, but not moderate-heat strain, perhaps due to regional differences in sweat rate and/or the need to preserve sweating at areas with the greatest capacity for heat loss.

Age-related decrements in sweat rate have previously been suggested to develop in a peripheral-to-central manner (Inoue et al., 1991; Kenney & Munce, 2003). However, previous investigations of this hypothesis employed experimental models eliciting regional variations in skin temperature (Coull et al., 2021; Gerrett et al., 2021; Inoue et al., 1991; Inoue & Shibasaki, 1996) or measured sweat rate at a single region on the upper and lower limbs (Smith, Alexander, et al., 2013). We therefore revisited this hypothesis by assessing sweat rate in young and older adults at four sites on the limbs to reflect the periphery and two sites on the torso to reflect the trunk (central). Contrary to the peripheral-to-central age-related decline documented previously (Inoue et al., 1991), we observed a greater reduction in sweat rate at the trunk compared to the limbs in the older relative to young adults at low-heat strain (Figure 3A). While there is a need for larger and more detailed studies to identify the mechanism(s) explaining this observation and the discrepancy between our findings and those of previous reports, this outcome advances understanding by providing evidence for a central-to-peripheral age-related reduction in sweating and at a minimum, indicates that previously held beliefs should be re-examined with more rigorous control of regional variations in skin temperature.

Our study was not designed to identify the physiological significance of the observed regional difference at low-heat strain (Figure 3A); however, this may partly reflect regional differences in sweat rate and/or the need to preserve sweating at areas with the greatest capacity for heat loss. The trunk is typically associated with higher sweat rates than the limbs (Taylor & Machado-Moreira, 2013) and this was confirmed

in the present study (Figure 3). It is possible, therefore, that aging impacts sweat rate to a greater extent at the trunk compared to the limbs, since this region has a greater capacity to be degraded; a mechanism akin to that associated with sarcopenia (Ata et al., 2019). Further, due to their high surface-area-to-mass ratio, the limbs have a greater relative capacity for evaporative heat loss compared to the trunk (Taylor & Machado-Moreira, 2013). Thus, it is plausible that sweating is preserved with aging at the areas with the greatest capacity for heat loss, albeit it remains uncertain as to whether such regional differences can be attributed to functional or structural changes. Nonetheless, these hypotheses remain speculative and represent an important area of future research for improving our understanding of age-associated changes in thermoregulatory function.

In contrast to the central-to-peripheral age-related decline in sweat rate observed at low-heat strain, a non-region-specific pattern of reduction was observed at moderate-heat strain (Figure 3B). This may be because sweat rate becomes more homogenous across the body surface with increasing heat strain (Kondo et al., 2001; Taylor & Machado-Moreira, 2013), reducing the magnitude of any regional differences in the age-related decline in sweating. We were unable to confirm this statistically, as indicated by a significant group-by-region-by-heating stage interaction, due to the large sample size required to perform a meaningful evaluation of such an effect (Heo & Leon, 2010). However, our findings are consistent with previous investigations employing models eliciting higher levels of heat strain (~0.8-1.0°C) (Gerrett et al., 2021; Smith, Alexander, et al., 2013) and indicate that any regional variation in the age-related decrement in sweat rate may be less apparent at higher levels of heat strain.

A secondary interest for this study was to compare the magnitude of any age-related decline in sweat rate between the individual sites comprising each region (trunk and limbs). Consistent with when grouped into trunk and limb regions, the chest had the greatest age-related reduction in sweat rate followed by the abdomen (Figure 4). Since both sites on the trunk (abdomen and chest) displayed a greater age-related reduction than the biceps, quadriceps, and calf, we can be reasonably certain that the central-to-peripheral pattern observed in our primary analysis (Figure 3) was not heavily influenced by one specific site and was region based. Additionally, at moderate-heat strain, the age-related reduction in sweat rate was similar between all six sites. This observation further supports the notion that sweat rate becomes more homogenous across the body surface with increasing levels of heat strain.

Our primary interest for this experiment was age and regional differences in sweat rate when body core temperature was raised and clamped (i.e., low- and moderate-heat strain). However, it is important to note that the regional difference in the age-related decline in sweat rate occurring during low-heat strain (Figure 3A) was not observed for the thermosensitivity of the sweating response, which did not differ between young and older men (Figure 2B). Further, while the onset of sweating was delayed in older compared to young men, this delay did not differ between the trunk and limbs (Figure 2A). This outcome is in line with previous work where a non-region-specific delay in onset threshold was observed in older compared to young adults (Inoue et al., 1991; Inoue & Shibasaki, 1996; Smith, Alexander, et al., 2013). Thus, although aging delays the onset of sweating, our findings support previous suggestions that sweat gland recruitment occurs in a generalized pattern across the body surface during thermal loading, irrespective of age (Frei et al., 2019).

Perspectives

Although our study was directed at advancing our understanding of age-related changes in thermoregulatory function, our findings may also aid in informing heat-mitigation strategies to protect older adults, who are particularly vulnerable to the adverse effects of extreme heat (Meade et al., 2020). To reduce the thermal and cardiovascular burden of heat stress, various low-cost heat-mitigation strategies have been proposed including misting and water dousing (Morris et al., 2019) , which serve to enhance evaporative cooling by wetting the skin. Such strategies may be particularly beneficial in older adults during hot-dry environments, due to their lower capacity for evaporative heat loss relative to young adults (Kenny et al., 2017). Given we observed a greater age-related decrement in sweat rate at the trunk compared to the limbs during low-heat strain (Figure 3), it is possible that older adults could maximize any benefit of these strategies by placing greater emphasis on wetting the trunk, as opposed to the limbs. Further, during moderate-heat strain, no evidence of regional variation in that age-related reduction occurred. Therefore, heat-mitigation strategies that aim to cool the whole-body, such as ensuring access to central air conditioning and urban redesign (e.g., cooling roofs) can improve thermal comfort in individuals when exposed to extreme heat (Broadbent et al., 2021; Quinn et al., 2017).

Considerations

There are several noteworthy considerations associated with the current study. First, activated sweat gland density was not measured in the current study. We were therefore unable to calculate sweat gland output and determine if age-related declines in sweat rate were due to reduced sweat gland output and/or fewer active glands. Second, we did not assess potential modulators for the full expression of sweating such as nitric oxide, which are known to be diminished in older adults (Amano et al., 2017; Stapleton et al., 2014), which may aid in explaining regional variations in the

age-related decline in sweat rate. Third, despite possessing a lower peak oxygen consumption ($\dot{V}O_{2peak}$) than their younger counterparts (Table 1), the older men in the current study would still be considered as relatively well-trained, with a $\dot{V}O_{2peak}$ in the 95th percentile of age- and sex-specific normative values (Hoffmann et al., 2019). Increased aerobic fitness, as indexed by $\dot{V}O_{2peak}$, can attenuate age-related reductions in evaporative heat loss during exercise-heat stress (Notley, Meade, & Kenny, 2020), which in turn may have reduced age-related reductions in sweat rate and the magnitude of regional variation in that decrement compared to less aerobically fit older adults. Fourth, we assessed the older and young adults in different seasons. It is possible that the age-related differences observed may have been slightly inflated due to seasonal acclimatization in the young adults. However, we anticipate this effect to be relatively small based on our previous work demonstrating comparable thermoregulatory function in young adults prior to and following summer (Notley, Meade, Akerman, et al., 2020). Fifth, we did not assess the effect of posture on the regional age-related decline in sweat rate. In young adults, regional variations in sweating are modified by posture (seated, supine) (Inukai et al., 2005; Shim & Choi, 1993), which is likely due to variations in skin pressure (i.e., when seated the thigh sweat rate is reduced relative to the forearm due to greater skin pressure on the lower limbs). Therefore, postural differences between studies may partly explain the inconsistencies in results within the existing literature assessing the regional age-related decline in sweat rate (2, 5, 6, 7, 9), and this represents an important area of future research. Finally, given our data are restricted to males, there is a need for further studies to determine whether sex modulates regional differences in the age-related decline in sweating. However, since evaporative heat loss during exercise-heat

stress may decline at a similar rate with increasing age in males and females (D'Souza et al., 2020), we would expect similar observations between sexes.

Conclusion

It has been suggested that age-related decrements in sweat rate may be more pronounced at the limbs compared to the trunk. However, we demonstrate that, when assessed at multiple regions on the skin surface of these areas during passive heating eliciting 0.6°C (low-heat strain) and 1.2°C (moderate-heat strain) elevations in body core temperature, sweat rate was attenuated in older compared to young adults to a greater extent at the trunk relative to the limbs at low-, but not moderate-heat strain. While larger, confirmatory studies are needed, these outcomes indicate that age-related reductions in sweat rate may develop in a central-to-peripheral direction, albeit with an important role for the level of heat strain at which sweat rate is assessed.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in Open Science Framework (OSF) at http://doi.org/10.17605/OSF.IO/CGAWB

COMPETING INTERESTS

The authors do not have any conflicts of interest to declare.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

REFERENCES

Akerman, A. P., Meade, R. D., Notley, S. R., Rutherford, M. M., & Kenny, G. P. (2021). Myths and methodologies: Reliability of non-invasive estimates of cardiac autonomic modulation during whole-body passive heating. *Experimental physiology, 106*(3), 593-614.

Amano, T., Fujii, N., Louie, J. C., Meade, R. D., & Kenny, G. P. (2017). Individual variations in nitric oxide synthase-dependent sweating in young and older males during exercise in the heat: role of aerobic power. *Physiological reports, 5*(6), e13208.

Ata, A. M., Kara, M., Kaymak, B., Gürçay, E., Çakır, B., Ünlü, H., Akıncı, A., & Özçakar, L. (2019). Regional and total muscle mass, muscle strength and physical performance: the potential use of ultrasound imaging for sarcopenia. *Archives of gerontology and geriatrics, 83*, 55-60.

Baecke, J. A., Burema, J., & Frijters, J. E. (1982). A short questionnaire for the measurement of habitual physical activity in epidemiological studies. *The American journal of clinical nutrition, 36*(5), 936-942.

Broadbent, A. M., Declet-Barreto, J. H., Krayenhoff, E. S., Harlan, S. L., & Georgescu, M. (2021). Targeted implementation of cool roofs for equitable urban adaptation to extreme heat. *Science of the total environment*, 151326.

Coull, N. A., West, A. M., Hodder, S. G., Wheeler, P., & Havenith, G. (2021). Body mapping of regional sweat distribution in young and older males. *European journal of applied physiology, 121*(1), 109-125.

CSEP. (1986). Determination of aerobic power. Canadian Society for Exercise Physiology.

D'Souza, A. W., Notley, S. R., & Kenny, G. P. (2020). The Relation between age and sex on whole-body heat loss during exercise-heat stress. *Medicine and science in sports and Exercise*.

DuBois, D., & DuBois, E. F. (1915). The measurement of the surface area of man. *Archives of internal medicine, 15*(5), 868-881. <Go to ISI>://WOS:000202579800005

Frei, R., Notley, S. R., Taylor, E. A., Burdon, C. A., Ohnishi, N., & Taylor, N. A. (2019). Revisiting the dermatomal recruitment of, and pressure-dependent influences on, human eccrine sweating. *Journal of thermal biology, 82*, 52-62.

Gemae, M. R., Akerman, A. P., McGarr, G. W., Meade, R. D., Notley, S. R., Schmidt, M. D., Rutherford, M. M., & Kenny, G. P. (2021). Myths and methodologies: reliability of forearm cutaneous vasodilatation measured using laser-doppler flowmetry during whole-body passive heating. *Experimental physiology, 106*(3), 634-652.

Gerrett, N., Amano, T., Inoue, Y., & Kondo, N. (2021). Eccrine sweat glands' maximum ion reabsorption rates during passive heating in older adults (50–84 years). *European journal of applied physiology*, 1-15.

Hardy, J. D., Du Bois, E. F., & Soderstrom, G. (1938). Basal metabolism, radiation, convection and vaporization at temperatures of 22 to 35 C. six figures. *The Journal of nutrition, 15*(5), 477-497.

Heo, M., & Leon, A. C. (2010). Sample sizes required to detect two-way and three-way interactions involving slope differences in mixed-effects linear models. *Journal of biopharmaceutical statistics, 20*(4), 787-802.

Hoffmann, M. D., Colley, R. C., Doyon, C. Y., Wong, S. L., Tomkinson, G. R., & Lang, J. J. (2019). Normative-referenced percentile values for physical fitness among canadians. *Health reports, 30*(10), 14-22.

Inoue, Y. (1996). Longitudinal effects of age on heat-activated sweat gland density and output in healthy active older men. *European journal of applied physiology and occupational physiology, 74*(1), 72-77.

Inoue, Y., Nakao, M., Araki, T., & Murakami, H. (1991). Regional differences in the sweating responses of older and younger men. *Journal of applied physiology, 71*(6), 2453-2459.

Inoue, Y., & Shibasaki, M. (1996). Regional differences in age-related decrements of the cutaneous vascular and sweating responses to passive heating. *European journal of applied physiology and occupational physiology, 74*(1), 78-84.

Inukai, Y., Sugenoya, J., Kato, M., Nishimura, N., Nishiyama, T., Matsumoto, T., Sato, M., Ogata, A., Taniguchi, Y., & Osada, A. (2005). Effects of body posture on local sweating and sudomotor outflow as estimated using sweat expulsion. *Autonomic neuroscience, 119*(1), 48-55.

Kenefick, R. W., & Cheuvront, S. N. (2012). Hydration for recreational sport and physical activity. *Nutrition reviews, 70*(suppl_2), S137-S142.

Kenney, W. L., & Munce, T. A. (2003). Invited review: aging and human temperature regulation. *Journal of applied physiology, 95*(6), 2598-2603.

Kenny, & Flouris. (2014). The human thermoregulatory system and its response to thermal stress. *Protective clothing*, 319-365.

Kenny, 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, 4*(1), 79-88.

Kondo, Shibasaki, M., Aoki, K., Koga, S., Inoue, Y., & Crandall, C. G. (2001). Function of human eccrine sweat glands during dynamic exercise and passive heat stress. *Journal of applied physiology, 90*(5), 1877-1881.

Lenth, R., Singmann, H., Love, J., Buerkner, P., & Herve, M. (2018). Emmeans: Estimated marginal means, aka least-squares means. *R package version, 1*(1), 3.

Meade, R. D., Akerman, A. P., Notley, S. R., McGinn, R., Poirier, P., Gosselin, P., & Kenny, G. P. (2020). Physiological factors characterizing heat-vulnerable older adults: a narrative review. *Environment international, 144*, 105909.

Morris, N. B., Gruss, F., Lempert, S., English, T., Hospers, L., Capon, A., & Jay, O. (2019). A preliminary study of the effect of dousing and foot immersion on cardiovascular and thermal responses to extreme heat. *JAMA, 322*(14), 1411-1413.

Nadel, E. R., Bullard, R. W., & Stolwijk, J. (1971). Importance of skin temperature in the regulation of sweating. *Journal of applied physiology, 31*(1), 80-87.

Notley, S. R., Meade, R. D., Akerman, A. P., Poirier, M. P., Boulay, P., Sigal, R. J., Flouris, A. D., & Kenny, G. P. (2020). Evidence for age-related differences in heat acclimatisation responsiveness. *Experimental physiology, 105*(9), 1491-1499.

Notley, S. R., Meade, R. D., & Kenny, G. P. (2020). Effect of aerobic fitness on the relation between age and whole-body heat exchange during exercise-heat stress: a retrospective analysis. *Experimental physiology, 105*(9), 1550-1560.

Patterson, M. J., Stocks, J. M., & Taylor, N. A. (2004). Humid heat acclimation does not elicit a preferential sweat redistribution toward the limbs. *American journal of physiology-regulatory, integrative and comparative physiology, 286*(3), R512-R518.

Pinheiro, J., Bates, D., DebRoy, S., Sarkar, D., Heisterkamp, S., Van Willigen, B., & Maintainer, R. (2017). Package 'nlme'. *Linear and nonlinear mixed effects models, version, 3*(1).

Quinn, A., Kinney, P., & Shaman, J. (2017). Predictors of summertime heat index levels in New York City apartments. *Indoor air, 27*(4), 840-851.

Ramanathan, N. L. (1964, May). A new weighting system for mean surface temperature of the human body. *Journal of applied physiology, 19*, 531-533. https://doi.org/10.1152/jappl.1964.19.3.531

Rutherford, M. M., Akerman, A. P., Notley, S. R., Meade, R. D., Schmidt, M. D., & Kenny, G. P. (2021). Regional variation in the reliability of sweat rate measured via the ventilated capsule technique during passive heating. *Experimental physiology, 106*(3), 615-633.

Sato, & Sato. (1983). Individual variations in structure and function of human eccrine sweat gland. *American journal of physiology-regulatory, integrative and comparative physiology, 245*(2), R203-R208.

Shibasaki, M., Okazaki, K., & Yoshimitsu, I. (2013). Aging and thermoregulation. *The journal of physical ftiness and sports medicine, 2*(1), 37-47.

Shim, H. S., & Choi, J. W. (1993). The effect of posture on the human thermoregulatory response. *Journal of the korean society of clothing and textiles, 17*(3), 415-427.

Siri, W. E. (1956). *Advances in biological and medical physics* (J. H. T. Lawrence, C.A., Ed.). Academic.

Smith, Alexander, & Kenney. (2013). Nonuniform, age-related decrements in regional sweating and skin blood flow. *American journal of physiology-regulatory, integrative and comparative physiology, 305*(8), R877-R885.

Stapleton, J. M., Fujii, N., Carter, M., & Kenny, G. P. (2014). Diminished nitric oxide-dependent sweating in older males during intermittent exercise in the heat. *Experimental physiology, 99*(6), 921-932.

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. *Extreme physiology & medicine, 2*(1), 4.

Team, R. C. (2018). R Foundation for Statistical Computing, Vienna, available at: www. *R-project. org*.

Todd, G., Gordon, C. J., Groeller, H., & Taylor, N. A. (2014). Does intramuscular thermal feedback modulate eccrine sweating in exercising humans? *Acta physiologica, 212*(1), 86-96.

FIGURE LEGENDS

Figure III-1. A) Visual representation of measurement locations for local sweat rates (large light grey circles) measured via ventilated capsules and skin temperature (small dark grey circles) measured via iButtons with the corresponding landmarking instructions used for the placement of the capsules and colored lines matching the line colors in panel B (created using BioRender.com). B) Representative profile of sweating demonstrating the periods used in data analysis. LSR, local sweat rate; ΔT_{eso}, change in esophageal temperature (black-dashed line); NHS, no-heat strain; LHS, low-heat strain; MHS, moderate-heat strain. Adapted with permission from Rutherford et al. (15).

Figure III-2. The onset threshold (panel A) and thermosensitivity (panel B) of sweating during whole-body passive heating in the young (n=14; blue, solid) and older (n=15; pink, dashed) men at the individual sites (left panel) and by region (middle panel; trunk: chest, abdomen; limbs: biceps, forearm, quadriceps, calf). All data are presented as mean (SD) with individual values overlayed in the panels on the left and middle with the associated mean difference [95% CI] in regional onset threshold and thermosensitivity between the older and young group on the right panels. P-values are provided for a linear mixed-effects model with nested intercepts (sites nested within region nested within participant), and with skin temperature at each site included as a covariate. *, denotes a significantly earlier onset compared to the older adults ($p<0.050$); #, denotes significantly greater than the limbs ($p<0.050$).

Figure III-3. Local sweat rate at low-heat strain (LHS; panel **A**) and moderate-heat strain (MHS; panel **B**) in young (n=14; blue, solid) and older (n=15; pink, dashed) men at the individual sites (far left panels) and the trunk and limb regions (middle panels;

trunk: chest, abdomen; limbs: biceps, forearm, quadriceps, calf) during whole-body passive (resting) heating to raise and clamp esophageal temperature 0.6°C (low heat strain) and 1.2°C (moderate heat strain) above baseline. Local sweat rate is presented as a mean (SD) with individual values overlayed in the panels on the left and middle with the associated mean difference [95% CI] in regional sweating between the older and young group on the right panels. P values are provided for a linear mixed-effects model with nested intercepts (sites nested within region nested within participant), and skin temperature at each site included as a covariate. *, denotes significantly greater than older adults; #, denotes significantly greater than the limbs ($p<0.050$); ‡, denotes significantly greater age-related difference versus the limbs ($p<0.050$).

Figure III-4. Between site difference in the age-related change in sweat rate between individual sites at the chest (red), abdomen (green), bicep (blue), forearm (orange), and quadriceps (purple) during whole-body passive (resting) heating to raise and clamp esophageal temperature 0.6°C (low heat strain, LHS, panel A) and 1.2°C (moderate heat strain, MHS; panel B) above baseline in young (n= 14) and older (n=15) men are presented on the panels on the left. For example, the difference in the age-related change at the chest vs. the abdomen (left most comparison) was calculated as (abdomen older – abdomen young) – (chest older – chest young). On the bottom of panel A and B, the corresponding uncorrected p-values and corrected p-values using Bonferroni-adjustments are provided. All data are reported from a linear mixed-effects model with the fixed effects of group and site (six levels: chest, abdomen, biceps, forearm, quadriceps, calf) with nested random intercepts (sites nested within region nested within participant), and skin temperature at each site included as a covariate.

*, denotes a significant difference ($p<0.050$) when p-values are uncorrected; #, denotes a significant difference ($p<0.050$) when p-values are corrected using Bonferroni-adjustments.

Table III-1. Physical characteristics of the young (n=14) and older (n=15) men.

		Age (years)	**Height** (cm)	**Mass** (kg)	**A_D** (m^2)	**Body fat** (%)	**$\dot{V}O_2$peak** (mL/min/kg)
Young	Mean (SD)	24 (5)	176 (5)	79.9 (12.3)	2.0 (0.2)	15.8 (5.7)	43.4 (8.3)
	Min-max	18-32	168-184	65.1-102.3	1.7-2.3	8.0-28.0	33.0-61.4
Older	Mean (SD)	69 (4)	171 (6)	74.9 (9.7)	1.9 (0.1)	21.1 (4.8)	33.0 (7.5)
	Min-max	65-77	160-182	58.7-94.1	1.6-2.1	14.6-24.7	19.5-51.4
	p value	<0.001*	0.029*	0.235	0.083*	0.001*	0.002*

Notes: A_D: body surface area; $\dot{V}O_{2peak}$: peak oxygen consumption; *p* values denote results from an unpaired, two-tailed *t*-test. *, significantly different from the young; P<0.05

Table III-2. Duration of heating, esophageal temperature, the change in esophageal temperature, mean skin temperature, and mean body temperature at all three heating stages in young (n=14) and older (n=15) men.

	Young	**Older**	**Diff. from Young**		***p* values**	
	Mean (SD)	Mean (SD)	Mean [95% CI]	Condition	Group	Interaction
Esophageal Temperature (°C)						
No-heat strain	36.9 (0.2)	36.5 (0.4)	-0.4 [-0.7, -0.2] *			
Low-heat strain	37.5 (0.2)	37.1 (0.3)	-0.4 [-0.6, -0.1] *	<0.001	0.001	0.317
Moderate-heat strain	38.1 (0.2)	37.7 (0.4)	-0.3 [-0.6, -0.1] *			
∆ Esophageal Temperature (°C)						
No-heat strain						
Low-heat strain	0.6 (0.1)	0.7 (0.1)	0.1 [-0.1, ,0.2]	<0.001	0.142	0.487
Moderate-heat strain	1.2 (0.1)	1.3 (0.2)	0.1 [0.0, 0.2]			
Mean skin temperature (°C)						
No-heat strain	34.9 (0.5)	34.0 (0.6)	-1.0 [-1.4, -0.5] *			
Low-heat strain	37.6 (0.3)	37.3 (0.4)	-0.3 [-0.6, 0.0] *	<0.001	<0.001	0.008
Moderate-heat strain	38.1 (0.4)	37.7 (0.3)	-0.4 [-0.7, -0.1] *			
Trunk skin temperature (°C)						
No-heat strain	35.2 (0.7)	34.1 (1.0)	-1.1 [-1.7, -0.4]			
Low-heat strain	37.6 (0.3)	37.5 (0.2)	-0.1 [-0.3 ,0.1]	<0.001	0.243	0.001
Moderate-heat strain	38.2 (0.4)	37.7 (0.6)	-0.5 [-0.9, -0.1]			
Limbs skin temperature (°C)						
No-heat strain	34.4 (0.6)	33.6 (0.7)	-0.8 [-1.3, -0.3] *			
Low-heat strain	37.5 (0.3)	37.1 (0.5)	-0.4 [-0.7, -0.1] *	<0.001	<0.001	0.254
Moderate-heat strain	38.1 (0.3)	37.7 (0.4)	-0.4 [-0.7, -0.1] *			
Mean body temperature (°C)						
No-heat strain	36.5 (0.3)	36.0 (0.4)	-0.5 [-0.8, -0.3] *			
Low-heat strain	37.5 (0.2)	37.2 (0.3)	-0.4 [-0.6, -0.1] *	<0.001	<0.001	0.006
Moderate-heat strain	38.1 (0.3)	37.7 (0.4)	-0.4 [-0.6, -0.1] *			

Notes: Mean skin temperature was calculated as a weighted average (arm: 30%, chest: 30%, biceps: 20%, quadriceps: 20%) (Ramanathan, 1964). Mean body temperature was estimated from the weighted sum of esophageal (0.8) and mean skin temperature (0.2) (Hardy et al., 1938). Trunk skin temperature represents the unweighted average of skin temperature on the chest and abdomen. Limbs skin temperature represents the unweighted average of skin temperature on the biceps, forearm, quadriceps, and calf. P values are provided for a linear mixed-effects model with the non-repeated factor of group (young, older) and repeated factor of condition (no-heat strain, low-heat strain, moderate-heat strain). *, significantly different from the young; P<0.05.

Figure III-1.

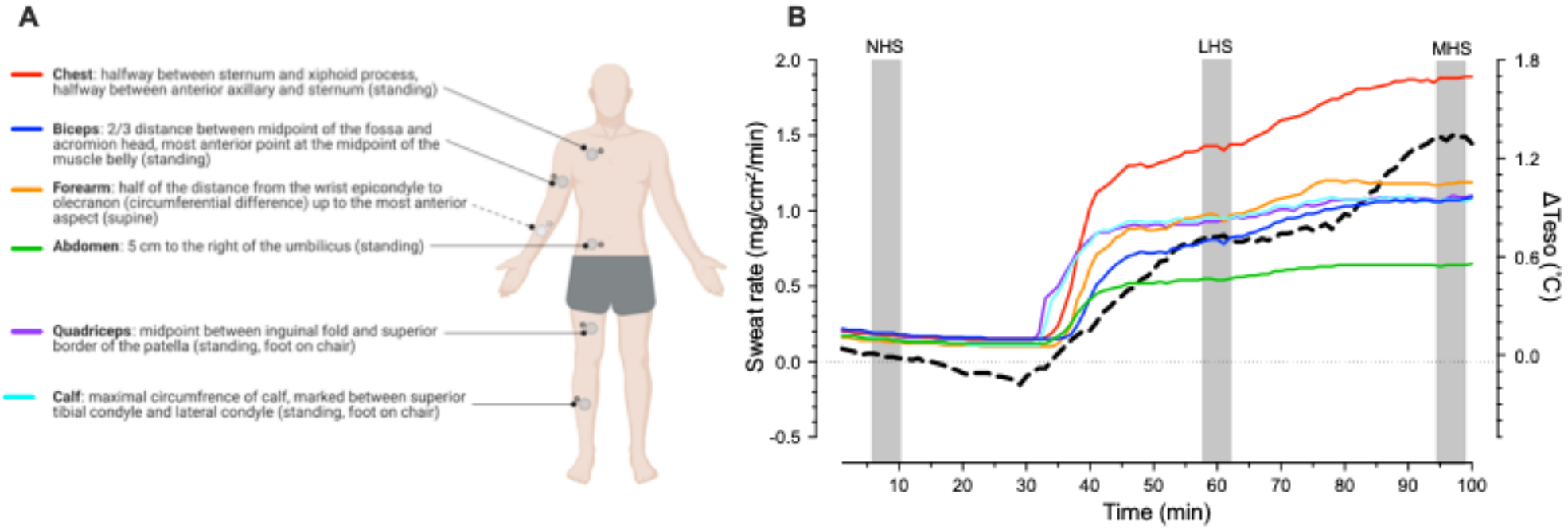

A
Chest: halfway between sternum and xiphoid process, halfway between anterior axillary and sternum (standing)
Biceps: 2/3 distance between midpoint of the fossa and acromion head, most anterior point at the midpoint of the muscle belly (standing)
Forearm: half of the distance from the wrist epicondyle to olecranon (circumferential difference) up to the most anterior aspect (supine)
Abdomen: 5 cm to the right of the umbilicus (standing)
Quadriceps: midpoint between inguinal fold and superior border of the patella (standing, foot on chair)
Calf: maximal circumfrence of calf, marked between superior tibial condyle and lateral condyle (standing, foot on chair)
B
NHS
LHS
MHS
Sweat rate (mg/cm²/min)
ΔTeso (°C)
Time (min)

Figure III-2.

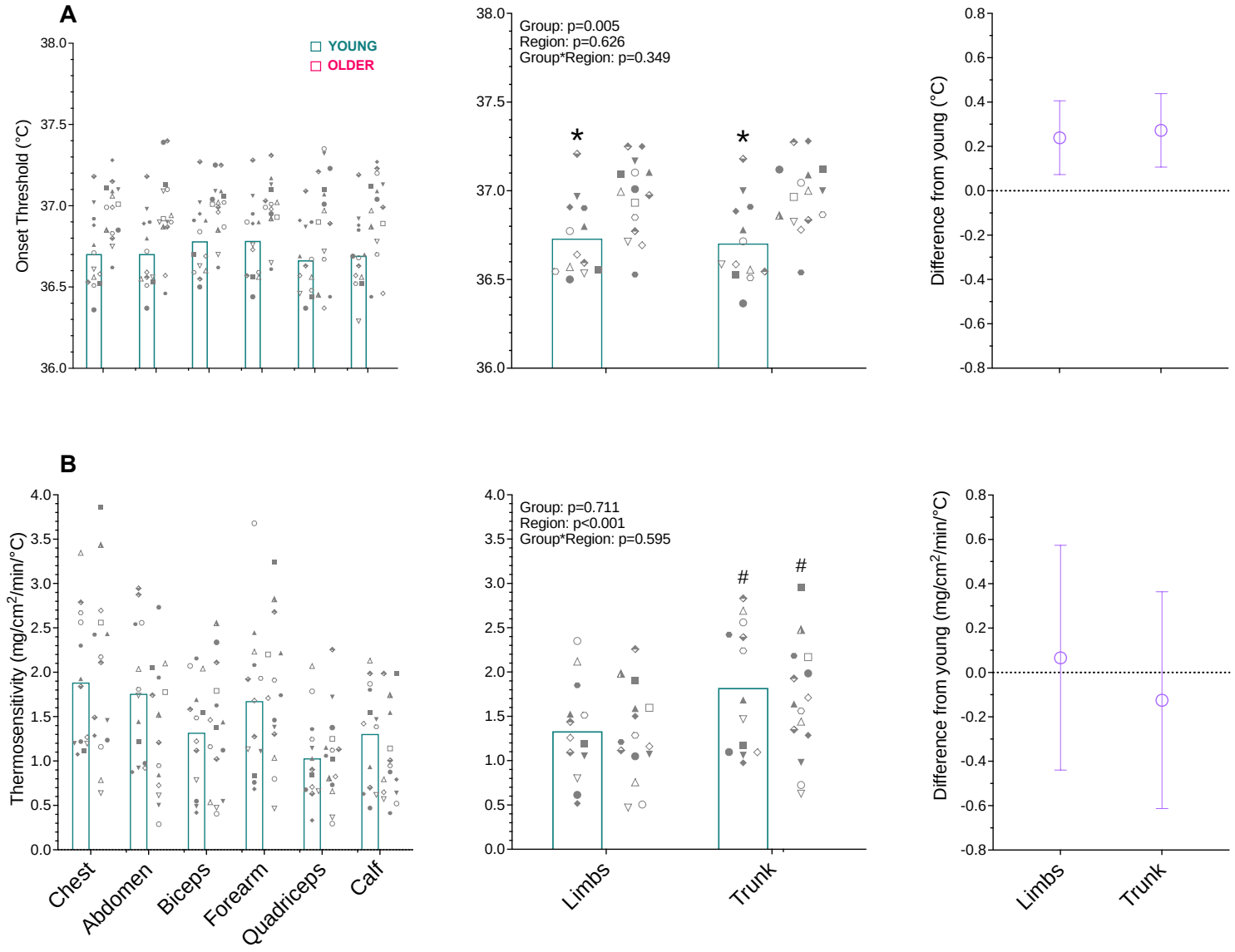

A
YOUNG
OLDER
Onset Threshold (°C)
38.0
37.5
37.0
36.5
36.0
Group: p=0.005
Region: p=0.626
Group*Region: p=0.349
*
*
Difference from young (°C)
0.8
0.6
0.4
0.2
0.0
-0.2
-0.4
-0.6
-0.8
B
Thermosensitivity (mg/cm²/min/°C)
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
Chest
Abdomen
Biceps
Forearm
Quadriceps
Calf
Group: p=0.711
Region: p<0.001
Group*Region: p=0.595
#
#
Limbs
Trunk
Difference from young (mg/cm²/min/°C)
Limbs
Trunk

Figure III-3.

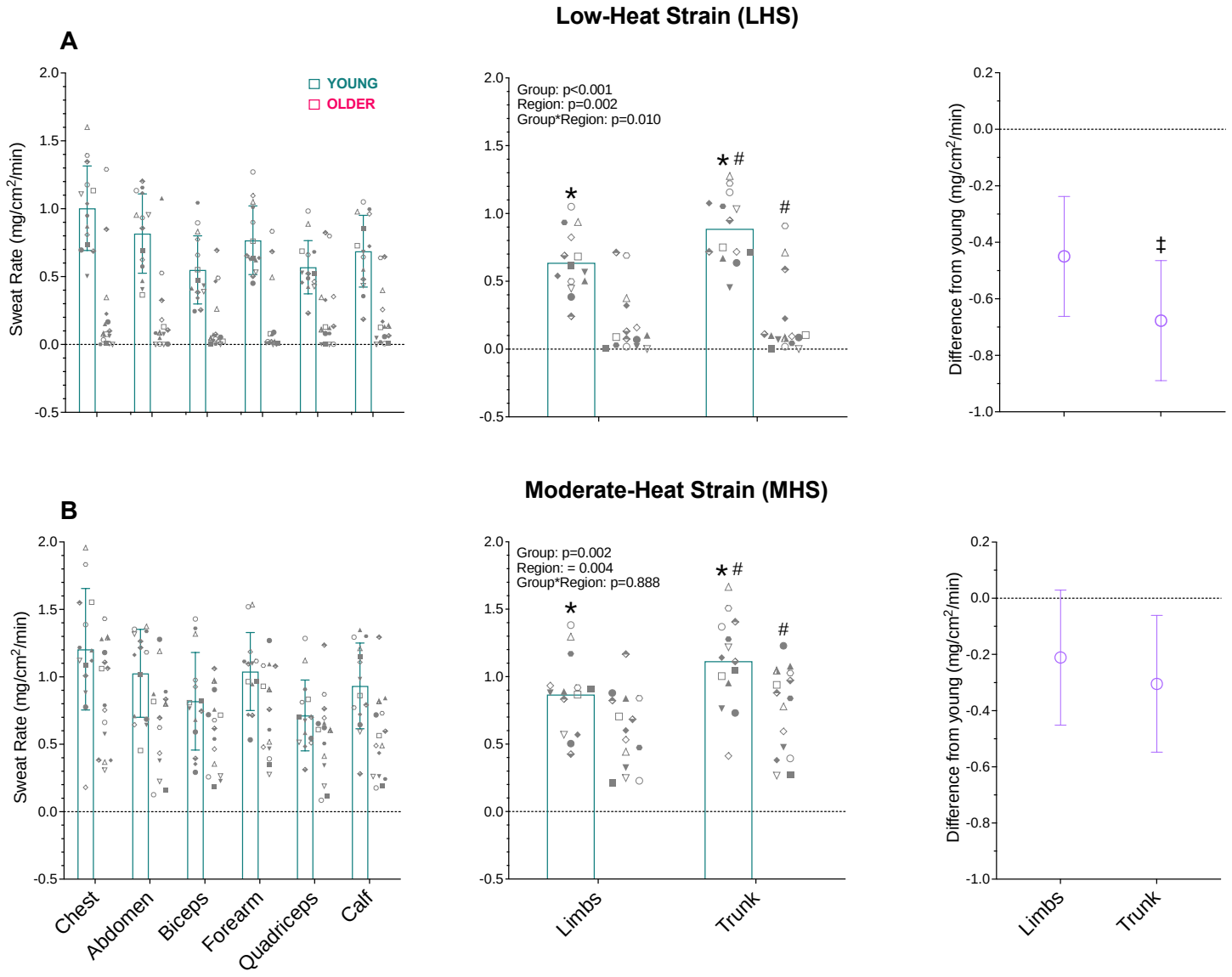
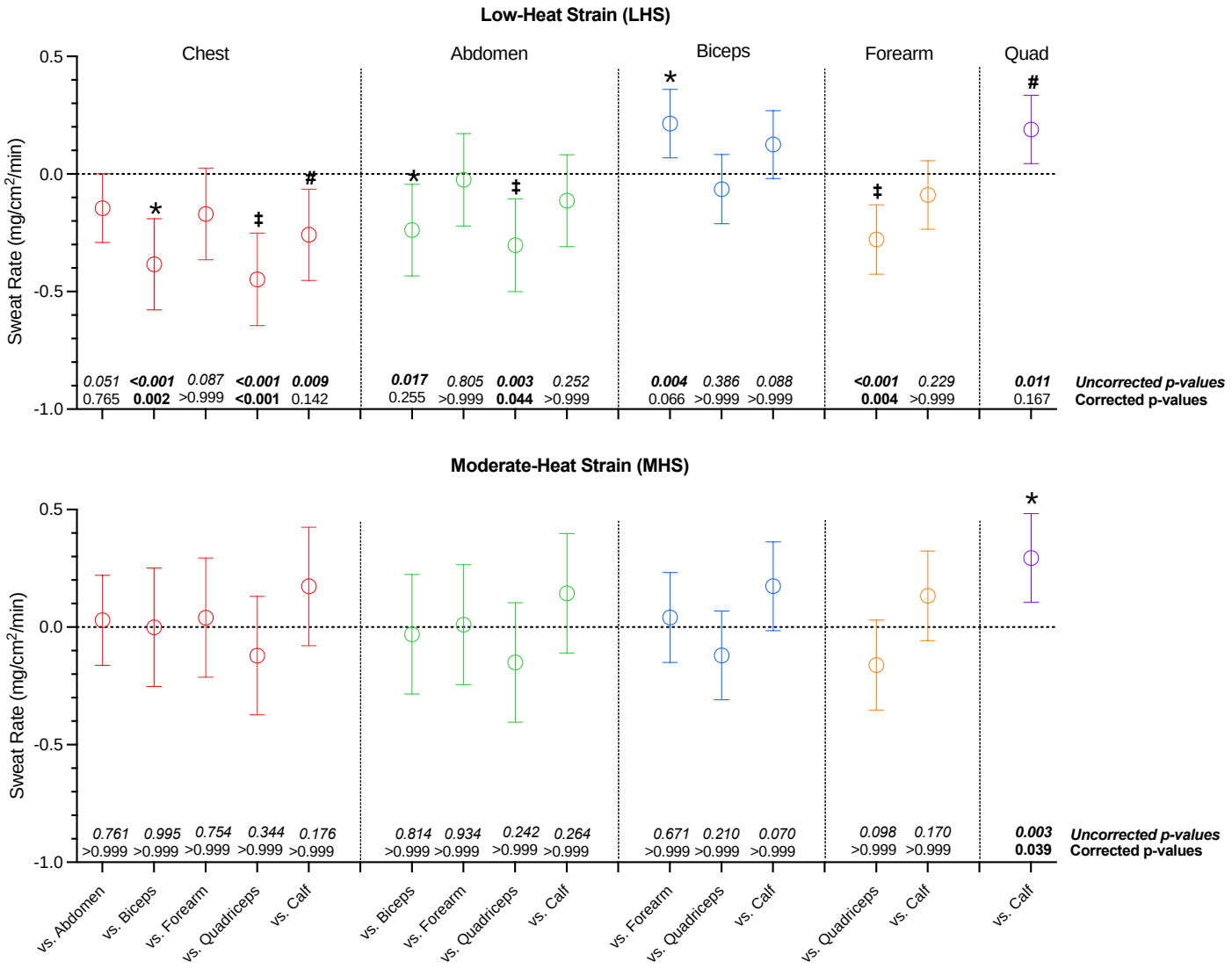

Low-Heat Strain (LHS)
A
YOUNG
OLDER
Sweat Rate (mg/cm²/min)
Group: p<0.001
Region: p=0.002
Group*Region: p=0.010
Difference from young (mg/cm²/min)
Moderate-Heat Strain (MHS)
B
Group: p=0.002
Region: = 0.004
Group*Region: p=0.888
Chest
Abdomen
Biceps
Forearm
Quadriceps
Calf
Limbs
Trunk

Figure III-4.


Low-Heat Strain (LHS)
Chest
Abdomen
Biceps
Forearm
Quad
Sweat Rate (mg/cm²/min)
0.5
0.0
-0.5
-1.0
0.051 <0.001 0.087 <0.001 0.009
0.765 0.002 >0.999 <0.001 0.142
0.017 0.805 0.003 0.252
0.255 >0.999 0.044 >0.999
0.004 0.386 0.088
0.066 >0.999 >0.999
<0.001 0.229
0.004 >0.999
0.011
0.167
Uncorrected p-values
Corrected p-values
Moderate-Heat Strain (MHS)
0.761 0.995 0.754 0.344 0.176
>0.999 >0.999 >0.999 >0.999 >0.999
0.814 0.934 0.242 0.264
>0.999 >0.999 >0.999 >0.999
0.671 0.210 0.070
>0.999 >0.999 >0.999
0.098 0.170
>0.999 >0.999
0.003
0.039
Uncorrected p-values
Corrected p-values
vs. Abdomen
vs. Biceps
vs. Forearm
vs. Quadriceps
vs. Calf
vs. Biceps
vs. Forearm
vs. Quadriceps
vs. Calf
vs. Forearm
vs. Quadriceps
vs. Calf
vs. Quadriceps
vs. Calf
vs. Calf

CHAPTER IV: GENERAL DISCUSSION

In the current study, we assessed regional variations in the age-related decline in sweat rate during a whole-body heat stress using a water-perfusion suit. The main finding was that, contrary to previous observations (Coull et al., 2021; Gerrett et al., 2021; Inoue, 1996; Inoue et al., 1991; Smith, Alexander, et al., 2013), we showed a greater age-related reduction in sweat rate at the trunk compared to the limbs at low-heat strain, with no evidence of regional variation in that age-related reduction during moderate-heat strain. Further, the onset threshold for sweating was delayed in the older adults but was not region dependent. The thermosensitivity of the sweating response did not differ between older and young men, nor was this response region dependent. These outcomes advance our understanding of the regional age-related decline in sweating by indicating that while aging is associated with an attenuated sweat rate, the reduction is greater in central (i.e., trunk) than peripheral (i.e., limbs) regions under low-heat strain.

Age-related decrements in sweat rate have previously been suggested to develop in a peripheral-to-central manner, such that the limbs demonstrate a greater magnitude in the age-related reduction in sweat rate followed by the trunk (Coull et al., 2021; Inoue et al., 1991; Inoue & Shibasaki, 1996; Kenney & Munce, 2003). However, prior investigations of this hypothesis neither controlled for body core nor skin temperature responses across measurement sites (Coull et al., 2021; Inoue et al., 1991; Inoue & Shibasaki, 1996). Further, while studies that used a water-perfusion suit could better control skin and core temperature responses, they did not assess the regional age-related decline in sweat rate when body core temperature was stable (Smith, Alexander, et al., 2013). Therefore, we revisited the peripheral-to-central age-related decline in sweating by assessing sweat rate in young and older adults at four sites on the limbs to reflect the periphery and two sites on the torso to reflect the trunk

(central). In addition, we used a water-perfusion suit to better control for elevations in body core temperature and provide a more homogenous skin temperature response across measurement sites. Further, we assessed the sweating response at two different levels of heat strain (0.6ºC and 1.2ºC above baseline), with both heating levels maintained for at least 10 minutes to ensure stable elevations in core temperature and, therefore, thermal drive for sweating. To ensure stable body core temperature at both heating levels, once the target core temperature was reached and the water bath temperature turned down, there was an approximate 15-minute waiting period. The time to ensure stable body core temperature, and thus sweating, was previously reported by Haqani et al. (2017) and piloted in the current study to ensure the timing was sufficient. Contrary to the peripheral-to-central age-related decline documented previously (Coull et al., 2021; Inoue et al., 1991; Inoue & Shibasaki, 1996), we observed a greater reduction in sweat rate at the trunk compared to the limbs in the older relative to young adults at a low-heat strain only. While there is a need for larger and more detailed studies to identify the mechanism(s) explaining this observation and the discrepancy between our findings and those of previous reports, these outcomes advance our understanding by providing evidence for a central-to-peripheral pattern of reduction (i.e., the age-related decrement in sweat rate first begins at the trunk and then occurs at the limbs).

It is possible that, at low-heat strain, the greater age-related reduction in sweat rate that occurred at the trunk may be due to structural changes, such as skin aging. Skin aging can affect the functional ability of the skin's temperature receptors, thereby altering thermal perception (Guergova & Dufour, 2011). Indeed, a report by Dufour and Candas (2007) showed that older individuals (≥60 years) are less sensitive to heat exposure and take longer to respond to temperature changes (i.e., decreased ability

to sense heat) than their younger counterparts. Therefore, an age-related decline in thermal receptor activity may partly explain the lower sweat rate in older individuals in the current study. Further, in young adults, thermal sensitivity is not uniform across the body, and the trunk has a greater thermal sensitivity than the limbs in younger adults (Dufour & Candas, 2007). While regional age-related changes in thermal sensitivity during heat exposure have not directly been assessed, the age-related reduction in sweat rate at the trunk may be due to a concurrent, localized age-related decline in thermal sensitivity at this region compared to the limbs.

Another possible explanation for a greater age-related reduction in sweat rate at the trunk, at low-heat strain, could be due to a reduced age-related deterioration in the sweating response in areas with the greatest capacity for heat loss (i.e., the limbs). A more efficient sweating response occurs in the limbs due to their relatively sizeable surface-area-to-mass ratio (a critical factor defining net evaporative heat loss) compared to the trunk (Taylor et al., 2014). Indeed, Taylor and Machado-Moreira (2013) estimated regional contributions to sweating and, therefore, net evaporative heat loss (assuming 100% evaporation) from 14 body regions during rest and exercise in dry heat in young adults. While they could not measure evaporative heat loss directly, their findings indicate that the relative contribution to net evaporative heat loss is greater at the thigh than at the chest and abdomen during rest and exercise in the heat. Moreover, during exercise, movement of the limbs is more pronounced relative to the trunk, which remains relatively stable. Thus, greater action from the limbs increases air velocity across the skin surface during locomotion, resulting in a greater rate of dry heat exchange and evaporative heat loss between the body and the environment (Taylor et al., 2014). Nonetheless, this hypothesis remains speculative

and represents an important area of future research for improving our understanding of age-associated changes in thermoregulatory function.

The central-to-peripheral pattern of the age-related decline in sweat rate observed at low-heat strain did not occur at a moderate-heat strain. Our observation that no specific regional age-related sweating pattern exists at moderate-heat strain is consistent with previous investigations that elicited similar increases in body core temperature (0.8-1.0°C) (Gerrett et al., 2021; Smith, Alexander, et al., 2013). These observations indicate that the level of hyperthermia, and associated increases in sweat rate, may be an important factor mediating the age-related reductions in sweat rate across body segments. Further, the sweating response across the body likely becomes more homogenous at increased levels of heat strain. A more homogenous sweating response is likely due to increased sweat gland output at the areas that demonstrated the greatest age-related reduction in sweating at low-heat strain (i.e., the trunk) (Kondo et al., 2001; Taylor & Machado-Moreira, 2013).

It is possible that age-related reductions in sweat gland output and a reduced number of heat-activated sweat glands at the trunk may occur at low- but not at moderate-heat strain. In young adults, sweat rate is dependent first on the activation of sweat glands, followed by the output from these glands (Kondo et al., 2001). However, as body core temperature increases and the need to dissipate heat becomes greater, increases in sweat rate are primarily due to changes in sweat gland output and are less dependent on the activation and recruitment of sweat glands (Kondo et al., 1998). The contribution of activated sweat glands and sweat gland output has further been observed in older women, where the number of heat-activated sweat glands was lower at the scapula than in younger women during the first 30 minutes of exercise heat stress (Anderson & Kenney, 1987). However, no differences

in the number of heat-activated sweat glands were observed past 30 minutes, although sweat gland output was reduced at the scapula in older women throughout the exercise test. Thus, it is plausible at low levels of heat strain, the number of heat-activated sweat glands, combined with a lower sweat output per gland at the abdomen and chest, could be driving the greater age-related reduction observed. While speculative, this may lead to new avenues of research, including the need to consider the contribution in the number of heat-activated sweat glands at different levels of heat strain between regions.

The use of ventilated capsules in the current study permits a more in-depth understanding of thermoeffector responses as defined by the onset threshold, thermosensitivity, and plateau (see section 2.1. for additional details). The onset threshold of sweat rate is characterized by a “central” (i.e., neural) modulation of thermoeffector output, with the preoptic anterior area of the hypothalamus being the likely integration site for driving thermally mediated sweating (Nadel et al., 1974; Nadel, Mitchell, et al., 1971). In the current study, the onset threshold was delayed (i.e., shifted to the right), on average, by ~0.3ºC in older compared to young adults. This observation suggests that aging delays the onset of sweating and is due to a greater change in mean body temperature required to activate the sweating response. Further, the onset threshold was not region dependent in either young or older adults. Across all six sites, the mean body temperature at the onset of sweating was similar within groups (i.e., all sites had an onset mean body temperature of ~36.96°C in older and ~36.72°C in young adults). This outcome is in line with previous work where a non-region-specific delay in onset threshold was observed in older compared to young adults (Smith, Alexander, et al., 2013). Thus, although aging delays the onset of sweating, our findings support previous suggestions that sweat gland recruitment

occurs in a generalized pattern across the body surface during thermal loading, irrespective of age (Frei et al., 2019; Smith, Alexander, et al., 2013).

The thermosensitivity of the sweating response is defined as the slope of the increase in sweat rate starting from the onset of sweating and encapsulates “peripheral” (i.e., end-organ) thermoeffector modulation (Nadel et al., 1974; Nadel, Mitchell, et al., 1971). In the current study, the thermosensitivity of the sweating response was reduced in older adults by ~0.08 mg/min/cm^2/ºC compared to their younger counterparts, albeit this was not statistically significant. Additionally, across the six sites, the thermosensitivity of the response was similar within each group, indicating that thermosensitivity is not region-specific. These findings suggest that although we observed a greater change in mean body temperature to activate sweat rate in the older adults (i.e., a delay in the onset threshold), there is no age- or region-dependent effect on thermosensitivity.

Lastly, the plateau phase of the sweating response is characterized by a flattening of the heat loss responses as they reach maximal values, whereby no further increase in heat loss responses occurs despite increasing mean body temperature (Kenny & Flouris, 2014). We did not observe a plateau in the heat loss responses in either the older or young adults indicating that neither age group achieved maximal sweating for a given change in mean body temperature. Further, we do not know if this response varies by region as we did not observe a maximal sweating response for a given change in body core temperature and, therefore, a plateau in the young and older adults. Future research may seek to investigate the regional age-related differences in sweating in response to an elevation in body core temperature above 1.2ºC to elucidate whether the plateau in the sweat response differs between regions and age groups.

4.2. Perspectives and future directions

Given we are experiencing increases in the frequency, intensity, and duration of extreme heat events (i.e., heatwaves), protecting older individuals from heat-related illness and injury has become increasingly important. The current thesis showed that while no region-specific pattern in the age-related reduction of sweating at moderate-heat strain occurred, sweat rate was still impaired in older adults at all sites assessed. These findings support the need for future research to investigate the mechanisms of this age-related impairment in sweating. The lack of regional differences in the age-related decline in sweating at moderate-heat strain has several important implications for future mechanistic studies. First, future studies investigating the underlying mechanisms associated with age-related impairments can be more confident that age-related differences at one site, under moderate-heat strain conditions, reflect differences across other body regions. Therefore, future research can focus on the underlying mechanisms causing this age-related impairment in sweating with less emphasis on the regional age-related reduction in sweat rate.

Information from this thesis can be used to direct future research and aid in developing heat-mitigation strategies, such as whether targeted or whole-body cooling strategies should be used to alleviate heat strain in older adults during heat exposure. To ease heat strain on a day-to-day basis in the warmer months (i.e., May-August), targeted cooling strategies (i.e., water-dousing and misting) at the trunk may benefit older adults (Morris et al., 2019). Further, these data may inform future investigations on cooling strategies during heatwaves and more severe instances where the core temperature is elevated past 0.6ºC. For example, Kenny et al. (2017) observed that during a 3-hour passive heat exposure (44ºC, 30% relative humidity; representative of an extreme heat event scenario), body core temperature in older adults increased by

~0.5°C and exhibited age-related regional differences in sweating. However, using measures of heat storage during the prolonged heat exposure, the authors predicted an ~1.6-fold increase in mean body temperature had the protocol been extended to 8 hours. Since we observed no specific pattern in the regional age-related decline in sweat rate at moderate heat-strain, heat-mitigation strategies at higher body temperatures may be most effective if they aim to cool the whole body. Thus, the insights from these data should be considered an important piece within this growing body of work regarding age-related impairments in the sweating response.

4.3. General conclusion

The current thesis sought to evaluate whether the age-related reduction in sweat rate occurred in a region-specific pattern. Our study expanded on previous reports by increasing the number of sites measured on each body region to ensure that one site did not overly influence regional sweat rates. With this unique approach, we were able to provide a more robust test of a peripheral-to-central decline in the age-related reduction in sweat rate. Moreover, by clamping and allowing for stable sweating at both a 0.6°C and 1.2°C change in body core temperature above baseline, we determined whether these effects were consistent across two different levels of heat strain. We demonstrated that the greatest age-related reduction in sweat rate occurred at the trunk at low-but, not moderate-heat strain. Further, the onset threshold and the thermosensitivity of the sweating response did not appear to occur in a region-specific pattern. These findings suggest that under controlled elevations of body core temperature and with a homogenous skin temperature response across measurement sites, the age-related reduction in sweat rate occurs in a central-to-peripheral pattern, a response which appears to occur under low levels of heat-strain only.

CHAPTER V: REFERENCES

Akerman, A. P., Meade, R. D., Notley, S. R., Rutherford, M. M., & Kenny, G. P. (2021). Myths and methodologies: Reliability of non-invasive estimates of cardiac autonomic modulation during whole-body passive heating. *Experimental physiology, 106*(3), 593-614.

Amano, T., Fujii, N., Louie, J. C., Meade, R. D., & Kenny, G. P. (2017). Individual variations in nitric oxide synthase-dependent sweating in young and older males during exercise in the heat: role of aerobic power. *Physiological reports, 5*(6), e13208.

Anderson, R. K., & Kenney, W. L. (1987). Effect of age on heat-activated sweat gland density and flow during exercise in dry heat. *Journal of applied physiology, 63*(3), 1089-1094.

Ata, A. M., Kara, M., Kaymak, B., Gürçay, E., Çakır, B., Ünlü, H., Akıncı, A., & Özçakar, L. (2019). Regional and total muscle mass, muscle strength and physical performance: the potential use of ultrasound imaging for sarcopenia. *Archives of gerontology and geriatrics, 83*, 55-60.

Baecke, J. A., Burema, J., & Frijters, J. E. (1982). A short questionnaire for the measurement of habitual physical activity in epidemiological studies. *The american journal of clinical nutrition, 36*(5), 936-942.

Baker, L. B., Barnes, K. A., Anderson, M. L., Passe, D. H., & Stofan, J. R. (2016). Normative data for regional sweat sodium concentration and whole-body sweating rate in athletes. *Journal of sports sciences, 34*(4), 358-368.

Balmain, B. N., Sabapathy, S., Louis, M., & Morris, N. R. (2018). Aging and thermoregulatory control: the clinical implications of exercising under heat stress in older individuals. *BioMed research international, 2018*.

Boulant, J. A., & Bignall, K. (1973). Hypothalamic neuronal responses to peripheral and deep-body temperatures. *American journal of physiology-legacy content, 225*(6), 1371-1374.

Brengelmann, G., McKeag, M., & Rowell, L. (1975). Use of dew-point detection for quantitative measurement of sweating rate. *Journal of applied physiology, 39*(3), 498-500.

Broadbent, A. M., Declet-Barreto, J. H., Krayenhoff, E. S., Harlan, S. L., & Georgescu, M. (2021). Targeted implementation of cool roofs for equitable urban adaptation to extreme heat. *Science of the total environment*, 151326.

Cain, B., & McLellan, T. M. (1998). A model of evaporation from the skin while wearing protective clothing. *International journal of biometeorology, 41*(4), 183-193.

Charkoudian, N., & Stachenfeld, N. (2016). Sex hormone effects on autonomic mechanisms of thermoregulation in humans. *Autonomic Neuroscience, 196*, 75-80.

Cotter, J. D., Patterson, M. J., & Taylor, N. A. (1995). The topography of eccrine sweating in humans during exercise. *European journal of applied physiology and occupational physiology, 71*(6), 549-554.

Cotter, J. D., & Taylor, N. A. (2005). The distribution of cutaneous sudomotor and alliesthesial thermosensitivity in mildly heat-stressed humans: an open-loop approach. *The journal of physiology, 565*(1), 335-345.

Coull, N. A., West, A. M., Hodder, S. G., Wheeler, P., & Havenith, G. (2021). Body mapping of regional sweat distribution in young and older males. *European journal of applied physiology, 121*(1), 109-125.

CSEP. (1986). Determination of aerobic power. Canadian Society for Exercise Physiology.

D'Souza, A. W., Notley, S. R., & Kenny, G. P. (2020). The Relation between Age and Sex on Whole-Body Heat Loss during Exercise-Heat Stress. *Medicine and science in sports and exercise*.

Drinkwater, B., Bedi, J., Loucks, A., Roche, S., & Horvath, S. (1982). Sweating sensitivity and capacity of women in relation to age. *Journal of applied physiology, 53*(3), 671-676.

DuBois, D., & DuBois, E. F. (1915, May). The measurement of the surface area of man. *Archives of Internal Medicine, 15*(5), 868-881. <Go to ISI>://WOS:000202579800005

Dufour, A., & Candas, V. (2007). Ageing and thermal responses during passive heat exposure: sweating and sensory aspects. *European journal of applied physiology, 100*(1), 19-26.

Frei, R., Notley, S. R., Taylor, E. A., Burdon, C. A., Ohnishi, N., & Taylor, N. A. (2019). Revisiting the dermatomal recruitment of, and pressure-dependent influences on, human eccrine sweating. *Journal of thermal biology, 82*, 52-62.

Gagnon, D., Ganio, M. S., Lucas, R. A., Pearson, J., Crandall, C. G., & Kenny, G. P. (2012). Modified iodine-paper technique for the standardized determination of sweat gland activation. *Journal of applied physiology, 112*(8), 1419-1425.

Gagnon, D., Jay, O., & Kenny, G. P. (2013). The evaporative requirement for heat balance determines whole-body sweat rate during exercise under conditions permitting full evaporation. *The journal of physiology, 591*(11), 2925-2935.

Gavin, T. P. (2003). Clothing and thermoregulation during exercise. *Sports medicine, 33*(13), 941-947.

Gemae, M. R., Akerman, A. P., McGarr, G. W., Meade, R. D., Notley, S. R., Schmidt, M. D., Rutherford, M. M., & Kenny, G. P. (2021). Myths and methodologies: reliability of forearm cutaneous vasodilatation measured using laser-doppler

flowmetry during whole-body passive heating. *Experimental physiology, 106*(3), 634-652.

Gerrett, N., Amano, T., Inoue, Y., & Kondo, N. (2021). Eccrine sweat glands' maximum ion reabsorption rates during passive heating in older adults (50–84 years). *European journal of applied physiology*, 1-15.

Graichen, H., Rascati, R., & Gonzalez, R. (1982). Automatic dew-point temperature sensor. *Journal of applied physiology, 52*(6), 1658-1660.

Guergova, S., & Dufour, A. (2011). Thermal sensitivity in the elderly: a review. *Ageing research reviews, 10*(1), 80-92.

Haqani, B., Fujii, N., Kondo, N., & Kenny, G. P. (2017). The mechanisms underlying the muscle metaboreflex modulation of sweating and cutaneous blood flow in passively heated humans. *Physiological reports, 5*(3), e13123.

Hardy, J. D., Du Bois, E. F., & Soderstrom, G. (1938). Basal metabolism, radiation, convection and vaporization at temperatures of 22 to 35 C. six figures. *The journal of nutrition, 15*(5), 477-497.

Havenith, G., Fogarty, A., Bartlett, R., Smith, C. J., & Ventenat, V. (2008). Male and female upper body sweat distribution during running measured with technical absorbents. *European journal of applied physiology, 104*(2), 245-255.

Hensel, H. (1981). Thermoreception and temperature regulation.

Heo, M., & Leon, A. C. (2010). Sample sizes required to detect two-way and three-way interactions involving slope differences in mixed-effects linear models. *Journal of biopharmaceutical statistics, 20*(4), 787-802.

Hertzman, A. B. (1957). Individual differences in regional sweating. *Journal of applied physiology, 10*(2), 242-248.

Hoffmann, M. D., Colley, R. C., Doyon, C. Y., Wong, S. L., Tomkinson, G. R., & Lang, J. J. (2019). Normative-referenced percentile values for physical fitness among Canadians. *Health reports, 30*(10), 14-22.

Inoue, Y. (1996). Longitudinal effects of age on heat-activated sweat gland density and output in healthy active older men. *European journal of applied physiology and occupational physiology, 74*(1), 72-77.

Inoue, Y., Havenith, G., Kenney, W. L., Loomis, J. L., & Buskirk, E. R. (1999). Exercise- and methylcholine-induced sweating responses in older and younger men: effect of heat acclimation and aerobic fitness. *International journal of biometeorology, 42*(4), 210-216.

Inoue, Y., Kuwahara, T., & Araki, T. (2004). Maturation-and aging-related changes in heat loss effector function. *Journal of physiological anthropology and applied human science, 23*(6), 289-294.

Inoue, Y., Nakao, M., Araki, T., & Murakami, H. (1991). Regional differences in the sweating responses of older and younger men. *Journal of applied physiology, 71*(6), 2453-2459.

Inoue, Y., & Shibasaki, M. (1996). Regional differences in age-related decrements of the cutaneous vascular and sweating responses to passive heating. *European journal of applied physiology and occupational physiology, 74*(1), 78-84.

Inoue, Y., Shibasaki, M., Hirata, K., & Araki, T. (1998). Relationship between skin blood flow and sweating rate, and age related regional differences. *European journal of applied physiology and occupational physiology, 79*(1), 17-23.

Inoue, Y., Shibasaki, M., Ueda, H., & Ishizashi, H. (1999). Mechanisms underlying the age-related decrement in the human sweating response. *European journal of applied physiology and occupational physiology, 79*(2), 121-126.

Inukai, Y., Sugenoya, J., Kato, M., Nishimura, N., Nishiyama, T., Matsumoto, T., Sato, M., Ogata, A., Taniguchi, Y., & Osada, A. (2005). Effects of body posture on local sweating and sudomotor outflow as estimated using sweat expulsion. *Autonomic neuroscience, 119*(1), 48-55.

Jay, O., & Kenny, G. P. (2010). Heat exposure in the Canadian workplace. *American journal of industrial medicine, 53*(8), 842-853.

Kenefick, R. W., & Cheuvront, S. N. (2012). Hydration for recreational sport and physical activity. *Nutrition reviews, 70*(suppl_2), S137-S142.

Kenefick, R. W., Cheuvront, S. N., Elliott, L. D., Ely, B. R., & Sawka, M. N. (2012). Biological and analytical variation of the human sweating response: implications for study design and analysis. *American journal of physiology-regulatory, integrative and comparative physiology, 302*(2), R252-R258.

Kenney, W. L., & Fowler, S. R. (1988). Methylcholine-activated eccrine sweat gland density and output as a function of age. *Journal of applied physiology, 65*(3), 1082-1086.

Kenney, W. L., & Munce, T. A. (2003). Invited review: aging and human temperature regulation. *Journal of applied physiology, 95*(6), 2598-2603.

Kenny, & Flouris. (2014). The human thermoregulatory system and its response to thermal stress. *Protective Clothing*, 319-365.

Kenny, & Jay. (2013). Thermometry, calorimetry, and mean body temperature during heat stress. *Comprehensive physiology, 3*(4), 1689-1719.

Kenny, 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, 4*(1), 79-88.

Kenny, Yardley, J., Brown, C., Sigal, R. J., & Jay, O. (2010). Heat stress in older individuals and patients with common chronic diseases. *Cmaj, 182*(10), 1053-1060.

Ko, Y., Seol, S.-H., Kang, J., & Lee, J.-Y. (2020). Adaptive changes in physiological and perceptual responses during 10-day heat acclimation training using a water-perfused suit. *Journal of physiological anthropology, 39*(1), 1-11.

Kondo, Shibasaki, M., Aoki, K., Koga, S., Inoue, Y., & Crandall, C. G. (2001). Function of human eccrine sweat glands during dynamic exercise and passive heat stress. *Journal of applied physiology, 90*(5), 1877-1881.

Kondo, Takano, S., Aoki, K., Shibasaki, M., Tominaga, H., & Inoue, Y. (1998). Regional differences in the effect of exercise intensity on thermoregulatory sweating and cutaneous vasodilation. *Acta physiologica Scandinavica, 164*(1), 71-78.

Larose, J., Boulay, P., Sigal, R. J., Wright, H. E., & Kenny, G. P. (2013). Age-related decrements in heat dissipation during physical activity occur as early as the age of 40. *PloS one, 8*(12), e83148.

Lenth, R., Singmann, H., Love, J., Buerkner, P., & Herve, M. (2018). Emmeans: estimated marginal means, aka least-squares means. *R package version, 1*(1), 3.

Machado-Moreira, C. A., Smith, F. M., van den Heuvel, A. M., Mekjavic, I. B., & Taylor, N. A. (2008). Sweat secretion from the torso during passively-induced and exercise-related hyperthermia. *European journal of applied physiology, 104*(2), 265-270.

Machado-Moreira, C. A., Wilmink, F., Meijer, A., Mekjavic, I. B., & Taylor, N. A. (2008). Local differences in sweat secretion from the head during rest and exercise in the heat. *European journal of applied physiology, 104*(2), 257-264.

Meade, R. D., Akerman, A. P., Notley, S. R., McGinn, R., Poirier, P., Gosselin, P., & Kenny, G. P. (2020). Physiological factors characterizing heat-vulnerable older adults: A narrative review. *Environment international, 144*, 105909.

Morris, N. B., Gruss, F., Lempert, S., English, T., Hospers, L., Capon, A., & Jay, O. (2019). A preliminary study of the effect of dousing and foot immersion on cardiovascular and thermal responses to extreme heat. *JAMA, 322*(14), 1411-1413.

Morrison, S. F., & Nakamura, K. (2011). Central neural pathways for thermoregulation. *Frontiers in bioscience: a journal and virtual library, 16*, 74.

Nadel, E., Pandolf, K., Roberts, M., & Stolwijk, J. (1974). Mechanisms of thermal acclimation to exercise and heat. *Journal of applied physiology, 37*(4), 515-520.

Nadel, E. R., Bullard, R. W., & Stolwijk, J. (1971). Importance of skin temperature in the regulation of sweating. *Journal of applied physiology, 31*(1), 80-87.

Nadel, E. R., Mitchell, J. W., Saltin, B., & Stolwijk, J. (1971). Peripheral modifications to the central drive for sweating. *Journal of applied physiology 31*(6), 828-833.

Notley, S. R., Meade, R. D., Akerman, A. P., Poirier, M. P., Boulay, P., Sigal, R. J., Flouris, A. D., & Kenny, G. P. (2020). Evidence for age-related differences in heat acclimatisation responsiveness. *Experimental physiology, 105*(9), 1491-1499.

Notley, S. R., Meade, R. D., & Kenny, G. P. (2020). Effect of aerobic fitness on the relation between age and whole-body heat exchange during exercise-heat stress: a retrospective analysis. *Experimental physiology, 105*(9), 1550-1560.

Park, S. J., & Tamura, T. (1992). Distribution of evaporation rate on human body surface. *The annals of physiological anthropology, 11*(6), 593-609.

Parsons, K. (2014). *Human thermal environments: the effects of hot, moderate, and cold environments on human health, comfort, and performance*. CRC press.

Patterson, M. J., Stocks, J. M., & Taylor, N. A. (2004). Humid heat acclimation does not elicit a preferential sweat redistribution toward the limbs. *American journal of physiology-regulatory, integrative and comparative physiology, 286*(3), R512-R518.

Pinheiro, J., Bates, D., DebRoy, S., Sarkar, D., Heisterkamp, S., Van Willigen, B., & Maintainer, R. (2017). Package 'nlme'. *Linear and nonlinear mixed effects models, version, 3*(1).

Quinn, A., Kinney, P., & Shaman, J. (2017). Predictors of summertime heat index levels in New York City apartments. *Indoor air, 27*(4), 840-851.

Ramanathan, N. L. (1964, May). A New Weighting System for Mean Surface Temperature of the Human Body. *Journal of applied physiology, 19*, 531-533. https://doi.org/10.1152/jappl.1964.19.3.531

Rawson, R. O., & Randall, W. C. (1961). Vascular and sweating responses to regional heating of the body surface. *Journal of applied physiology, 16*(6), 1006-1010.

Rutherford, M. M., Akerman, A. P., Notley, S. R., Meade, R. D., Schmidt, M. D., & Kenny, G. P. (2021). Regional variation in the reliability of sweat rate measured via the ventilated capsule technique during passive heating. *Experimental physiology, 106*(3), 615-633.

Saga, K. (2002). Structure and function of human sweat glands studied with histochemistry and cytochemistry. *Progress in histochemistry and cytochemistry, 37*(4), 323-386.

Sato, & Dobson. (1970). Regional and individual variations in the function of the human eccrine sweat gland. *Journal of investigative dermatology, 54*(6), 443-449.

Sato, & Sato. (1983). Individual variations in structure and function of human eccrine sweat gland. *American journal of physiology-regulatory, integrative and comparative physiology, 245*(2), R203-R208.

Sato, K. (1988). Effect of aging on pharmacological sweating in man. *Cutaneous aging*, 127-134.

Shibasaki, M., & Crandall, C. G. (2010). Mechanisms and controllers of eccrine sweating in humans. *Frontiers in bioscience (Scholar edition), 2*, 685.

Shibasaki, M., Okazaki, K., & Yoshimitsu, I. (2013). Aging and thermoregulation. *The journal of physical fitness and sports medicine, 2*(1), 37-47.

Shibasaki, M., Wilson, T. E., & Crandall, C. G. (2006). Neural control and mechanisms of eccrine sweating during heat stress and exercise. *Journal of applied physiology, 100*(5), 1692-1701.

Shim, H. S., & Choi, J. W. (1993). The effect of posture on the human thermoregulatory response. *Journal of the korean society of clothing and textiles, 17*(3), 415-427.

Siri, W. E. (1956). *Advances in biological and medical physics* (J. H. T. Lawrence, C.A., Ed.). Academic.

Smith, Alexander, & Kenney. (2013). Nonuniform, age-related decrements in regional sweating and skin blood flow. *American journal of physiology-regulatory, integrative and comparative physiology, 305*(8), R877-R885.

Smith, & Havenith. (2011). Body mapping of sweating patterns in male athletes in mild exercise-induced hyperthermia. *European journal of applied physiology, 111*(7), 1391-1404.

Smith, & Havenith. (2012). Body mapping of sweating patterns in athletes: a sex comparison.

Smith, Kenney, & Alexander. (2013). Regional relation between skin blood flow and sweating to passive heating and local administration of acetylcholine in young, healthy humans. *American journal of Physiology- regulatory integrative comparative physiology, 304*(7), R566-R573.

Stapleton, J. M., Fujii, N., Carter, M., & Kenny, G. P. (2014). Diminished nitric oxide-dependent sweating in older males during intermittent exercise in the heat. *Experimental physiology, 99*(6), 921-932.

Stapleton, J. M., Poirier, M. P., Flouris, A. D., Boulay, P., Sigal, R. J., Malcolm, J., & Kenny, G. P. (2015). Aging impairs heat loss, but when does it matter? *Journal of applied physiology, 118*(3), 299-309.

Taylor, & Machado-Moreira. (2013). Regional variations in transepidermal water loss, eccrine sweat gland density, sweat secretion rates and electrolyte composition in resting and exercising humans. *Extreme physiology & medicine, 2*(1), 4.

Taylor, N. A. (2006). Challenges to temperature regulation when working in hot environments. *Industrial health, 44*(3), 331-344.

Taylor, N. A., Machado-Moreira, C. A., van den Heuvel, A. M., & Caldwell, J. N. (2014). Hands and feet: physiological insulators, radiators and evaporators. *European journal of applied physiology, 114*(10), 2037-2060.

Taylor, N. A., Nykvist, Å., Powers, N., & Caldwell, J. N. (2019). Thermoeffector threshold plasticity: the impact of thermal pre-conditioning on sudomotor, cutaneous vasomotor and thermogenic thresholds. *Journal of thermal biology, 83*, 37-46.

Team, R. C. (2018). R foundation for statistical computing, Vienna, available at: www. *R-project. org*.

Todd, G., Gordon, C. J., Groeller, H., & Taylor, N. A. (2014). Does intramuscular thermal feedback modulate eccrine sweating in exercising humans? *Acta physiologica, 212*(1), 86-96.

Van Beaumont, W., & Bullard, R. W. (1963). Sweating: its rapid response to muscular work. *Science, 141*(3581), 643-646.

Weiner, J. (1945). The regional distribution of sweating. *The journal of physiology, 104*(1), 32-40.

Wendt, D., van Loon, L. J., & Lichtenbelt, W. D. M. (2007). Thermoregulation during exercise in the heat. *Sports medicine, 37*(8), 669-682.

CHAPTER VI: APPENDICES

APPENDIX A: Ethics Certificate

Université d'Ottawa University of Ottawa
Bureau d'éthique et d'intégrité de la recherche Office of Research Ethics and Integrity

Health Sciences and Science Research Ethics Board

APPROVAL OF MODIFICATIONS

March 27, 2021

Glen Kenny
School of Human Kinetics
Faculty of Health Sciences
125 University
Ottawa, ON K1N 6N5

RE: Understanding and managing the limits of physiological tolerance in heat vulnerable Canadians during rest and physical activity/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. (H 05-16-07)

Dear Professor Kenny,

The Health Sciences and Science Research Ethics Board has examined your request for ethics approval of the following modifications to your research project:

- Madison Schmidt, a research assistant on the project, will use part of the data for her master's thesis project supervised by the Principal Investigator.
- The consent form has been modified to take this change into account.

Your request has been accepted. The certificate of ethics approval renewed on July 11, 2020 and valid until July 10, 2021 covers these modifications.

During the course of the study, any further modifications to the protocol or forms may not be initiated without prior written approval from the REB. You must also promptly notify the REB of any adverse events that may occur.

If you have any questions, please do not hesitate to contact me at extension 5387.

Sincerely yours,

Germain Zongo
Protocol Officer for Research Ethics
For Daniel Lagarec, Chair of the Health Sciences and Sciences REB

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